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The link between gut microbiota dysbiosis, inflammation and psoriasis

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Chapter I

Psoriasis

1.1 Introduction

The Greek words "Psora" (which means to itch) and "iasis" (which means a condition) are the origin of the word "psoriasis".[1]

The development of psoriasis is a chronic immune-mediated inflammatory condition of the skin, which is the result of a complex interaction between immunological, environmental, and genetic mechanisms.[2]

Generally, this disease is characterized by hyperproliferation and aberrant differentiation of the keratinocytes, resulting in red, scaly plaques that occur most frequently on elbows, knees, scalps, and lower backs, although it may affect any surface of the body. Multifactorial immunopathogenic mechanisms underlie the disease.[3]

The pathogenic functions of keratinocytes in psoriasis have been extensively debated. Several studies have shown that immune activation leads to abnormal differentiation and hyperproliferation of keratinocytes.[4] Since psoriasis is understood to be an autoimmune disease, it has become known to have significant health implications beyond the skin.[5]

It is important to note that patients may also present with systemic symptoms, such as cardiovascular disease, metabolic syndrome, depression, and joint involvement due to psoriatic arthritis, in addition to skin manifestations. The adverse effects of psoriasis on quality of life have also been demonstrated in several studies.[6]

1.2 Epidemiology

An inflammatory disease, psoriasis affects between 0.1 and 3% of the population[7] and more than 125 million people worldwide.[8] Around eighty-one percent of countries lack psoriasis epidemiological information. There is an unequal distribution of this disease across

geographical regions and it can effect anyone at any age[9]. In this way, ethnicity, genetic background, and environmental factors may play a role in its onset.[10]

A mean onset age of 33 years is observed for psoriasis in men and women equally.[11] Incidence data confirm a bimodal age pattern for psoriasis onset, with the first and second peaks occurring between 30 and 39 and 60 and 69 years of age, respectively. Evidence suggests that women present slightly earlier than men with this condition.[12]

1.3 Genetic

As a multifactorial disease, psoriasis is strongly influenced by genetic factors.[13] Genetic factors have a significant impact on the disease's pathogenesis.[14] Studies have indicated that relatives of patients with psoriasis are more likely to develop the disease than the general population.[15] Genetic factors may also affect the severity of their disease since, on average, those with early-onset psoriasis (type I psoriasis) have a more severe disease, and their family history is generally positive, whereas those with late-onset psoriasis (type II) tend to have milder forms and a negative family history.[16]

The main psoriasis risk allele within a complicated genetic predisposition is HLA-C*06:02 on psoriasis susceptibility locus PSORS1 (6p21.33).[17] One of the alleles most closely linked to psoriasis susceptibility is HLA-Cw6. It consistently affects illness progression, phenotypic characteristics, severity, comorbidities, and treatment results.[18] The HLA-C*06:02 allele is the genetic variant that contributes most to psoriasis susceptibility; it accounts for more than 6% of the diversity in disease risk, and each copy of the allele raises a person's chance of developing psoriasis by a factor of five.[19]

Heritability is the main risk determinant for developing psoriasis, Individuals who have both parents affected by psoriasis are at a 41% risk of developing psoriasis, and individuals who only have one affected parent are at a 14% risk.[20]

Compared to dizygotic twins, the risk is two to three times higher in monozygotic twins. Additionally, monozygotic twins have a 73% concordance rate for psoriasis.[21]

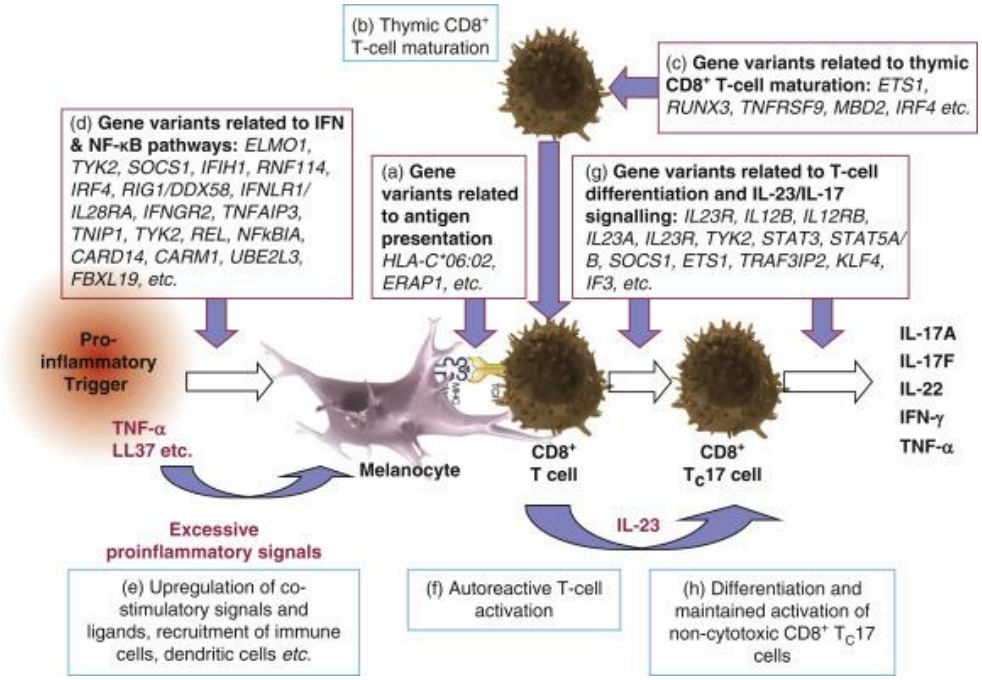

Fig. 1.1 Hypothetic model of the autoimmune response in psoriasis.[22]

1.4 Risk factors for psoriasis

Psoriasis risk factors can be divided into two categories: extrinsic and intrinsic. Each of these components will be discussed, along with their effects on psoriasis development.[14]

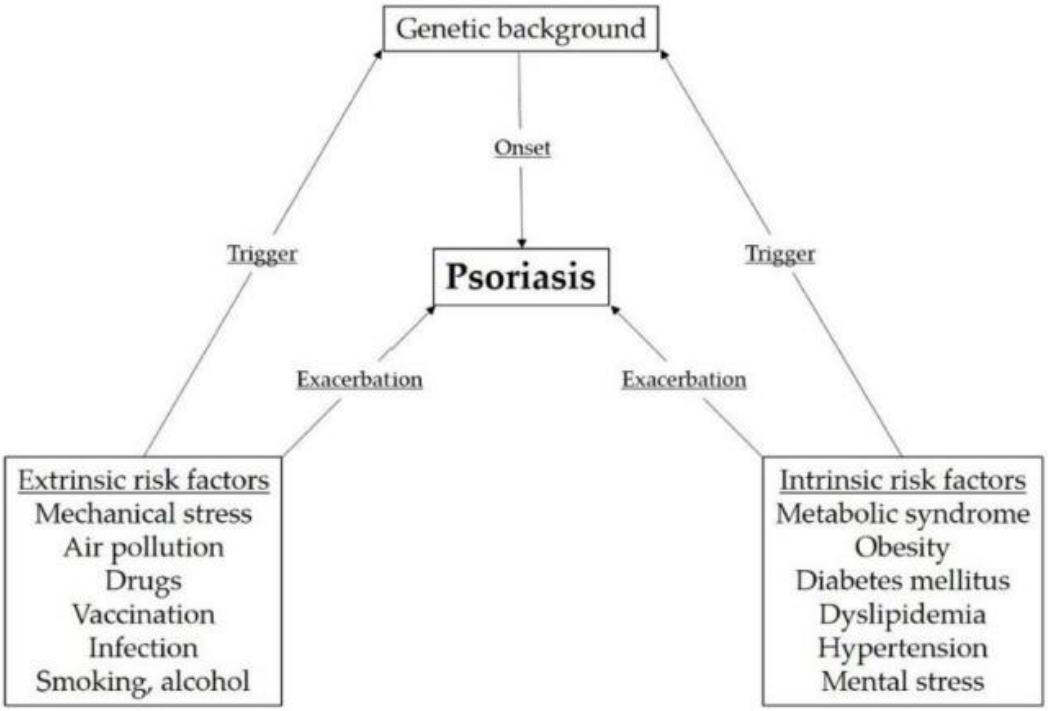

Fig. 1.2 Risk factors for the onset and exacerbation of psoriasis.[14]

1.4.1 Extrinsic Risk Factors

1.4.1.1 Mechanical Stress

One of dermatology's most well-known phenomena is the Koebner phenomenon. In 1876, Heinrich Koebner described it as the development of psoriatic lesions after cutaneous trauma in psoriatic patients.[23]

The Koebner phenomenon occurs when skin lesions appear in uninvolved areas after various injuries in patients with psoriasis.[24] There are several factors that can affect the pathogenesis of Koebner syndrome, including trauma type, site, depth, and degree of trauma.[25]

1.4.1.2 Air Pollutants and Sun Exposure

Increasing levels of air pollution have had a significant impact on human skin over the years. As the skin serves as the outermost barrier to the environment, various pollutants like ultraviolet rays, polycyclic aromatic hydrocarbons, volatile organic compounds, particulate matter and ozone can affect it in various ways. The oxidative stress caused by air pollutants damages the skin.[26] In some cases, an increase in these pollutants may lead to flares of psoriasis triggered by prolonged or repetitive exposure.[27]

1.4.1.3 Drugs

Considering psoriasis is a common skin disorder, understanding what induces, triggers, or exacerbates the disease is essential to clinical practice. As new pharmaceuticals are often added to the list of potential variables that may affect the course of the disease, drug use is a significant worry in this regard.[28] Patients with pre-existing psoriasis may be exacerbated by drug ingestion, psoriatic lesions may be induced on clinically uninvolved skin, or psoriasis may be precipitated in individuals without family history of the disease or predisposed to it.[29]

1.4.1.4 Vaccination

Immune-mediated inflammatory disorders (IMIDs), such as RA, IBD, or psoriasis, increase the risk of infection in patients. This risk is mostly due to the use of immunomodulatory or immunosuppressive medications during therapy. For this reason, vaccinations are recommended to prevent specific infections. However, vaccinations can often trigger psoriasis flares.[30]

According to a retrospective study, psoriasis is more frequently diagnosed after vaccination against adenovirus.[31] Other vaccines such as the tetanus-diphtheria vaccine and the pneumococcal polysaccharide vaccine may also trigger psoriasis.[32,33] Though the exact

pathomechanisms of vaccination-induced psoriasis are still unknown, it is believed that these vaccines cause T helper 1 (Th1) and Th17 immune responses, which cause the onset and worsening of psoriasis. There are very few cases of psoriasis triggered by vaccination; rather, vaccines are therapeutically effective in patients with the disease.[14]

1.4.1.5 Infection

The onset of acute guttate psoriasis was associated with streptococcal infection more than 100 years ago. The disease has been traditionally associated with throat infections, but can also follow streptococcal vulvovaginitis and perianal streptococcal infections. Although this kind of psoriasis usually resolves on its own, it might reappear after additional streptococcal infections or trigger a more severe case of plaque psoriasis.[34] Another well-known risk factor for psoriasis is the human immunodeficiency virus (HIV).[35] Additionally, endogenous retroviruses, retroviruses, and papillomaviruses have been implicated in the development of psoriasis.[36]

1.4.1.6 Lifestyle

There is evidence that diet-induced dysbiosis may be related to the pathogenesis of psoriasis, as changes in the gut microbiome are crucial.[37] The chronicity and incurability of psoriasis influence harmful habits such as smoking and drinking alcohol in patients with psoriasis.[38] Alcohol consumption and cigarette smoking are risk factors for both the onset and exacerbation of psoriasis.[39] The risk of psoriasis among current and former smokers is higher compared to non-smokers.[40]

1.4.2. Intrinsic Risk Factors

1.4.2.1 Obesity

As a chronic low-grade inflammatory condition, obesity, especially abdominal obesity, contributes actively to the development of metabolic syndrome and cardiovascular disease through the release of proinflammatory adipokines and cytokines that contribute to these

pathophysiologic conditions. Psoriasis and obesity have been shown to be genetically, pathogenic, and epidemiologically linked, with important health consequences. As a result of the bidirectional relationship between the two diseases, obesity seems to be a risk factor for psoriasis and psoriasis seems to favor obesity in many cases.

Patients with obesity are also more likely to experience adverse effects after consuming conventional systemic medications, and they may experience reduced efficacy and/or higher cost when consuming biologic agents, which should be dosed according to their weight.[41]

1.4.2.2 Diabetes Mellitus

There is a spectrum of serious adverse effects associated with diabetes and psoriasis. Diabetes is a risk factor for psoriasis and vice versa, and we consider them to be common comorbidities. It is our contention, however, that these diseases are not simply comorbidities but have underlying pathophysiologies that are shared (genes, epigenetic changes, inflammation, abnormal environments, and insulin resistance).

Environmental factors, inflammation, and insulin resistance can all affect epigenetic changes through genes. The potential for treating diabetes as well as psoriasis can be seen by viewing both conditions from the same perspective.[41]

1.4.2.3 Dyslipidemia

The condition has been linked to inflammatory pathways associated with psoriasis, and dyslipidemia is a strong risk factor for cardiovascular disease. Understanding the link between psoriasis and dyslipidemia can have a significant impact on clinical outcome. The relationship between the metabolism of fats and psoriasis will be clarified by further study.[42,43]

1.4.2.4 Hypertension

Compared to those who do not have psoriasis, patients with psoriasis had an increased risk of hypertension, according to the findings of this meta-analysis. In severe psoriasis, hypertension rates were higher than in mild psoriasis, and psoriasis patients in Europe and Asia were more likely to develop hypertension than non-psoriasis patients.[44]

1.4.2.5 Mental Stress

Most patients with psoriasis and physicians believe that mental stress worsens their condition, and mental stress has been well-established as a trigger for psoriasis.[45] Patients with acute psychosocial stress were also evaluated for cell subsets. Monocyte and CD4+ cell number were significantly higher in psoriatic patients than in controls in a study done on 23 patients with psoriasis and 25 healthy controls who were exposed to a standardized laboratory stressor, and CD3+/CD5+ were significantly lower in psoriatic patients than in controls. It is possible that these changes explain how stressors trigger psoriatic eruptions, according to the authors.[46]

1.5 Pathogenesis of psoriasis

Several cell types and numerous cytokines interact in a dynamic manner to cause psoriasis in genetically predisposed individuals, resulting in a disruption of skin immune homeostasis.[47] According to the current theory, keratinocytes, neutrophils, mast cells, T cells, and dendritic cells interact with one another to form pro-inflammatory and proliferative circuits that are regulated by cytokines and chemokines. Recent autoantigens, Toll-like receptor agonists, chemerin, and thymic stromal lymphopoietin are a few of the triggers that may activate the pathogenic cascade, increasing the production of pro-inflammatory and proliferation-inducing mediators like interleukin (IL)-17, tumor necrosis factor (TNF)-, IL-23, IL-22, interferon (IFN), and IFN- by immune cells.[48]

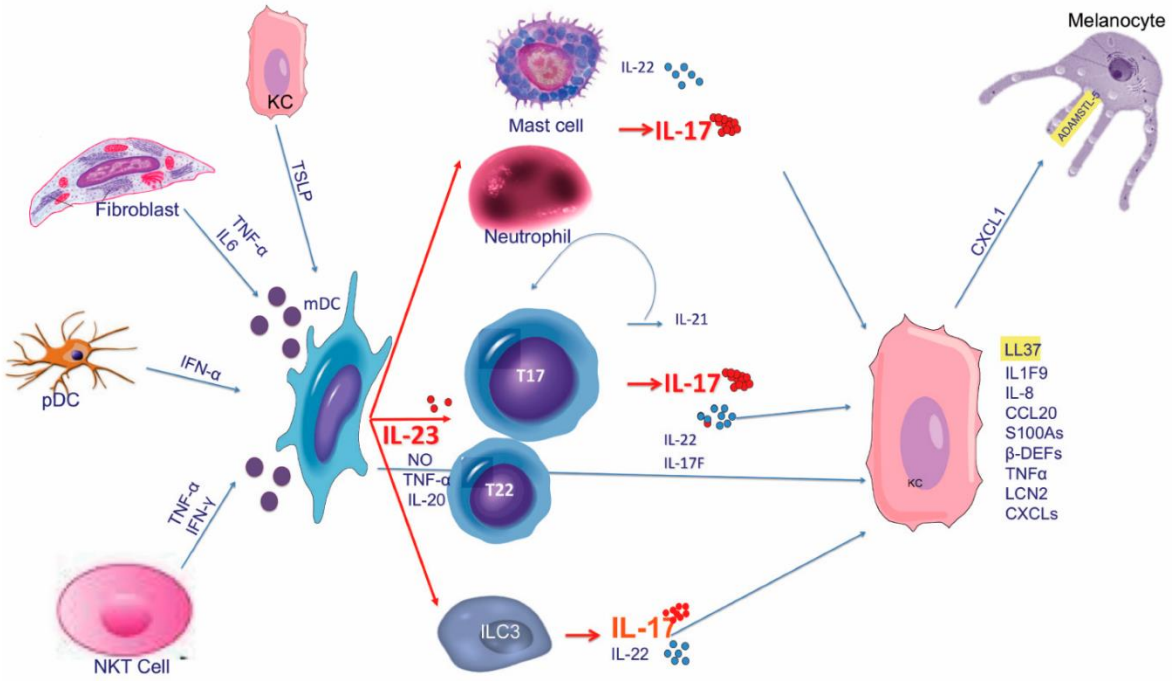

Fig. 1.3 The pathogenic model based on the IL-23/IL-17 axis inducing the development of psoriatic phenotype.[48]

There are several factors that play a role in the development of psoriasis, including genetics, immune system dysfunction, and environmental factors. Environmental factors can have a significant impact on its genetics and immune system. Antigen-presenting cells (APC) in the epidermis stimulate naïve T cells, encouraging them to develop into T-helper (Th)1 and Th17 cells, which increase Th1 and Th17 cells while decreasing Th2 and regulatory T cells (Treg). Then, lymph nodes stimulate activated T cells to produce plenty of cytokines by migrating to the skin. In this way, these cytokines induce changes in epidermal and dermal cells, such as proliferation of keratinocytes and epidermal thickness.[49]

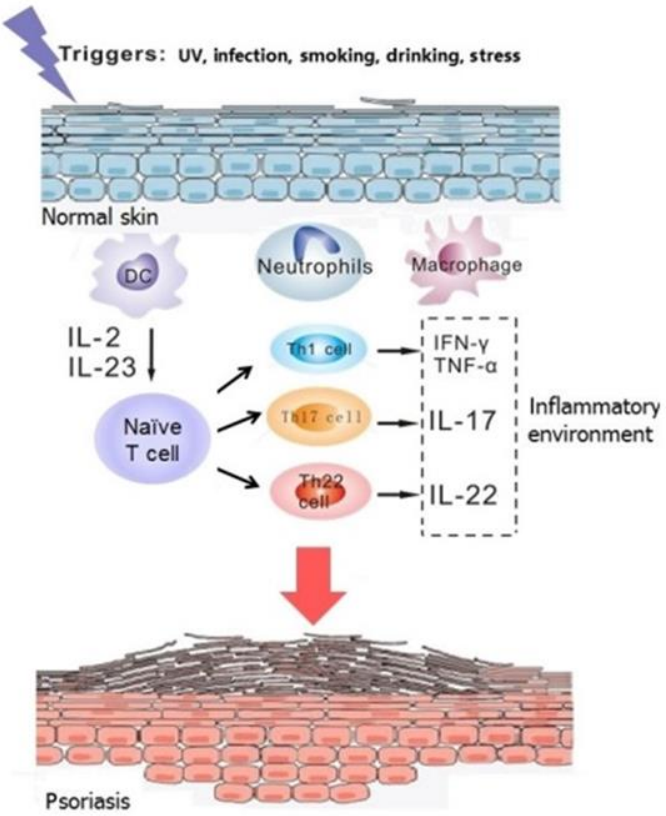

Fig. 1.4 Psoriasis pathogenesis.[49]

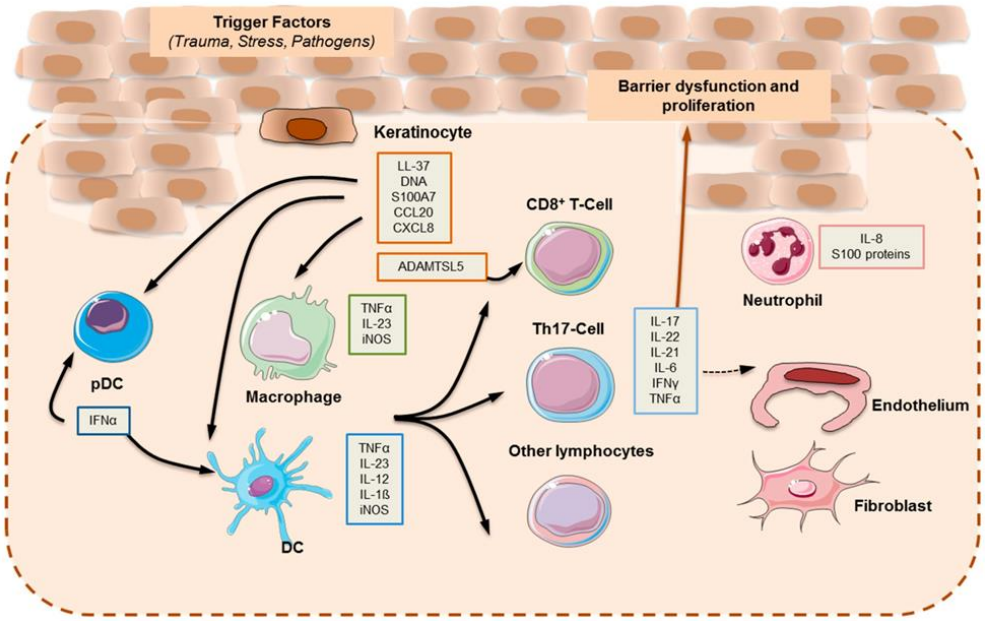

Fig. 1.5 The pathogenesis of psoriasis.[50]

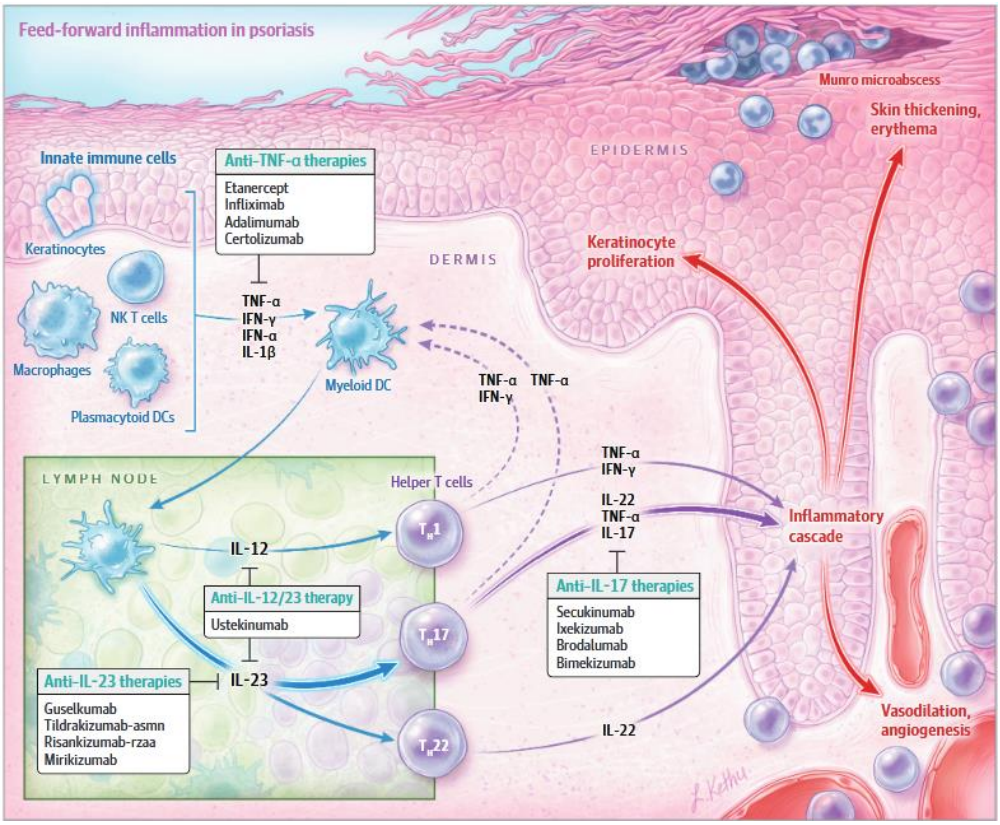

Fig. 1.6 Pathophysiology of Psoriasis [51]

1.6 Types of psoriasis

Clinically, psoriasis can be divided into several subtypes:

Plaque psoriasis (also called psoriasis vulgaris)[52]; guttate (droplet) psoriasis (also known as eruptive psoriasis) with teardrop-shaped scaly spots[53]; inverse psoriasis, found on the folds of the skin, also called intertriginous or flexural psoriasis[54]; pustular psoriasis, There are two forms of pustular psoriasis: palmoplantar pustulosis (palms and soles swollen with pustular psoriasis), and generalized pustular psoriasis (rare and serious); erythrodermic psoriasis, a dangerous complication of psoriasis, which is rare but very serious[55]; Psoriatic arthritis, also known as PsA, is a chronic, inflammatory condition that affects the joints, ligaments, and tendons[56]; Nail psoriasis, A specific or non-specific clinical change in the nail.[57]

1.6.1 Plaque psoriasis

The most common form of psoriasis is chronic plaque psoriasis, which is characterized by red patches of thickened skin (plaques) covered by white or silvery scales; plaques have different sizes, thicknesses, and shapes.[58] Symptoms can appear anywhere on the body, but the knees, elbows, lower back, and scalp are most common. Depending on the severity of the disease, it can involve one plaque or more than 90% of the skin surface.[59] Traumatic incidents may contribute to this predisposition.[60]

1.6.2 Guttate (droplet) or eruptive psoriasis

Small, reddish, and scaly papules on the trunk and extremities are the hallmarks of guttate psoriasis in adolescents and young adults. Symptoms are strongly associated with human leukocyte antigen (HLA)-Cw6 and streptococcal infection or elevated anti-streptolysin O (ASO) levels.[61]

Oftentimes, guttate psoriasis is associated with chronic plaque psoriasis or a flare-up of a preexisting condition.[62] Since guttate psoriasis involutes rapidly and usually remits for longer periods than other types, it is generally considered to have a better prognosis than other types.[63] When the eruption occurs spontaneously, it can progress to chronic plaque psoriasis or recur.[15]

1.6.3 Inverse psoriasis

A well-demarcated, erythematous lession, also known as inverse psoriasis or intertriginous psoriasis, affects the axilla, anogenital, and inframammary folds of the body. Unlike plaque psoriasis, which typically affects extensor surfaces like the knees, elbows, and sacrum, and the scalp.[64] Typically, plaque psoriasis lesions are present elsewhere on the body in addition to inverse psoriasis, but it is possible that intertriginous lesions are the only affected areas.[65] A lack of diagnostic guidelines regarding specific body areas makes estimating the prevalence of inverse psoriasis difficult. A textbook indicates that between 2 and 6% of patients with plaque

psoriasis have inverse psoriasis, while a second report indicates that 44% have perianal involvement.[66]

1.6.4 Pustular psoriasis

As its name implies, pustular psoriasis causes sterile pustules that contain neutrophils, making it a very rare infection. Psoriasis pustular is often life-threatening as opposed to plaque psoriasis.[67,68] In addition to localized lesions, pustular psoriasis can present with generalized widespread skin lesions as well. Pustules appear on the soles and palms of the patient with palmoplantar pustulosis (PPP), and the nail apparatus with acrodermatitis continua of Hallopeau (ACH).[69]

1.6.5 Erythrodermic psoriasis

In 1-2.25% of psoriatic patients, erythrodermic psoriasis (EP) can occur as a severe, rare condition. Patients with poorly controlled psoriasis are usually affected by this condition. In addition to abrupt withdrawal of systemic medications, such as corticosteroids, drug interactions with lithium, and underlying systemic infections may also cause EP. More than 75% of the body's surface area is affected by EP due to generalized erythema and scaling.[70,71]

1.6.6 Psoriatic arthritis

Associated with inflammation throughout the joints and entheses, including those of the axial skeleton, psoriatic arthritis is a chronic, immune-mediated disease.[72] PsA can manifest in different ways in the musculoskeletal system, including arthritis, spondylitis, dactylitis, and enthesitis (inflammation of the tendon, ligament, or joint capsule). Psoriasis (either psoriasis vulgaris or plaque psoriasis) and nail disease are two symptoms of PsA that can manifest on the skin. In addition to the musculoskeletal and skin signs of PsA, patients suffer from fatigue,

limited physical function, sleep disturbances, as well as impaired social participation and work capacities.[73]

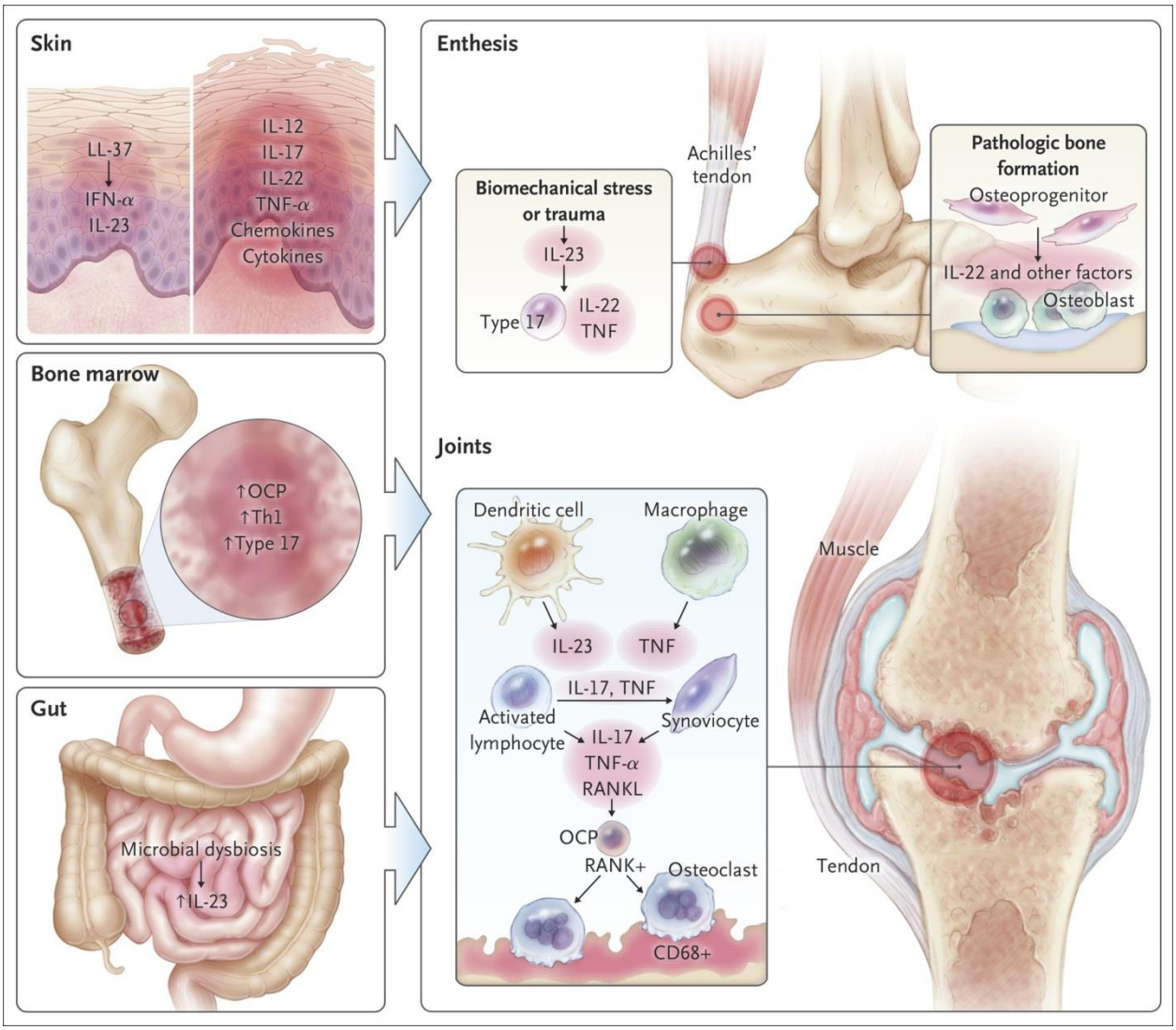

Fig. 1.7 Pathogenic Pathways in Psoriatic Arthritis.[73]

1.7 Psoriasis treatment

1.7.1 Treatments for Mild Psoriasis

There are different definitions of mild psoriasis, but generally, it is declared to involve less than 3% to 5% of the surface of the body that is affected. It is important to evaluate for psoriatic arthritis before treating psoriasis. If there is active psoriatic arthritis, treatment options may

change in favor of options that are effective for both psoriasis and psoriatic arthritis, regardless of the extent of psoriasis.[74] There are a number of treatment options available for patients suffering from mild psoriasis, including the use of topically applied corticosteroids, vitamin D analogs, calcineurin inhibitors, keratolytics, and targeted phototherapy.[75]

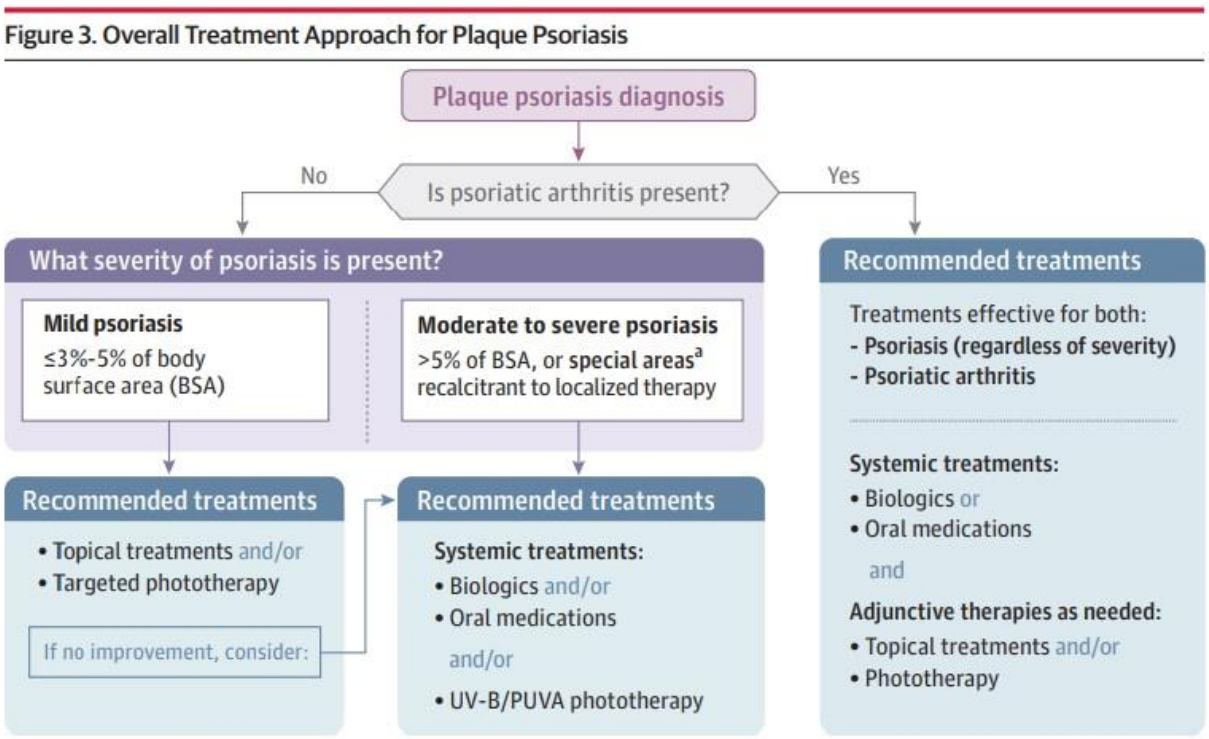

Fig. 1.8 Overall Treatment Approach for Plaque Psoriasis [51]

1.7.1.1 Topical corticosteroids

The use of corticosteroids remains the standard of care for all grades of psoriasis, either as a monotherapy or to complement the use of systemic therapy. Among the preparations are gels, creams, ointments, foams, lotions, oils, and sprays.[76]

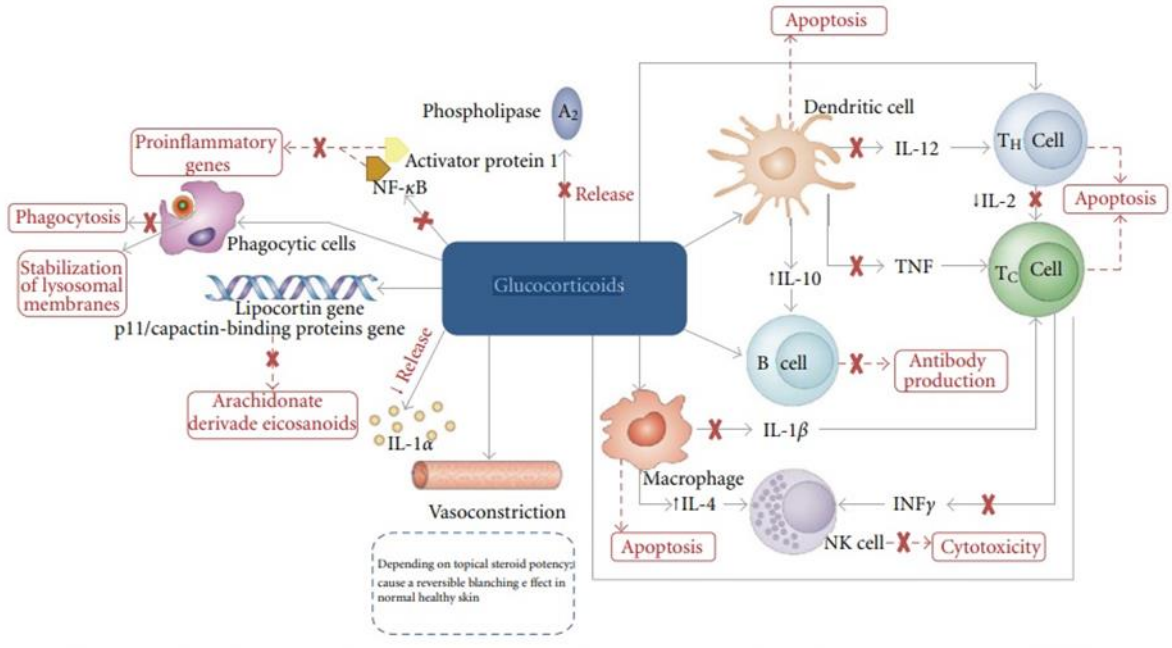

Fig. 1.9 Anti-inflammatory, immunosuppressive, and vasoconstrictive effects of topical corticosteroids[77]

Infants and children should be treated with low-potency corticosteroids primarily on their faces, groins, axillae, and in the groin area. In adults, mid- and higher-potency corticosteroids are used as initial therapy in all areas. There are several indications for the use of superpotent corticosteroids, including stubborn plaques, lesions, and dermatoses on the palms, soles, and/or scalp.[78,79]

There is no restriction on the use of topical corticosteroids in conjunction with topical vitamin D analogues or keratolytic agents. They can be applied as 2 separate medications at various times or as a single medication in a combined formulation. Examples of combination formulations are (1) topical corticosteroids combined with a keratolytic agent like halobetasol propionate and tazarotene, or (2) topical corticosteroids mixed with a topical vitamin D analogue like betamethasone dipropionate and calcipotriene. There is generally a higher efficacy, fewer adverse effects, and longer remission in combination formulations than in monotherapy.[80,81]

Corticosteroids are prescribed according to protocols that consider the potency of the steroids, the age of the patient, severity of the dermatoses, and the preference of the patient.[82]

1.7.1.2 Topical Vitamin D Analogues

Chronic plaque psoriasis can be effectively treated with vitamin D analogs. Treatment of psoriasis of the nails and of the scalp caused by chronic plaque psoriasis can also be provided with them. A synthetic Vitamin D analog, which was prepared by altering the side chain, enhances Vitamin D3's antipsoriatic properties and reduces hypercalcemia.[83] Psoriasis can be treated with calcipotriene, calcitriol, and tacalcitol, which are all analogs of Vitamin D.[84] As their mechanism of action is based on binding to the intracellular Vitamin D receptor, Vitamin D analogs indirectly regulate genes that are involved in epidermal proliferation, inflammation, and keratinization.[85]

By inhibiting keratinocyte proliferation and enhancing differentiation, vitamin D analogues have beneficial effects on the skin.[86] The synergistic, complementary effects of topical vitamin D agents make them the first-line therapy for psoriasis as a monotherapy or in combination with topical steroids.[87]

1.7.1.3 Topical Calcineurin Inhibitors

Tacrolimus, tacrolimus, and a similar medicine called sirolimus all have well-defined molecular mechanisms of action in T cells that entail inhibiting vital signaling pathways that control T cell activation. For instance, calcineurin phosphatase activity is inhibited by tacrolimus and cyclosporin, which prevents the transcription factor NFAT from being activated.[88] Double-blind and open studies have shown that topical tacrolimus and pimecrolimus are effective in treating psoriasis. In psoriatic lesions of the face, genital region, and intertriginous tissue, these agents play a special role since they do not cause cutaneous atrophy.[89]

1.7.1.4 Topical Keratolytics

As a conventional adjuvant therapy for psoriasis, topical preparations containing urea or salicylic acid are recommended as an internationally recognized standard of care for all severity states.[90] There are many benefits associated with urea, including proteolysis, keratolysis, hydrating, hygroscopic properties, penetration enhancement, epidermis-thinning, and anti-pruritic properties. Urea has been widely studied and widely accepted for its moisturizing properties in dry and scaly skin conditions.[91,92]

One of the most commonly used and extensively studied keratolytic compounds is salicylic acid.[91] A combination of it and topical corticosteroids (TCS) will improve the absorption of of the latter into psoriatic plaques.[83]

There are two pathways that lead to corneocyte desquamation by salicylic acid. By dissolving the intercellular cement material, it reduces the intercellular cohesiveness of horny cells. In addition, it reduces the pH level of the stratum corneum, which results in increased hydration and softness of the skin.[93]

Topical retinoids such as tazarotene reduce keratinocyte proliferation, promote keratinocyte differentiation, and reduce inflammation. Tazarotene treatment is recommended for 8-12 weeks for patients with mild to moderate psoriasis. Tazarotene gel 0.1% and tazarotene cream 0.1% and 0.05% were successful in treating plaque psoriasis in multiple randomized control trials (RCTs).[94,95]

1.7.1.5 Targeted Phototherapy

Psoriasis, eczema, and vitiligo are all examples of inflammatory skin conditions that are treated using phototherapy. Ancient Egyptians used natural light combined with herbal extracts to treat skin diseases using this therapy; it is among the oldest treatment modalities in dermatology.[96] The wavelengths delivered by phototherapy are therapeutic for psoriasis, and they minimize

carcinogenic wavelengths. Psoriasis with localized plaques can often be treated with targeted phototherapy, rather than full-body-surround phototherapy.[51]

Targeted phototherapy with the 308-nm excimer laser was previously introduced to treat mild to moderate psoriasis, representing a significant advance in treatment.[97] UVB radiation is delivered to the psoriasis plaque directly, sparing healthy skin from unnecessary treatments, potentially reducing the chance of long-term side effects including carcinogenic effects.[98] Targeted phototherapy is similar in terms of clinical outcome and remission periods to conventional phototherapy.[99]

1.7.2 Treatments for Moderate to Severe Psoriasis

Psoriasis that affects >10% and >20% of the body surface area, respectively, is considered moderate-severe or severe and cannot be treated by topical medications alone.[100] They may be treated with UV light-based therapies, such as UVB phototherapy and photochemotherapy which combines UVA with psoralens, along with conventional systemic drugs.[101,102]

1.7.2.1 Phototherapy

When topical treatment modalities fail or are contraindicated or not feasible, such as in extensive guttate psoriasis, phototherapy is commonly used.[103]

Psoriasis has been treated with artificial light sources since the 1920s. According to Gockerman, in 1925, topical coal tar and subsequent UV-B radiation were the most frequently used treatment regimens for psoriasis.[104,105]

Psoralen plus UVA (PUVA), broadband UVB (BB-UVB), and narrowband UVB (NB-UVB) phototherapy are all mainstays of psoriasis treatment.[106] Broad-band (BB) UV-B radiation with wavelengths between 280 and 320 nm has been used since the 1970s.[107] Psoriasis was first treated with narrow-band (NB) UV-B phototherapy in 1988 using Philips (Eindhoven, Netherlands) TL-01 fluorescent lights, emitting between 311 and 313 nm.[96] One of the most

common types of phototherapy for people with psoriasis is narrowband UVB (NBUVB), which uses light with wavelengths between 311 and 313 nm. It is a successful first-line treatment for generalized plaque psoriasis. By stimulating Langerhans cells in the epidermis with UV light, the immune system is inhibited and antigen can't be presented to the T cells.[108]

Besides downregulation of cytokine expression, other mechanisms include interference with protein and nucleic acid synthesis to inhibit epidermal hyperproliferation.[109]

Psoralen medicine combined with ultraviolet A light (UVA) (320–400 nm) is known as PUVA phototherapy. In 90% of cases, PUVA, initially developed in the 1970s, has been effective at treating psoriasis.[110]

NBUVB has been found to be more effective than BBUVB and safer than PUVA in studies. Numerous studies assessing NBUVB's carcinogenic risk have not found an increased risk of skin cancer.[106,111]

1.7.2.2 Biologics

As biological therapies have advanced in the last two decades, the management of psoriasis and psoriatic arthritis has changed significantly. Since then, many biological treatments for psoriasis and psoriatic arthritis have received approval, and more are being developed. As demonstrated by efficacy and safety data in clinical trials, biological therapies have unique mechanisms of action, benefits, and side effects.[112,113]

For individuals with moderate-to-severe psoriasis, biologic medicines, antibodies, soluble cytokine receptors, and fusion proteins that bind to certain antigens and cytokines and block the immunopathogenesis of psoriasis may provide safer systemic therapeutic alternatives. Unlike methotrexate and cyclosporine, biologic treatments for psoriasis do not cause collateral organ damage.[114]

It is important to note that biologic agents approved for the treatment of psoriasis differ from country to country. However, they can generally be classified into three kinds of biologic agents, including tumor necrosis factor (TNF)-α inhibitors, interleukin (IL)-23 inhibitors, and IL-17 inhibitors.[115]

Chapter II

Gut Microbiome

2.1 Introduction

Microorganisms are not confined to just the planet Earth; they have also found their niche within various organisms, including humans. One of the significant locations where microorganisms exert their influence is in the gut. The gut, also known as the gastrointestinal tract, is home to a vast and diverse community of microorganisms, including bacteria, viruses, and fungi.[116,117] The microbiota includes all living microorganisms, while the microbiome encompasses both these microorganisms and the molecules they produce. It encompasses structural elements, metabolites, and molecules shaped by the host and environmental conditions. It is important to note that mobile genetic elements such as phages, viruses, and extracellular DNA are not considered part of the microbiota based on this definition.[118]

Lederberg et al. suggested how the microbiota might affect health and disease.[119] Research on the microbiome has since expanded, and scientists have developed sophisticated technology to study the microbiome and its role in health and disease.[120]

Even though an adult's gut microbiome tends to be relatively stable over time, many environmental factors can influence it. An aberrant host-microbe relationship can result in disease development if the homeostasis of the microbial community is disrupted. It is important to note that there is great variability in gut microbiota due to many factors, including age, genetics, dietary habits, geographic location, and antibiotic use.[121]

The mucosal surface of the gastrointestinal system is the biggest of all the mucosae where microbiota is found. Thus, the gut is estimated to contain over 500 different species of microorganisms, which are the largest community with the highest diversity.[122] It is well established that the health of the host depends on the diverse gut microbiota, which is closely related to growth, development, the metabolism of substances, and the immune system's functioning.[123] Assisting digestion[124], synthesizing nutrients[123,125,126], maintaining immune

system homeostasis, modulating lipid metabolism, and supporting anti-infection immunity are all important functions of gut microbiota.[126]

Gut microbiota play a significant role in intestinal barrier strength, permeability regulation, and intestinal functional integrity.

In addition, environment, diet, and host immunity system can influence gut microbiota in a reciprocal way.[127] The reciprocal "host-gut microbiota" axis may also have a role in the development of several autoimmune diseases, such as rheumatoid arthritis, spondyloarthritis, and systemic lupus erythematosus by altering the gut immune system.[128] Microorganisms in the gut are tightly related to the innate immune compartment.[129] By understanding the crosstalk between gut microbiota and the innate immune system, numerous unknown causes of diseases could perhaps be clarified.

2.2 Human Microbiota Composition in Different Locations

The human microbiota is the collection of microorganisms that live on and in the human body. The composition of the microbiota can vary depending on the location of the body. Here are some search results that provide information on the microbiota composition in different locations:

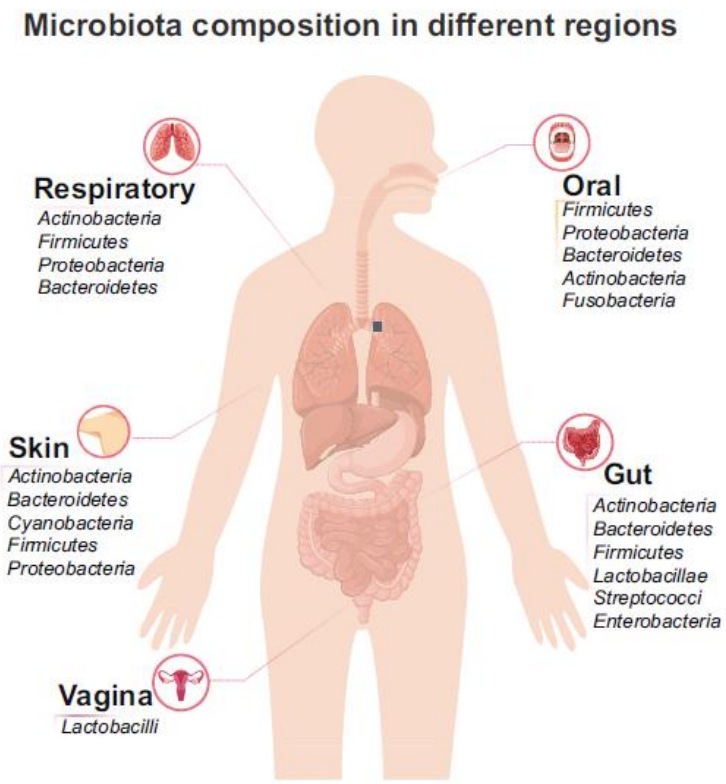

Figure 2.1 Human microbiota composition in different locations. Predominant bacterial genera in the oral cavity, respiratory tract, skin, gut, and vagina are highlighted [130]

2.2.1 Mouth's Microbiota

The oral cavity serves as another significant habitat where the microbiota can establish a presence. The oral microbiota consists of around 50 species, with over 1000 subspecies. Pathogens present in the oral cavity have the ability to stimulate immune responses, including pro-inflammatory reactions. On the other hand, changes in the host's immune system can also influence the composition of the oral microbiota community. For example, immune-inflammatory responses associated with gingivitis, a prevalent human condition, involve the recruitment of neutrophils to the gingival tissues.[131] In the case of periodontal disease, inflammation has emerged as a significant factor that promotes the proliferation of pathogenic microorganisms. The inflammatory process contributes to tissue destruction and leads to tissue

damage which provides a source of nutrients for the growth of microbiomes.[132] Nonetheless, it is important to note that inflammation can subsequently initiate bactericidal actions by the immune system. This presents a paradox in dysbiosis, where the downregulation of the host immune system can result in nutrient deficiency for the microbiomes. However, certain bacteria associated with periodontitis, like P. gingivalis, have evolved mechanisms to elicit the host immune response without triggering bactericidal activity. P. gingivalis has the ability to initiate a C5aR1-TLR2 signal in neutrophils of both humans and mice. This signal separates the TLR2-MyD88 pathway from the TLR2-MyD88-Mal-PI3K pathway, resulting in inflammation and hindered phagocytosis. In summary, the oral microbiota can have a dual nature, potentially providing benefits through the stabilization of microbial diversity, but also causing harm by contributing to the development of pathogenic outcomes.

2.2.2 Lung's Microbiota

The dominant microbial groups in the lungs include Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria.[133] These microorganisms contribute to the establishment of immune tolerance, thereby protecting the host from undesirable inflammatory responses.[134] The interaction between commensal bacteria and immune cells in the lungs mediates this function. Considering the essential role of the lung microbiota in maintaining lung homeostasis, examining the composition of the lung microbiota can be a valuable approach for monitoring lung health conditions.[135] Pattern recognition receptors (PRRs), which are essential for recognizing microbial molecules, play a significant role in the interactions between the lung microbiota and local immunity cells. The aforementioned TLRs are classified as PRRs. Activation of PRRs can stimulate ligand engagement and lead to the expression of immune-related genes, promoting an immune response against pathogens.[136]

Moreover, the lung microbiota was discovered to have a role in regulating antigen presenting cells and regulatory T cells. In studies involving mice, it was observed that newborn mice displayed excessive airway eosinophilia, release of Th2 cytokines, and increased responsiveness to allergens. As the bacterial load increased during the subsequent two weeks, there was a shift in the composition of the microbiota (from Gammaproteobacteria and Firmicutes to Bacteroidetes), which led to a decrease in allergen responsiveness. As a result of changes in the lung commensal bacteria community, Helios-regulatory T cells appear.[137]

2.2.3 Vagina's Microbiota

The vaginal microbiota plays a crucial role in maintaining a woman's reproductive and gynecological health. It is primarily dominated by Lactobacillus species, which help maintain a healthy environment in the vagina by producing lactic acid and other antimicrobial substances.[138] The balance of the vaginal microbiota can be influenced by various factors, including hormonal changes, infections, diet, lifestyle, and hygiene practices.[139]

The innate immune response is influenced by the composition of the vaginal microbiota. In particular, the vaginal microbiota stimulates pattern recognition receptors (PRRs) found on the epithelial cells that line the vagina and upper genital tract, initiating cytokine signaling pathways.[140] Immune cells such as Natural killer (NK) cells, macrophages, CD4 + helper T-cells, CD8 + cytotoxic T-lymphocytes, and B-lymphocytes are recruited or activated through the release of cytokines like interleukin (IL)-1β/6/8 and Tumour Necrosis Factor alpha (TNF-α).[141] Bacterial vaginosis (BV) is characterized by the displacement of Lactobacillus spp. and an elevation in BVAB, resulting in a vaginal dysbiosis. Notably, Pathogenic microbiomes such as G. vaginalis and P. bivia, commonly associated with BV, have been shown inhibit the host's inflammatory response in the vaginal epithelium.[142]

2.2.4 Skin's Microbiota

The human skin harbors a dense and diverse assemblage of microbiomes. Recent findings have revealed that the skin microbiota consists of various prokaryotes (bacteria and archaea) as well as eukaryotes (fungi and metazoic parasites). Just like the gut microbiota, the skin microbiota also contributes to the development of the innate immune system. For instance, S. epidermidis generates lipoteichoic acids that help protect the skin from inflammation caused by injuries. This is achieved by inhibiting cytokine release and modulating immune responses through the TLR2 pathway.[143] Interestingly S. epidermidis can actually promote the expression of specific antimicrobial peptides, such as human β-defensins (hBDs), which play a role in bolstering the skin's defense mechanisms.[144] Furthermore, it is believed that S. epidermidis can enhance the function of skin lymphocytes, thereby playing a role in enhancing skin immunity.[145] In summary, the skin, being a crucial component of the human immune system, contains a wide range of cells involved in immune responses, including macrophages, dendritic cells, lymphocytes, and various subsets of T cells.

2.2.5 Gut Microbiota

The human intestine is home to a diverse and complex community of microorganisms, collectively known as the gut microbiota. The main microbes and bacteria in the intestine's microbiota include members of the phyla Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes.[146] Some of the specific genera found in the gut microbiota include Bifidobacterium, Escherichia, Streptococcus, and Lactobacillus.[147,148]

The gut microbiota plays a crucial role in the immunological response, as enteric microorganisms can promote the transport of macromolecules and antigens across the gut epithelium.[149] Flagellin, the primary component of bacterial flagellum, plays a key role in the interplay between gut epithelial integrity and host immunity. TLR5 recognizes flagellin and is

prominently expressed in B-cells and CD4 + T-cells. B-cells that have undergone differentiation produce IgA, which helps neutralize pathogens and prevent potential subsequent infections.[150]

The immune system development is influenced by the gut microbiota through the presence of gut-associated lymphoid tissues, including Peyer's patches (PPs), plasma cells, and lymphocytes. Research conducted in the past has demonstrated the interaction between gut bacteria and mucosal antibodies, which are absorbed by CD11 + dendritic cells located in the PPs. Research findings have also demonstrated an increase in the presence of luminal microbiota bound to SIgA in Peyer's patches (PPs). In the intraepithelial compartment of the intestine, CD8 + T cells are predominantly found, and the microbiota plays a significant role in preserving the function of these CD8 + T cells.[151]

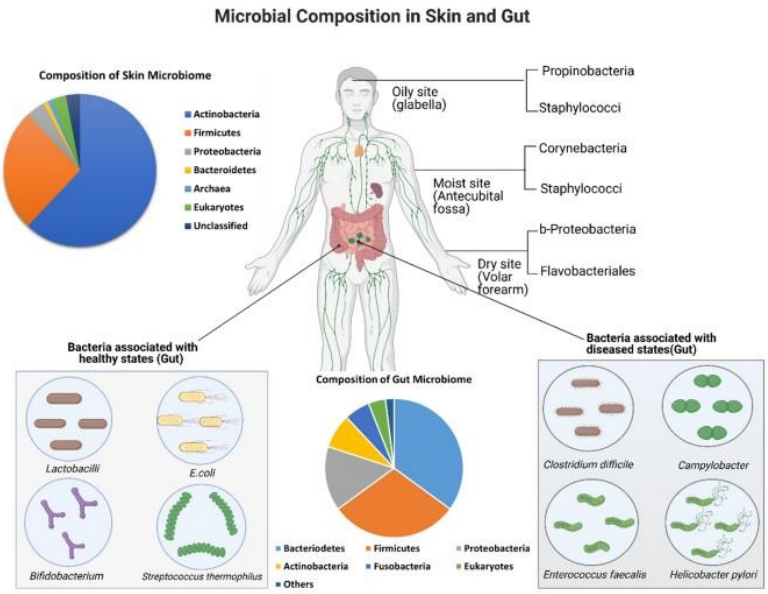

Fig2.2 Microbial composition of gut and skin.

Table 1. Microbial species and metabolites from the gut that have been associated with skin effects.

A. Microbial species

Organism	Effects on skin	Mechanism	References
Faecalibacterium prausnitzii, Akkermansia muciniphila and *Ruminoccocus*	Protection against psoriasis	Prevention of colonization of pathogenic flora on skin by competitive inhibition and the SCFAs production	158,159,169,213
Helicobacter pylori	Rosacea-related signs and symptoms	Production of cytotoxin and by proliferating the production of reactive oxygen species-nitric oxide [NO], which causes gut mucosal inflammation and changes physiological processes in the skin including vasodilation, inflammation and immunomodulation.	194
Faecalibacterium prausnitzii	Chronic atopic dermatitis progression resulting in gut epithelial barrier impairment	Dysregulation of gut epithelial inflammation	180
Lactobacillus casei	Decrease skin inflammation	Alteration of the number of cytotoxic CD8 + T cells	171
Lactobacillus paracasei	Reduce the size of acne lesions as well as inflammation	Inhibition of mast cell degranulation, TNF-α release, edema and vasodilation, and thereby speeding up the restoration of barrier function	145,171 136
Bifidobacterium animalis subsp. *lactis* [LKM512]	Reduce the scratching behavior in atopic dermatitis	Increase of levels of the kynurenic acid metabolite	223
Bacteroides thetaiotaomicron	Alleviate the allergic symptoms of atopic dermatitis as well as Crohn's disease like other chronic inflammatory diseases	Anti-inflammatory action	228
Larger number of *Clostridium difficile* and *Escherichia coli*	Onset of atopic dermatitis symptoms in childhood	Immune dysregulation as a result of decreased Treg cell inducing beneficial bacteria	16,224
Decrease in Firmicutes and increase in Bacteroides	Development of acne vulgaris	Dysbiosis by altering the serological cytokine levels promoting inflammation	15,188

B. Metabolites

Metabolites	Effects on skin	Mechanism	References
SCFAs	Increase the epithelial barrier function and skin-inflammation	Development of Tregs within the colon, DCs precursors, and IL-10 production	120,229 13,106
GABA	Itch restriction	Inhibition of neurons which are responsible for itch-signaling in the spinal cord	230,223
Tryptophan	Regulate skin inflammation	Activation of AhR and inhibition of TSLP production in keratinocytes	231
Dopamine	Inhibition of hair growth	Through the stimulation of catagen induction	98
Serotonin	Involved in skin pigmentation	Modulation of melatonin	16,223
Acetylcholine	Barrier function	Not reported	16
Phenol & p-cresol	Impaired epidermal barrier function	Skin hydration reduction and disruption of keratinization	171,232
Propionic acid	Promote skin homeostasis by reducing inflammation	Antimicrobial effects	2
Sodium butyrate	Treat psoriasis and other hyperproliferative skin diseases	Modulation of several key cellular processes including differentiation, proliferation, and apoptosis.	137
Galactoligosaccharides and fructooligosaccharides	Reduction of infant eczema and allergy	Through the stimulation of Tregs	13,107
Polysaccharide A and retinoic acid	Suppress inflammation	Induction of accumulation of Tregs	153
Saturated fats and higher amount of glycemic load	Development of acne	Impairment in nutrient signaling. SREBP-1 overexpression and increased sebum synthesis of fatty acids (e.g., free oleic acid) and triglycerides which promotes flourishing. *P. acnes* growth	107
High-peptides and unsaturated omega-3 fatty acids	Act against hypersensitivity (allergies) and asthma	Through the development of Tregs	13
High-fat and alcohol	Promote skin inflammation and oxidative stress. Impairment of colonic epithelial integrity and barrier function.	Increase of pro-inflammatory cytokines secretion	122,123

2.3 Disruption in Microbiome

Skin function and integrity are negatively affected by intestinal dysbiosis, a state of imbalanced gut microbiome. It has been shown that the metabolic products of aromatic amino acids, such as phenol and p-cresol, can become absorbed into the bloodstream, causing disruption of both the skin barrier integrity and epidermal differentiation. A disturbed gut microbiota with adverse outcomes is characterized by the presence of these metabolites produced by certain pathogenic bacteria, such as Clostridium difficile. Serum levels of p-cresol are strongly correlated with impaired keratinization and reduced hydration of the skin.[152,153] The increase in epithelial permeability caused by intestinal dysbiosis activates effector T cells, disrupting the balance between these cells and immunosuppressive regulatory T cells. The release of proinflammatory cytokines further increases epithelial permeability, resulting in chronic systemic inflammation.[154,155] Different types of inflammatory skin disorders, such as psoriasis, are associated with skin dysbiosis.[156] In addition, environmental incursions, impaired host-microbiome interfaces, and altered immune responses can disturb the gut microbiome, resulting in the dissemination of commensal microorganisms systemically, susceptibility to pathogenic invasion, and abnormal immune responses. A variety of 'noncommunicable' gastrointestinal diseases, including inflammatory bowel disease (IBD) [157]and celiac diseases[158], are linked to microbiome-immune interactions besides regulation of infection and commensal spread.

It is unclear whether skin dysbiosis is the cause or result of these disorders, but it has been suggested that pathology may be influenced by locally amplified immune responses to specific skin microbes or increased microbial load in the presence of a compromised skin barrier and genetic predisposition.[159]

In a mouse model of atopic dermatitis, for instance, skin colonization with *Staphylococcus aureus* enhances skin allergy through δ-Toxin-induced mast cell activation.[160]

In addition, mice lacking JunB expression in skin epithelial cells are characterized by increased Th2 and Th17 type immune responses, accompanied by an increased colonization of *S aureus*. JunB expression in epithelial cells plays a key role in immune-microbiota interactions.[161]

2.3.1 Role of microbiome in diseases

Recent studies have indicated that the gut microbiome plays an important role in many autoimmune and inflammatory diseases. Inflammatory diseases arise as a result of an aberrant immune response due to intestine functional integrity, barrier strength, and permeability control affected by gut microbiota. It is important to note that the gut microbiota's composition can vary between individuals due to factors such as genetics, diet, and environmental exposure. Additionally, the abundance and diversity of microbes in the colon are closely related to host health, with imbalances in the gut microbiota being associated with various diseases and disorders.[148]

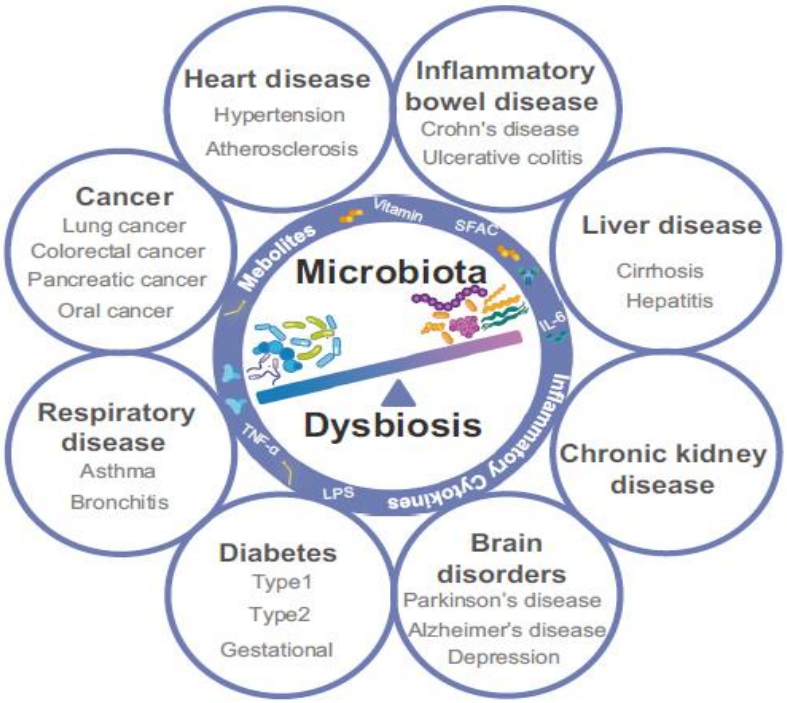

Fig 2.3 Human microbiota dysbiosis contributes to various diseases[130]

Chapter III

The link between gut microbiota dysbiosis, inflammation, and psoriasis

3.1 Introduction

Skin and gut both are host a wide range of microbiomes and need to function correctly for organisms to achieve homeostasis and ensure their survival.[162,163] The skin, being the largest organ, acts as a protective barrier against injuries and microbial attacks. In contrast, the gut consists of trillions of microbial communities and the gut microbiome has both positive and negative effects on the normal physiology and homeostasis of both gut and skin tissues.[154]

The microbiome plays a crucial role in maintaining the health of the human body, particularly in the immune system. When there is a change in the variety of gut microbes, known as dysbiosis, it can enhance the vulnerability of the host and disrupt the normal immune response in the gut. This can lead to subsequent effects on the health of the skin.[164] Intestinal dysbiosis is associated with various dermatologic conditions, including psoriasis, atopic dermatitis, and rosacea.[165] Numerous studies have established a connection between gastrointestinal health and homeostasis and allostasis of the skin, indicating a reciprocal relationship between the gut and the skin. The members of the gut microbiome can affect skin conditions through their metabolic activity and influence on the immune system.[166]

Several environmental factors, such as diet, exposure to chemicals, and antibiotic use, can influence the gut microbiome and contribute to disease development.[167]

In psoriasis, a common autoimmune skin disease, the gut microbiome has been shown to have a distinct profile compared to healthy individuals. Research has found that patients with psoriasis have a significantly lower metagenomic species richness in their gastrointestinal microbiota compared to healthy controls. The composition of the gut microbiome can dramatically affect immune development and susceptibility to diseases, especially autoimmune disorders such as psoriasis.[168]

The gut microbiome can also influence the expression of genes related to inflammation and immune response, which may contribute to the development of diseases. For example, micro-ribonucleic acids (miRNAs) are small endogenous non-coding RNAs that have been confirmed to be involved in an interplay with microbiota to regulate host gene expression. This interplay between the gut microbiome and miRNAs can influence host gene expression in various human disorders, including psoriasis.[169]

In conclusion, the microbiome plays a vital role in maintaining the health of the human body, particularly in the immune system. Dysbiosis of the microbiome can contribute to the development of autoimmune and inflammatory diseases like psoriasis by affecting gene expression and increasing inflammation in the body. Understanding the complex interactions between the microbiome, immune system, and environmental factors can help develop therapeutic strategies to prevent and treat these diseases.

3.2 Allostasis and homeostasis of the skin: Role of the gut microbiome

By influencing signaling pathways that coordinate epidermal differentiation, the gut microbiome affects skin homeostasis. The processes through which intestinal microbiota exert their influence on skin homeostasis appear to be connected to their modulatory effect on systemic immunity, though they are not yet fully understood.[154] In the gut, certain microbes (Bacteroides fragilis, Faecalibacterium prausnitzii, and bacteria that belong to Clostridium cluster IV and XI) and their metabolites (retinoic acid and polysaccharide A) facilitate anti-inflammatory responses by aggregating regulatory T cells.[170] Immune cells are also activated and apoptotic by SCFAs, another class of metabolites. In particular, butyrate suppresses histone deacetylase activity, which promotes the growth of regulatory cells engaged in a variety of physiological processes in the skin, such as controlling the differentiation of hair follicle stem cells and wound healing.[171] Additionally, there is emerging evidence that the diffusion of gut microbiota and their metabolites from the gut to other tissues, including the skin, may affect skin physiology, pathology, and the immune response more directly.[172] As an example, intestinal bacteria DNA has been isolated successfully from the plasma of patients suffering from psoriasis. Additionally, intestinal bacteria and their metabolites can access the bloodstream when the intestinal barrier is disrupted, impairing skin homeostasis.[154] The gut microbiome and skin homeostasis appear to be directly linked, a finding that is only just beginning to be explored. Through its role in both the innate and adaptive immune system, the intestinal microbiota also contributes to skin allostasis.[173–175] When the skin barrier function is disrupted, intestinal bacteria can enhance the response. In response to various immune stimuli, commensal gut bacteria are capable of stimulating skin allostasis through their influence on T cell differentiation. As both skin and intestine are in direct contact with the environment, Th17 cells are also targets of the GI tract microbiome.[176] Psoriasis, Behcet's disease, and contact

hypersensitivity are all chronic inflammatory dermatoses associated with these cells and their proinflammatory cytokines.[177] There is a strong correlation between the gut microbiome and the balance between Th17 effector cells and regulatory T cells.[178] Th17 cells can be eliminated from the intestinal lumen or can acquire an immunosuppressive regulatory phenotype (rTh17), limiting pathogenicity.[179]

3.3 The Role of the Gut Microbiota in Maintaining a Healthy Gut Ecosystem

In addition to digesting food, gut microbes and their metabolites maintain the homeostasis of the immune system and have a significant impact on the health of the host. As well as digesting complex polysaccharides, the gut flora plays a vital role in producing some of some essential nutrients.[125,180,181] Certain nutritional components, such as vitamin K, are produced by gut microbiota by breaking down indigestible complex polysaccharides. As a result, it has a significant effect on the host's immune system. The GI tract's microorganisms promote immunological tolerance to environmental and dietary antigens and protect against pathogens. It does this directly, by binding to epithelial cells and indirectly, by stimulating immune responses.[155,182] The gut microbiota is essential for maintaining the integrity of the epithelial barrier and developing a mucosal immune system to defend against the invasion of exogenous pathogens. In addition, bacteria produce metabolites and components that balance host defense and tolerance to dietary and environmental antigens. It's important to note that gut microbiota, its metabolites, and intestinal epithelial cells are all involved in maintaining a healthy gut ecosystem. Gut microbiota is non-self entity, and immune cells within the intestinal mucosa would eliminate them if they recognized it. The intestinal epithelium acts as a barrier to isolate the intestinal mucosa's immune cells and the intestinal lumen's microbiota, but it also permits microbial metabolism to enter host cells, interact with them, and so regulate immunological responses. Bacterial components and metabolites play a major role in microbiota-host

interactions. Through interactions with Toll-like receptors and pattern recognition receptors on the surface of innate immune cells, the gut microbiota influences innate immune responses.[183,184] Additionally, gut microbes contribute to the adaptive immune response by triggering the release of immunoglobulin A (IgA), as well as by influencing the operation of effector T cells (Th1, Th2, and Th17), regulatory T cells, and Tfh cell.[35,185–187] Metabolites produced by the microbiota in the intestine affect multiple organs throughout the body and balance the immune system's activation and suppression. For example, in order to maintain the balance between host defense and microbiota homeostasis, tryptophan microbial metabolites play a significant role. A product of tryptophan catabolism by gut microbiota, Indole-3-aldehyde (IAld), modulates mucosal reactivity through IL-22 and protects against colonization by Candida albicans. Tryptophan microbial metabolites also influence astrocyte activity and inflammation in the central nervous system. Additionally, a tryptophan metabolite from the skin's microbiota known as IAld lowers inflammation in atopic dermatitis sufferers by binding to the aryl hydrocarbon receptor.[188,189] Patients with psoriasis also exhibit an upregulated tryptophan metabolism pathway, although the role of microbes in the pathway has yet to be explored.[190] Commensal Clostridia, Faecalibacterium prausnitzii, and Bacteroides fragilis produce metabolites, including polysaccharide A and retinoic acid, that trigger the formation of regulatory T (Treg) cells, which suppress inflammation.[170]

3.4 Microbiota in immune systems development and inflammation

There is a complex symbolic relationship between the human immune system and the microbiota.[127] Initially, microbiota is introduced to the child through vertical transmission from the mother's microbiota. Due to this, infants born via cesarean section receive bacteria of epidermal origin that could increase the risk of allergies and asthma in comparison to infants

receiving microbes from their mothers' vaginal flora.[191] Gradually and during growth, such a difference in the immune system and microbiota eliminates. It is important to note that breastfeeding plays a crucial role in the establishment of an infant's immune system and microbiota. As well as providing nutrition and antimicrobial proteins, breast milk contains slgA, which is shaped by the microbiota of the mother.

The mammalian immune system plays a vital role in host defense against potentially harmful external factors and endogenous disturbances of homeostasis.[192] It is important to maintain immune tolerance against innocuous stimuli and prevent overexploitation of host resources.[193,194]

Microbiota interact extensively with human immune system responses, both adaptive and innate. As well as regulating the adaptive response to the microbiota, the innate immune response keeps a homeostatic environment by eliminating pathogenic bacteria. Toll-like receptor 5 (TLR5), autophagy, and inflammasomes are involved in mediating these effects. SlgA has the ability to reduce the inflammatory response that results from an abundance of bacteria in the organs. The sIgA response can however be altered by dysbiosis of microbiota, resulting in uncontrolled bacterial growth. In addition, microbiota dysbiosis can lead to altered sIgA response and irregular bacterial growth.[195] Induction of sIgA as a gradual response to current bacterial exposure suggests crosstalk between the microbiota and the immune system. Maintaining a healthy microbiota and immune balance also requires the adaptive immune response. Specifically, the process of educating the adaptive immune response involves the maturation and differentiation of B and T cells, as well as the development of immune tolerance towards the microbiota. CD4 T cell responses differ greatly based on bacteria species. Consequently, distinct subsets are formed and pro-inflammatory cytokines are released such as interferon-γ and interleukin IL-17A.[196] Neutrophil migration is one way gut microbiota affects

the immune system, resulting in various types of T cells, such as helper T cells (Th1, Th2, and Th17) and regulatory T cells. As the immune system matures, disorders in microbiota development can worsen immunological tolerance and cause autoimmune diseases.[197] Aside from that, microbiota may produce heterogeneous molecules that can stimulate an immune response and cause inflammation or chronic tissue damage.[198] A diagram of the general interactions between the microbiota and the response of immune system during healthy and diseased states is shown in Fig 3.2. Germ-free (GF) animal models have been used extensively to study the mechanistic relationship between commensal microbiota and host immunity. It has been demonstrated that the absence of commensal microbes is associated with profound defects in lymphoid tissue architecture and immune function in GF animals.[199]

GF mice exhibit a significant decrease in αβ and γδ intra-epithelial lymphocytes (IELs) compared to conventionally colonized animals, but their levels can be significantly increased upon new colonization. The basis of protective humoral mucosal immunity, IgA antibodies significantly decrease in infants and GF animals but are quickly recovered by microbial colonization.[200] Some components of dietary fibre are not digestible by humans due to the lack of enzymes needed to break them down.[201] The production of short-chain fatty acids (SCFAs) is possible with certain species of microbes because they produce specific enzymes that convert indigestible carbohydrates into absorbable forms. Inflammatory and immunomodulatory effects may be attributed to these SCFAs.[202]

components of the bacteria itself, such as lipopolysaccharides, cell capsule carbohydrates, and other endotoxins, may also be released and cause secondary effects to the host in addition to the enzymes and other metabolites generated. There are several effects of these compounds, including maintenance of gut epithelial epithelium (and therefore integrity of the gut wall), production of vitamins, and activation and inhibition of specific immune system responses.[203]

Furthermore, gut microorganisms carry out drug metabolism and affect aspects of pharmacokinetics.[204] By maintaining the mucosa and competing against pathogenic species, they serve as a natural defense against pathogens. Microorganisms inhabiting the gut can cause or prevent inflammation through their contact with the immune system. They could activate immune system regulatory cells to limit inflammation through anti-inflammatory mechanisms.[205]

On other side, certain bacteria can promote a "leaky gut" when they regulate intestine permeability, allowing metabolic products associated with these microbes to leave the gut and enter the bloodstream. Cytokines and other mediators are produced in response, thereby triggering an inflammatory response in the body.[206]

In a similar manner, intestinal epithelial cells deliver bacterial metabolites to immune cells, The gut epithelium also delivers bacterial metabolites to immune cells, causing local and systemic inflammation. Chronic or subacute inflammation may result from the persistence of this condition, which may result in inflammatory bowel disease or cardiovascular disease.[205]

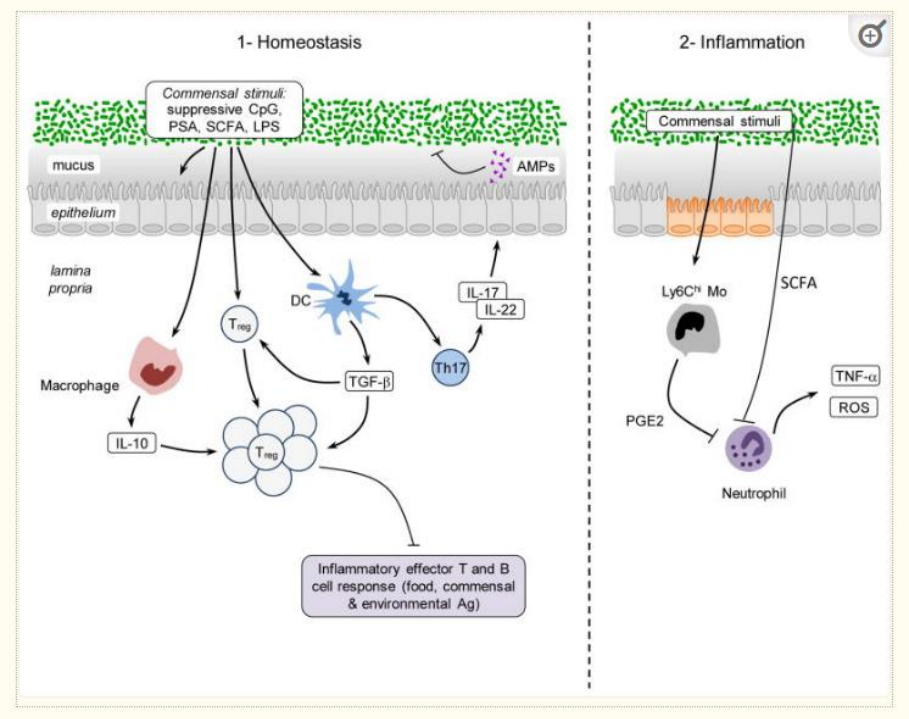

Figure 3.1 Promotion of immune regulation by the microbiota during steady state and inflammation.[207]

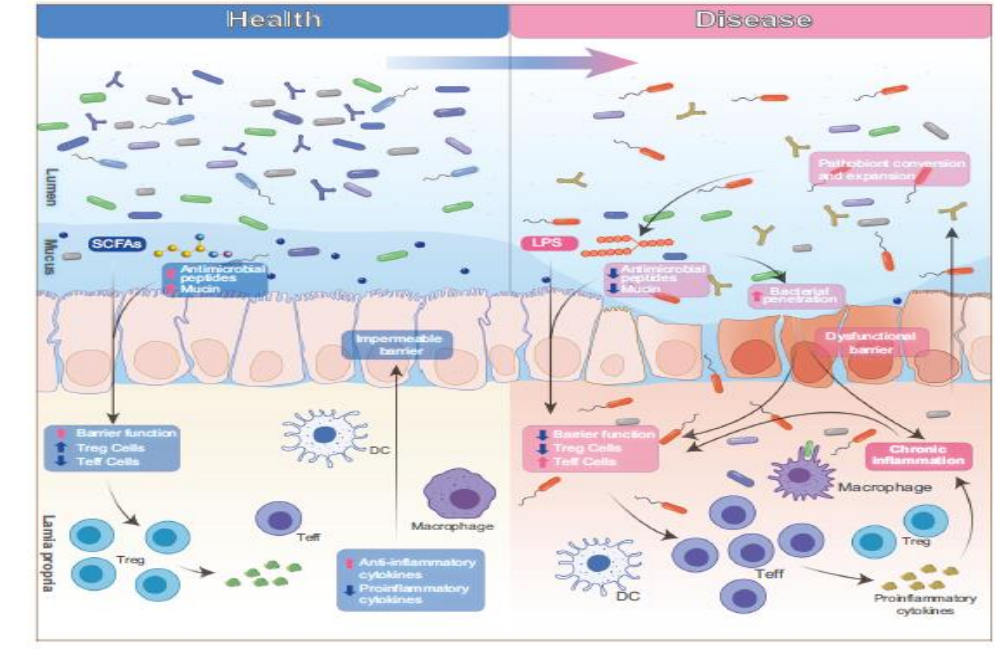

Fig 3.2 Factors affecting microbiota-associated chronic inflammation in healthy and disease state.[130]

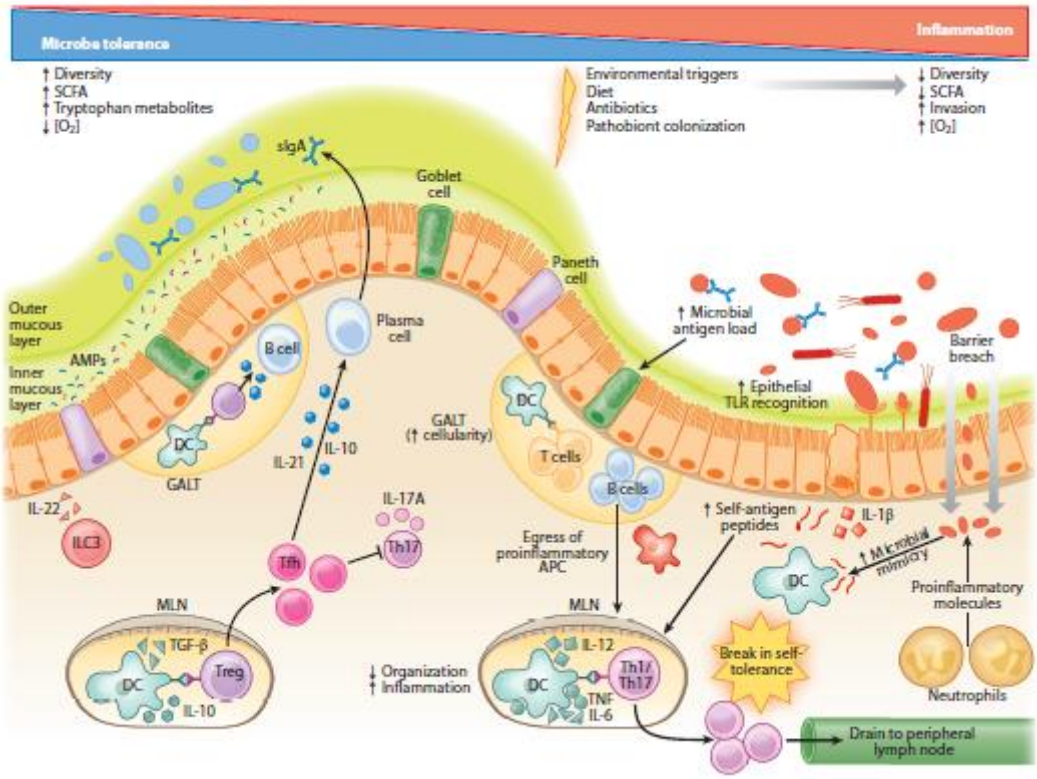

Fig. 3.3 Consequence of intestinal inflammation of systemic immunity.[208]

3.5 Microbiota-mediated manipulation of T cell function

The development of autoimmune and inflammatory diseases is significantly influenced by activation of self-reactive memory T cells. The intestinal microbiota and CD4+ T cells interact during inflammation and homeostasis in order to orchestrate adaptive and innate immune responses.[209]

Interactions between intestinal tracts and extraintestinal tissues are crucial during health and disease. The majority of activated CD4+ T cells reside in tissue environments colonized by microorganisms, and the best-studied examples are from the gastrointestinal tract. The active immune response of CD4+ T cells against intestinal microbiota was traditionally linked to pathogenesis and inflammatory bowel disease (IBD).[210]

Additionally, gut-resident CD4+ T cells have T cell receptors (TCRs) that are responsive to microbial antigens under homeostasis and are required for microbiota-specific IgA responses, which support colonization and gut homeostasis while preventing systemic inflammation.[211] Thus, the gut immune system actively responds to all microorganisms it encounters and does not ignore commensal microbiota antigens to distinguish pathogens from commensals. It is possible through epigenetics to preprogramme tolerance mechanisms to these antigen encounters.[212] As well, cross-reactivity between T cells, which can lead to recognition of self-peptides, may be essential to maintaining a sufficient number of T cells capable of responding to any presentable foreign peptide.[213,214]

According to one study, a single T cell clone might react to up to one million distinct peptides at various avidities.[215] Microbiota, through self-peptides mimicry, may predispose the host to autoimmunity; however, CD4+ T cells are able to recognize microbiota and self in many cases and may not cause disease if properly regulated. This regulation is influenced by the microbiota. They contribute to CD4+ T cells' activation, polarization, and function. By inducing defined subsets of CD4+ T cells, individual commensal species can modulate the CD4+ T cell compartment.[216] There are four major categories of CD4+ T cells polarized by microbiota-derived signals: T-bet+ Th1, GATA3+ Th2, RORγt+ Th17, and FOXP3+ Tregs, as summarized below and in Figure 3.4.

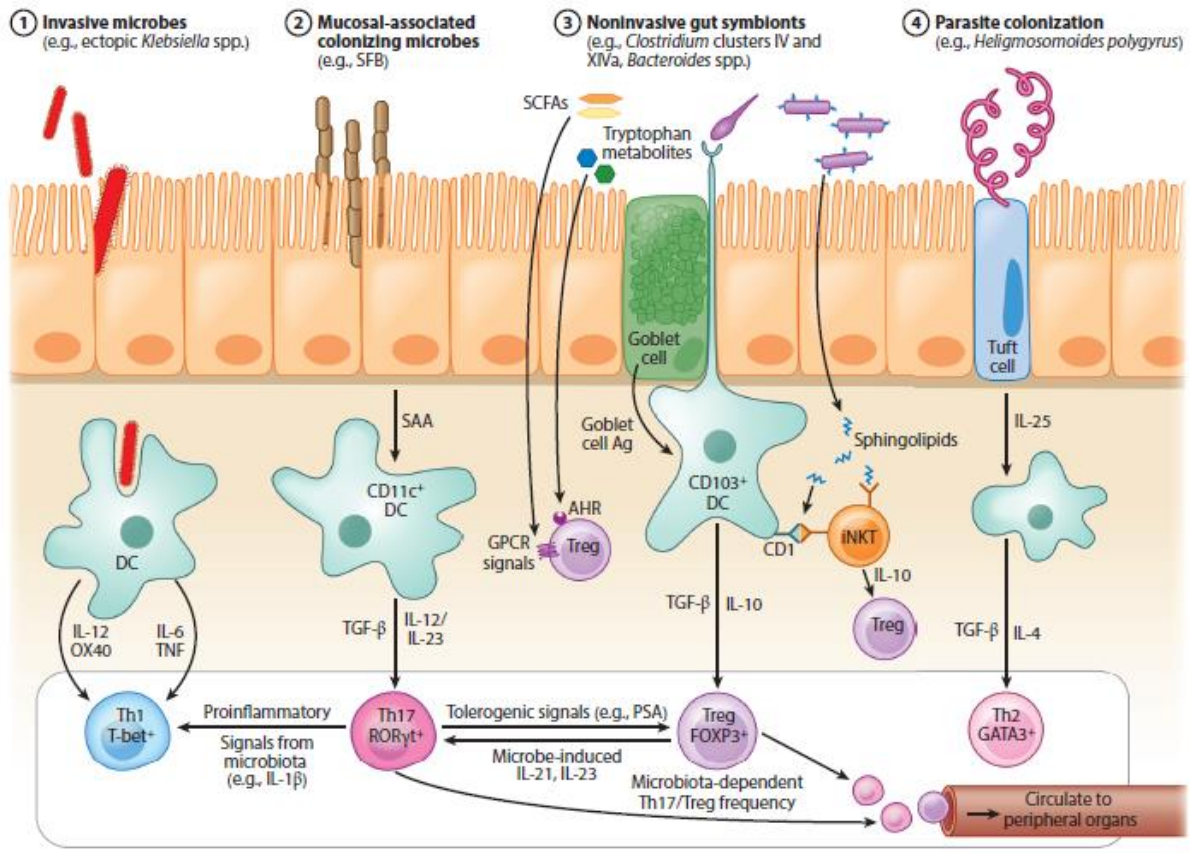

Fig 3.4 Direct and indirect microbiota–CD4+ T cell interactions.[208]

3.6 Gut-skin communication through immuno-cross-linking

The interaction between the gut and the skin involves the engagement of immunological components that are present between these two organs. The immune system plays a essential role in controlling the host's interaction with the microbiota, resulting in a substantial volume of immune cells within regions colonized by commensal, including the skin and the GI tract. Preserving the host's homeostatic balance requires limiting the interaction between microorganisms and the gut epithelial membrane to reduce inflammatory responses and microbial translocation.[166] The 'mucosal firewall' is a shield formed by the gut epithelial cell barrier, mucus layer, T cells, IgA, and dendritic cells (DCs). (Figure 3.5). The mucosal firewall acts as a protective barrier, preventing the migration of commensal bacteria to lymphoid tissues and thereby averting inflammation in the gut and skin.[217]

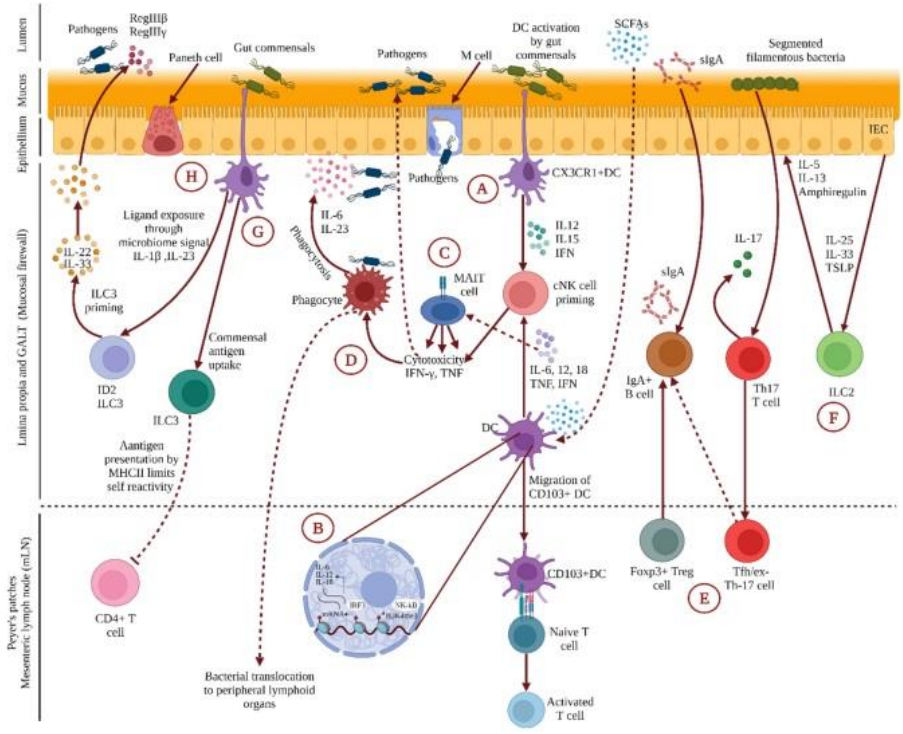

Figure 3.5 Gut-Skin communication through immuno-cross-linking.[166]

These specific lymphoid tissues are recognized as gut-associated lymphoid tissues (GALTs). GALTs, which are mucosa-associated lymphoid tissues (MALTs), act as a barrier between the host and the surrounding environment.[218]

They consist of various cell types, including microfold cells (M cells), conventional lymphocytes (such as regulatory T cells, helper T cells, cytotoxic T lymphocytes, and IgA-producing B cells), professional phagocytes (such as dendritic cells, mast cells, neutrophils, and macrophages), and unconventional lymphocytes like innate lymphoid cells (ILCs) and mucosal-associated invariant T (MAIT) cells.[219] The development of GALTs is closely associated with the gut microbiota, as indicated by recent studies. The main histological constituents of GALTs include Peyer's patches, crypt cells located in the intestinal epithelium, isolated lymphoid follicles (ILFs) within the intestine, the appendix, and mesenteric lymph nodes (mLNs).[220,221] The formation of secondary lymphoid organs in the gut is influenced by the interplay between LTi cells, which are hematopoietic cells, and the colonization of gut microbiota.[218] Conventional lymphocytes and professional phagocytes play a role in preserving homeostasis by producing antimicrobial peptides (AMPs). Gut epithelial cells, paneth cells, and immunological cells in the digestive tract produce compounds known as AMPs.[222] Localized immune cell types, including macrophages, T cells, B cells, and mast cells (MC), secrete antimicrobial peptides (AMPs) such as α- and β-defensins. Additionally, mast cells (MC) are capable of producing the AMP cathelicidin, thereby playing a role in maintaining the balance between the microbiome and tissue in the dermis. The binding of pathogens or their components to Toll-like receptors (TLRs), (NOD)-like receptors (NLRs), and (RIG-I)-like receptors (RLRs) can directly activate complement receptors in mast cells (MCs). This activation leading to release of inflammatory mediators that contribute to antimicrobial immune responses. TLR4, through the expression of costimulatory molecules and the secretion of inflammatory cytokines,

plays a role in initiating innate immune responses.[223] Peyer's patch activation through Toll-like receptor (TLR) pathways can result in the production of various antimicrobial peptides (AMPs), including REGIIIβ and REGIIIγ. Conversely, the inhibition of TLR pathway can lead to enteric bacterial infection.[224] Dendritic cells (DCs), functioning as antigen-presenting cells, have a crucial role in generating tight junction proteins and extending dendrites through the junctions into the lumen.[225] Binding to C-X3-C Motif Chemokine Receptor 1 (CX3CR1), DCs initiate the process of trans-epithelial dendrite formation, facilitating the delivery of antigens for sampling. Furthermore, DCs exhibit the capability to form trans-epithelial dendrites and phagocytose invading enteric pathogens.[226] In various tissues, including the intestine, lungs, skin, liver, adipose tissue, and mesenteric lymph nodes, ILCs play vital roles in immunity, homeostasis, and the modulation of inflammatory responses.[227] The frequency of ILC1, one of the subsets of helper ILCs, is comparably low in the fetal intestine where the gut microbiome is not yet established. This suggests that the development of ILC1 is influenced by the presence of commensal bacteria.[226] Notably, both Th1 cells and ILC1s play a crucial role in combating viruses, bacteria, or protozoa in the body through the production of IFN-γ. The development of allergies and the elimination of helminths are facilitated by Th2 cells and ILC2 cells, which produce IL-5 and IL-13, respectively. Additionally, ILC3s and Th17 cells contribute to autoimmunity by secreting IL-17 and IL-22, respectively, providing defense against fungal and extracellular bacterial infections.[228] Among T-cell subgroups, the mucosal-associated invariant T (MAIT) cells, known as evolutionarily conserved T-cells, are the most common at identifying bacterial particles. [229] MAIT cells play a critical role in eliminating bacterial infections and have also been recognized for their potential in defending against viral infections.[230] MAIT cells recognize antigens through the Major histocompatibility complex class I-related gene protein (MR1), which is primarily found on B cells.[231]

3.7 Mechanisms of the interaction at the gut-skin axis

The homeostasis of the skin can be significantly impacted by gut integrity disruption and microbial community imbalance.[232] The intricate connection between the gut and the skin is referred to as the gut-skin axis.[233] Through interactions with the immune system, the gut microbiome interacts with the skin primarily to control both local and systemic inflammation.[234]

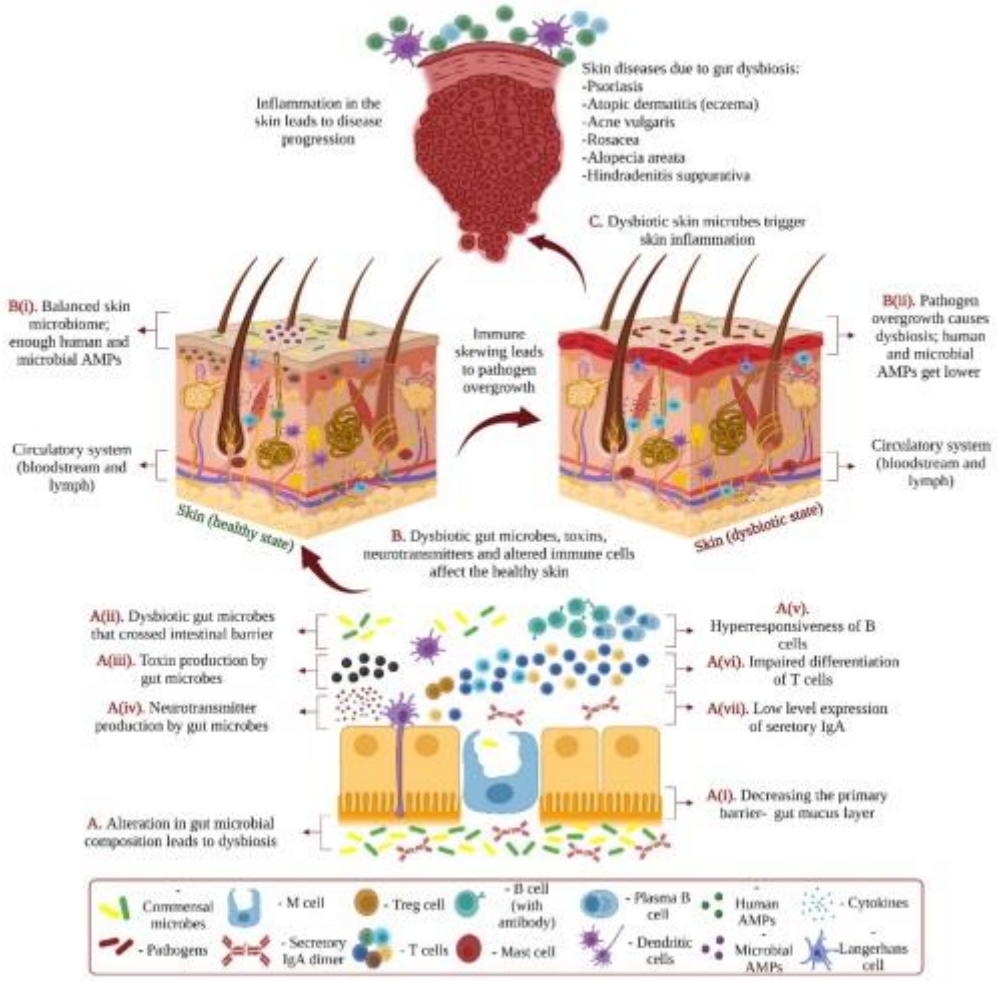

Figure 3.6 Mechanisms of the interaction at the gut-skin axis[166]

Microbial communities play a crucial role in preserving the integrity of the gut barrier by transforming complex polysaccharides, which are indigestible, into vitamins (particularly K and B12) and short-chain fatty acids (specifically butyrate and propionate)[235]. The primary function of the gut's mucus layer is to serve as a protective barrier, preventing microbes from migrating to other tissues within the host. By acting as the main barrier, the mucus layer in the gut prevents the movement of microbes to other parts of the host's body.[236] The innate immune cells of GALT play a crucial role in protecting the gut mucosa by identifying general infections and triggering both the innate and adaptive immune responses through antigen presentation.[237] To prevent the translocation of pathogenic microbes, AMPs, macrophages, and CD103+ CD11b+ DCs play a crucial role in eliminating them.[151] Defensins, a class of antimicrobial peptides, disrupt bacterial membranes by creating pores, which can result in cell death if specific thresholds are exceeded. Cathelicidins, including LL-37 in humans, contribute significantly to preserving the integrity of the epithelial barrier. Their main mechanism involves disrupting bacterial membranes, while also possessing immunomodulatory properties.[222] The presentation of commensal antigens by DCs leads to the differentiation of gut commensal bacteria-specific regulatory T cells, B cells that produce IgA antibodies, and Th17 cells. DCs play a crucial role in establishing the specificity of CD4+ Th17 cells towards commensal microbes through Major Histocompatibility Complex II (MHCII) antigen presentation. The production of Interleukin 22 (IL-22) by CD4+ Th17 cells leads to an increase in the secretion of host AMPs.[238] The preservation of skin homeostasis relies on several factors, including the integrity of the intestinal barrier, along with the functions of mucus, immune cells, IgA, and AMPs synthesized by epithelial cells. These mechanisms prevent the translocation of gut bacteria into the bloodstream.[217] By spatially separating the host tissue and gut microbes, secretory IgA regulates the inflammatory reactions to the gut microbes.[239] The accumulation of commensal bacteria-

specific lymphocytes in Peyer's patches and the lamina propria of the gut plays a crucial role in shaping the microbial profile of the gut, promoting homeostatic equilibrium. Despite ongoing research, the connection between skin health and immunological responses influenced by the gut microbiome remains largely uncertain and necessitates additional study.[240]

Dermatologists Stokes and Pillsbury were pioneers in proposing, during the early twentieth century, the idea of a communication pathway between the gut, skin, and the brain.[241] The production of neurotransmitters, including GABA, acetylcholine, dopamine, and serotonin, is carried out by gut microbes. These neurotransmitters have the capacity to impact the function of the skin through the nervous system and can have systemic effects as they traverse the intestinal epithelium and enter the bloodstream.[242]

3.8 The connection between the gut and the occurrence of skin disorders

When there is an overgrowth of microorganisms and a decrease in diversity within the gut microbiome, it can contribute to the onset of a skin condition. The specific metabolic byproducts generated by these gut microbes have a direct influence on the normal functioning of the body and the progression of various diseases. Various factors that impact the diversity and composition of the gut microbial community can be classified into three categories: non-host factors (such as environmental determinants), host factors (including pancreatic enzymes, bile acids, and pH), and bacterial factors (such as microbial enzymes and adhesive properties).[243] The presence of gut dysbiosis contributes to the occurrence of three prevalent skin disorders: psoriasis, atopic dermatitis, and acne. Furthermore, there are reports suggesting a correlation between gut dysbiosis and less common yet potentially more severe diseases such as rosacea, alopecia areata, hidradenitis suppurativa, erythema nodosum, and pyoderma gangrenosum.[234,244] The skin plays a vital role in maintaining the body's homeostasis by carrying out essential functions like regulating water balance and controlling temperature. To

fulfill these functions, the skin undergoes a process called skin regeneration, which involves renewal and turnover. After stem cells differentiate into epidermal cells, they undergo a specific process known as keratinization, which is regulated by transcriptional processes. The gut microbiome influences the signaling mechanisms involved in epidermal differentiation, consequently impacting the homeostasis of the skin.[245] Several studies have expanded our understanding of the relationship between the gut microbiome and the health of the skin by providing more information.

Disease	Observed changes
Psoriasis	↑*Bacteroidetes* ↓*Firmicutes, Proteobacteria, Actinobacteria*[51]
Psoriatic arthritis	↓ *Akkermansia, Ruminococcus, Pseudobutyrivibrio*
Acne vulgaris	↑ *Proteobacteria, Bacteroides* ↓ *Actinobacteria, Bifidobacterium, Butyricicoccus, Coprobacillus, Lactobacillus, Firmicutes*[69,70]
Rosacea	↑ *Acidaminococcus, Megasphaera, Lactobacillales* ↓ *Peptococcaceae, Methanobrevibacter, Slackia, Coprobacillus, Citrobacter, Desulfovibrio*[85]
Hidradenitis suppurativa	= *Faecalibacterium prausnitzii, Escherichia coli*[95]
Atopic dermatitis	↑ *Escherichia/Shigella, Veillonella, Faecalibacterium, Lachnospiraceae incertae sedis, Clostridium XIVa, Faecalibacterium prausnitzii, Ruminococcus gnavus* ↓ *Bifidobacterium*[106,107]

Table 3.1 Changes observed in gut microbiome composition in the course of selected skin diseases [246–251]

3.8.1 Atopic dermatitis (eczema)

Several studies examining the impact of gut microbiome on the development of atopic dermatitis (AD) in infants and children indicate that infants with a less diverse gut microbiome are more likely to develop AD in the future. On the other hand, there are contradictory results

indicating that increased diversity in gut microbial composition actually facilitates the development of AD.[252,253] As an example, a comparative analysis between patients with atopic dermatitis (AD) and healthy controls revealed a decreased abundance of Bifidobacterium in the gut of AD patients.[251,254] However, it is crucial to understand that the changes in gut microbial composition alone do not serve as a direct causative factor for AD development. A more comprehensive understanding of AD pathogenesis requires considering the intricate interplay between specific microbial species, the immune system, and external factors like dietary patterns. An imbalance in Th1 and Th2 responses is involved in the immunopathology of atopic dermatitis (AD) prognosis. In AD patients, the skin-resident dendritic cells responsible for immune activation travel to the nearby lymph nodes, where they stimulate naïve T lymphocytes, prompting their differentiation into the Th2 effector subtype.[165] Following activation and recruited back to the skin, Th2s cells play a significant role in the production of inflammatory cytokines, including IL-4, IL-5, and IL-13. These cytokines contribute to an increased production of IgE, a characteristic feature often observed in patients with atopic dermatitis (AD).[255] Two metagenomic studies carried out in South Korea focused on analyzing fecal samples from patients diagnosed with atopic dermatitis (AD). The findings indicated a decreased abundance of Faecalibacterium prausnitzii and a significant reduction in the production of short-chain fatty acids (SCFAs) when compared to the fecal samples of healthy controls.[256,257] As per a research study, the imbalance in Faecalibacterium prausnitzii (F. prausnitzii) in people with atopic dermatitis (AD) was linked to an elevated expression of multiple nutrients. These nutrients, including GalNAc and L-fucose, which are components of mucin, were found to be released from the impaired gut epithelium. This suggests the presence of a leaky gut and dysregulated inflammation in the gut epithelium. The presence of a damaged gut epithelium resulted in an augmented intestinal permeability, enabling the entry of diverse

toxins and pathogens into the blood circulation. Subsequently, these metabolites and toxins reached the skin, triggering Th2-type immune responses by releasing inflammatory cytokines, which contribute to the progression of atopic dermatitis (AD).[257] According to Zheng et al., the presence of a higher abundance of Akkermansia muciniphila in infants with atopic dermatitis (AD) was linked to impaired intestinal barrier function and worsening of skin lesions.[258]

3.8.2 Alopecia areata

Alopecia areata (AA), also known as spot baldness, is an autoimmune condition characterized by hair loss that can occur in specific areas or affect the entire body. This condition is not limited by age and can manifest in individuals of any age group.[234] Alopecia areata (AA) is an autoimmune disease characterized by the interaction between autoreactive T lymphocytes and a follicular auto-antigen presented by perifollicular or follicular cells. This interaction triggers the activation and induction of T lymphocytes, particularly Th1 cells, which release pro-inflammatory cytokines such as IFNγ. The presence of IFN-γ disturbs the normal anagen growth phase, ultimately causing hair loss and other symptoms associated with AA.[259] Individuals diagnosed with alopecia areata (AA) show a higher prevalence of ulcerative colitis in comparison to the healthy population, suggesting a link between the gut and AA.[260] The underlying mechanism behind this correlation involves the generation of autoreactive T lymphocytes that that develop tolerance to apoptotic cell death. This leads to persistent chronic inflammation and subsequent hair loss, driven by the production of inflammatory cytokines (such as IFN-γ and IL-2) by the autoreactive Th1 cells.[259]

3.8.3 Rosacea

Rosacea is a prevalent skin disorder characterized by symptoms such as pustules, persistent redness, excessive fibrous tissue growth, papules and telangiectasia. The presence of various gastrointestinal comorbidities alongside rosacea has been noted, suggesting a link between the condition and changes in the gut microbiome. Furthermore, the pathogenesis of rosacea may potentially be linked to the presence of Helicobacter pylori infection, inflammatory bowel disease (IBD), and small intestinal bacterial overgrowth (SIBO). The interaction between the immune system and gut-related conditions further highlights the association between the gut and rosacea.[244] Based on reports, the involvement of H. pylori in the development of rosacea is linked to various immune-related and inflammatory factors.[261,262] For example, H. pylori has the ability to significantly elevate the generation of reactive oxygen species (ROS), which exerts an inflammatory impact on the gut. Within the group of reactive oxygen species (ROS), nitric oxide (NO) specifically induces inflammation in the gut mucosa and disrupts the normal physiological processes of the skin, such as vasodilation, inflammation, and immunomodulation. These alterations contribute to the development of the clinical symptoms associated with rosacea. Another mechanism that provides support for the association between H. pylori and rosacea is the cytotoxin-mediated induction of pro-inflammatory cytokines, including TNF-α and IL-8. The release of these inflammatory cytokines promotes inflammation in the gastric mucosa, resulting in the observed clinical symptoms of rosacea.[263]

3.8.4 Psoriasis

The impact of psoriasis on a patient's quality of life is significant. The disease is an inflammatory skin condition accompanied by a number of comorbidities. The prevalence of associated comorbid diseases such as depression, cardiometabolic dysfunction, and metabolic syndrome is also higher among patients with psoriasis. It is an immune-mediated, genetic

disease manifested by lesions with or without joint involvement. These years, worldwide attention has been drawn to psoriasis because of its increasing prevalence and complex pathogenesis.[264,265] Several factors may play a role in the pathogenesis of psoriasis, including infection, genetics, and exceptional immunity. It has also been widely accepted that the immune system plays a role in psoriasis pathogenesis.[48] Specifically, Th17 cells play a crucial role in psoriasis pathogenesis. The gut microbiome plays a role in the connection between psoriasis and inflammatory bowel disease (IBD), which is the second identified comorbidity of psoriasis.[266] In psoriasis, Th17 cells, along with Th1 cells and keratinocytes secrete inflammatory mediators IL/6, IL-12, IL-17A, IL-22, and IL-23 participating in psoriasis pathophysiology.[51] Moreover, intestinal flora alteration may trigger an abnormal immune response, ultimately resulting in psoriasis.[267] It has not been reported whether the gut microbiota correlates with the level of inflammatory factors, or whether microbiome dysbiosis correlates with psoriasis severity. Psoriasis has a complex pathogenesis that is not fully understood. According to current research, many immunological and environmental factors (e.g., trauma, infection, drugs, UV and X-rays, chemical burns, smoke, alcohol, and stress), as well as genetic predispositions, contribute to the production of proinflammatory cytokines by keratinocytes.

It is a relatively new field to study the psoriatic microbiome, preliminary studies have revealed intriguing differences in microbiome composition between psoriatic lesions and unaffected skin in subjects with psoriasis and PsA.[268,269] Compared to healthy controls, patients with psoriasis have a higher relative abundance of Streptococcus and a lower level of Propionibacterium in their cutaneous microbiome. Researchers have found that the proportion of Firmicutes and Bacteroidetes in the gut microbiome is different in people with psoriasis compared to healthy people.[268] In individuals with psoriasis, there is a noticeable decrease in the abundance of Bacteroidetes (including the Bacteroides genus), Proteobacteria, and Actinobacteria, as well as

lower levels of Akkermansia muciniphila and a reduced prevalence of the Firmicutes phylum.[246] In addition, actinobacteria are relatively underrepresented among psoriasis patients compared to healthy individuals.[269] In every sample, Staphylococcus and Corynebacterium were the most common bacteria. Psoriasis patients may be at greater risk for PsA development if their skin microbiome flora diversity is reduced.[270]

3.9 Intestinal Dysbiosis in Psoriasis

Researchers have demonstrated that the gut microbiota plays a role in maintaining the equilibrium between Th17 effector cells and regulatory T cells. They found that germ-free mice exhibited less severe psoriasis-like skin inflammation induced by imiquimod compared to conventional mice, indicating that gut dysbiosis may contribute to the pathogenesis of psoriasis by enhancing the Th17 response.[178,271] The immune-modulating potential of metabolites generated by the intestinal microbiome is instrumental in shaping the balance between immune tolerance and inflammation. These metabolites exert their effects by influencing the differentiation of naïve T cells, directing them towards either regulatory or Th17 lineages. The metabolic demands of these cells distinguish them from others. Effector T cells, in particular, have an anabolic metabolism and primarily utilize glycolysis as their main source of adenosine triphosphate (ATP) production. On the other hand, memory and resting T cells are characterized by a catabolic metabolism. These cells utilize fatty acids, amino acids, and glucose to produce ATP through oxidative phosphorylation. Adenosine monophosphate-activated kinase and rapamycin serve as the principal transcription factors orchestrating the lipogenic and glycolytic pathways, respectively. Both adenosine monophosphate-activated kinase and rapamycin act as energy sensors, their activity regulated by the presence of nutrients in the gut lumen. The resident microbiota can modulate the availability of these nutrients.[272] In addition, disruptions in the gut microbiota result in the production of endotoxin-peptidoglycan superantigens that

promote autoimmune and inflammatory conditions often seen in psoriasis. Exposure to toxins produced by gut microorganisms elicits an immune response, and patients with psoriasis display a positive skin test for antigens originating from gut bacteria.[273–277]

Besides the contribution of specific gut bacteria, the human microbial community encompassing fungi and yeast (microbiome) is increasingly recognized as a vital factor in maintaining good health. The interactions between yeast and fungi and their human hosts primarily occur in the intestines and on the skin. Recent research has identified numerous fungal species within the oral and colonic microbiota. The majority of these fungi reside on the skin, genitalia, and gastrointestinal mucosa without causing any disease.[278]

A fascinating discovery in this field is the identification of a decrease in the population of Saccharomyces cerevisiae, also known as baker's yeast, in the gut of psoriasis patients. This particular fungus is highly abundant in the human gut and is generally acknowledged for its immunomodulatory effects, which are considered beneficial.[279] The gastrointestinal microbiome of people with psoriasis exhibited distinct characteristics, including a significantly lower level of metagenomic species diversity, when compared to the microbiome of healthy controls. Additionally, there were findings suggesting a link between the intensity of psoriasis and the makeup of the microbial composition. For instance, more severe forms of the disease were associated with elevated levels of Actinobacteria and Euryarchaeota phyla, along with an increase in Methanobacteriaceae. In contrast, there were no indications of seasonal variations affecting the composition of the microbiota, supporting the notion that the gastrointestinal microbiome remains stable over extended periods.[280] Multiple studies have now documented disruptions in the gastrointestinal microbiota of psoriasis patients; however, few of these studies have conducted longitudinal monitoring or provided insights into dietary patterns.[281] Conversely, the study did offer functional information, such as the levels of

Methanobacteriaceae and reduced potential for butyrate production, both of which exhibited a correlation with disease severity. Notably, short-chain fatty acids, such as butyrate, are renowned for their anti-inflammatory properties and their ability to modulate the immune response, particularly by impacting dendritic cells, resulting in reduced interleukin-23 production and promoting the differentiation of naive lymphocytes into regulatory T cells instead of T helper 17 cells.[282,283] An important connection to dietary factors is established, where the consumption of red meat is linked to an imbalance in the gastrointestinal microbiota, leading to a reduction in the synthesis of butyrate. This relationship has been observed in mice, highlighting the influence of diet on butyrate production.[284]

Numerous studies have provided evidence of substantial disparities in the gut microbiota between people with psoriasis and those without the condition. Tan et al. demonstrated a notable decrease in the levels of Akkermansia muciniphila among patients with psoriasis.[285] In their research, Chen Y. J. et al. found an elevated presence of the Firmicutes phylum in psoriasis patients, particularly the genera Ruminococcus and Megasphaera, along with a decreased prevalence of the Bacteroidetes phylum. This observation may be linked to impaired cobalamin and iron transport. Huang et al. conducted a study that supported the notion that Bacteroidia played a pivotal role in microbiota dysbiosis observed in psoriasis patients, whereas the phylum Firmicutes had a significant influence on the microbiota composition in healthy subjects. These findings were consistent with a previous study that reported an altered Firmicutes to Bacteroidetes ratio in people with psoriasis.[246] No significant differences in the composition of intestinal microbial were found among psoriasis patients with varying degrees of severity. The research conducted by Codoner et al. identified distinct characteristics of the gut microbiome in psoriatic patients, including elevated levels of Faecalibacterium, reduced abundance of Bacteroides, and increased presence of Akkermansia and Ruminococcus genera.[286] Shapiro et

al. conducted a study that revealed a notable rise in the Firmicutes and Actinobacteria phyla in patients with psoriasis compared to the control group. Psoriatic individuals exhibited significant increases in the abundances of specific species like Ruminoccocus gnavus, Dorea formicigenerans, and Collinsella aerofaciens. Conversely, species such as Prevotella copri and Parabacteroides distasonis were significantly lower in psoriasis patients compared to controls. The gut microbiome plays a crucial role in modulating systemic immunity, thereby regulating the functionality and potential disruptions in distant organ systems. Disturbances in microbial composition and communication, referred to as dysbiosis, can disrupt the normal functioning of the gut barrier, resulting in heightened permeability. This increased permeability allows the translocation of microbial antigens and their metabolites from the gut into the bloodstream, leading to immune activation.[287] The disruption of intestinal integrity and increased permeability of the gut, consequences of systemic inflammation triggered by gut dysbiosis, are believed to play a role in the local and systemic immune responses, and the development of psoriasis.[288] The relationship between the skin and the gut is intricate and complex, yet the precise mechanism behind it remains not fully comprehended. This phenomenon is, to some extent, linked to the disruption of the intestinal barrier.[155,173,289] By administering S. aureus and Streptococcus danieliae, both commonly found in the inflammatory skin mouse model, the severity of skin inflammation associated with imiquimod-induced psoriasis like dermatitis was intensified. This exacerbation was linked to elevated levels of TNF-a, IL-17A, IL-17F, and IL-22, providing further evidence of the potential contribution of gut dysbiosis to the development of psoriasis.[290] Furthermore, Sikora et al. examined non-invasive indicators of intestinal barrier integrity in people with psoriasis, such as levels of claudin-3 and intestinal fatty acid binding protein (I-FABP) in the bloodstream of both psoriasis patients and healthy individuals. The study revealed higher levels of plasma claudin-3 and I-FABP in patients with psoriasis,

providing evidence that the dysfunction of the intestinal barrier in psoriasis disrupts the homeostatic interaction between the microbiota and the immune system. Sikora's subsequent study confirmed the association between I-FABP and the severity of psoriasis.[291] Figure 3.7 illustrates the proposed connection between gut dysbiosis and the development and progression of psoriasis. In their study, Codo~ner et al. investigated the hypothesis proposed by Ramirez-Bosca and colleagues, which suggests that the formation of psoriatic plaques is initiated by bacterial DNA present in the bloodstream, originating from the gut lumen. They discovered bacterial DNA in the blood samples of 29.6% of the psoriasis patients included in their research. Taking this into consideration, Codo~ner and colleagues examined the composition of fecal microbiota in 52 people with psoriasis, identifying specific microbial characteristics that were associated with an increased risk of bacterial translocation. In particular, they identified an elevated prevalence of Prevotella and a decreased ratio of Bacteroides to Faecalibacterium, which were correlated with the transfer of bacteria from the gut to the bloodstream in people with psoriasis.[286] This finding lends support to the hypothesis that particular gastrointestinal dysbiosis patterns contribute to the formation of psoriatic plaques. According to this hypothesis, these patterns provoke a localized inflammatory reaction and subsequent increased permeability in the gastrointestinal tract. This, in turn, facilitates the movement of bacterial antigens, such as bacterial DNA, into the systemic circulation. These antigens can then disseminate to distant sites, including the skin, and trigger an immune response.[292]

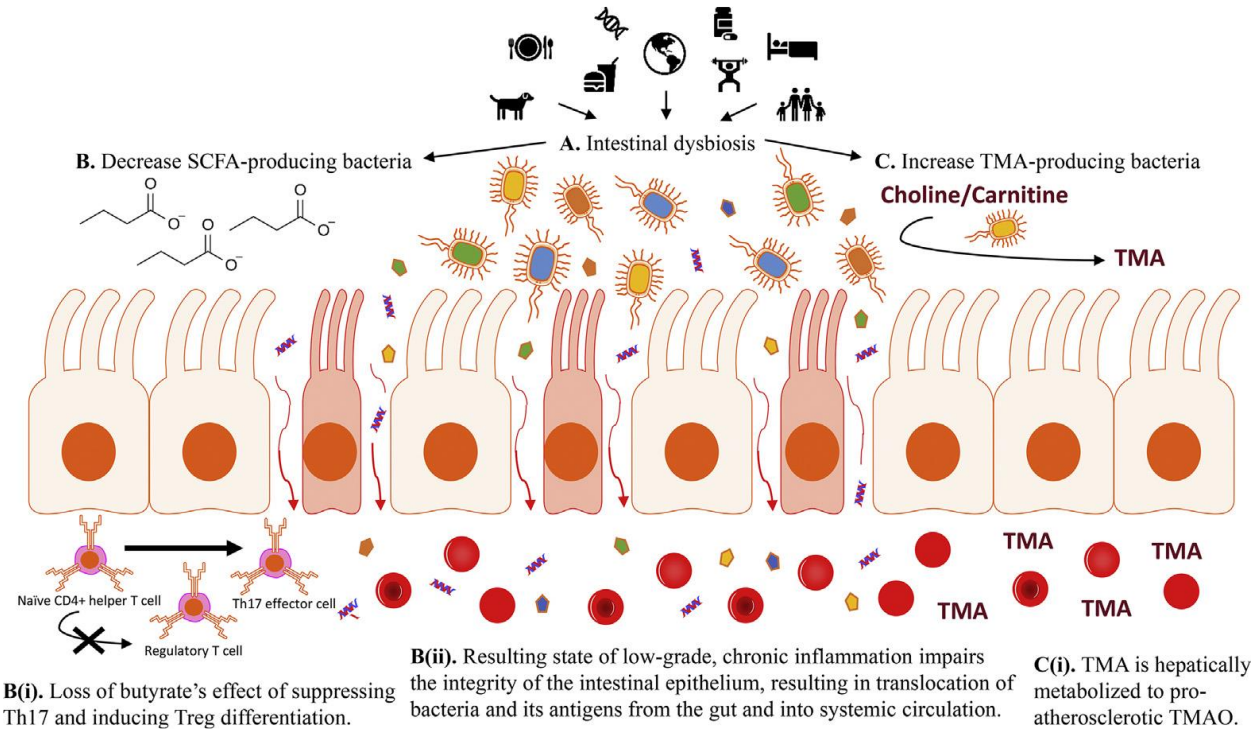

Fig. 3.7 The influence of intestinal dysbiosis on psoriasis and its comorbidities [293]

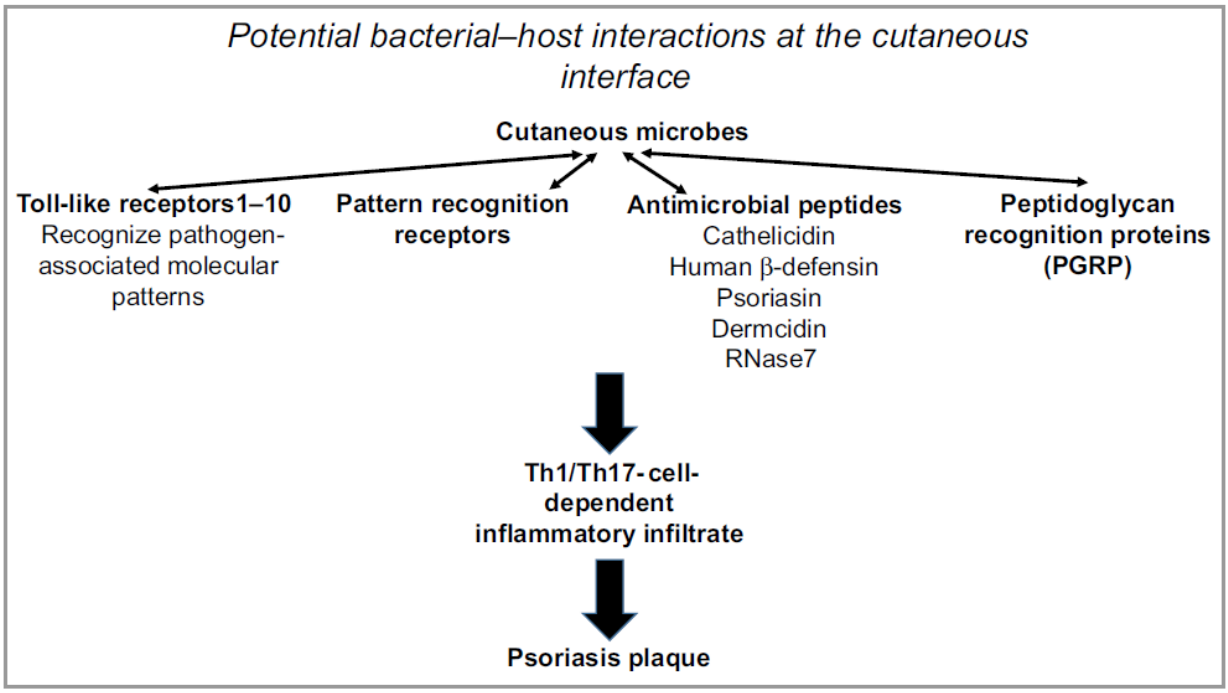

Fig. 3.8 Bacterial interactions with the host at the skin interface [270,294]

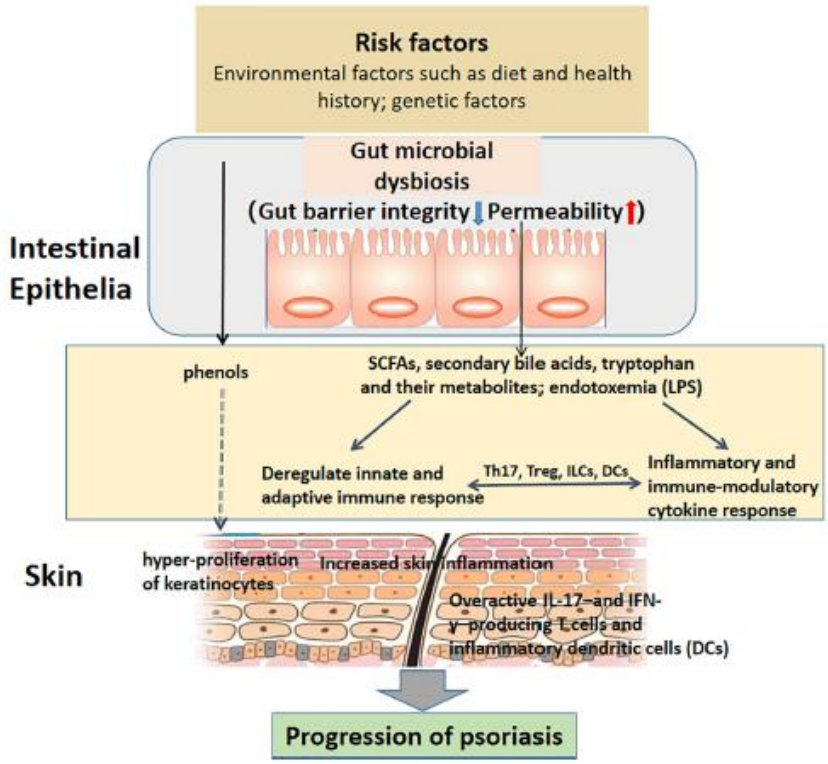

Fig. 3.9 The putative relationship between gut dysbiosis and psoriasis onset and progression.[295]

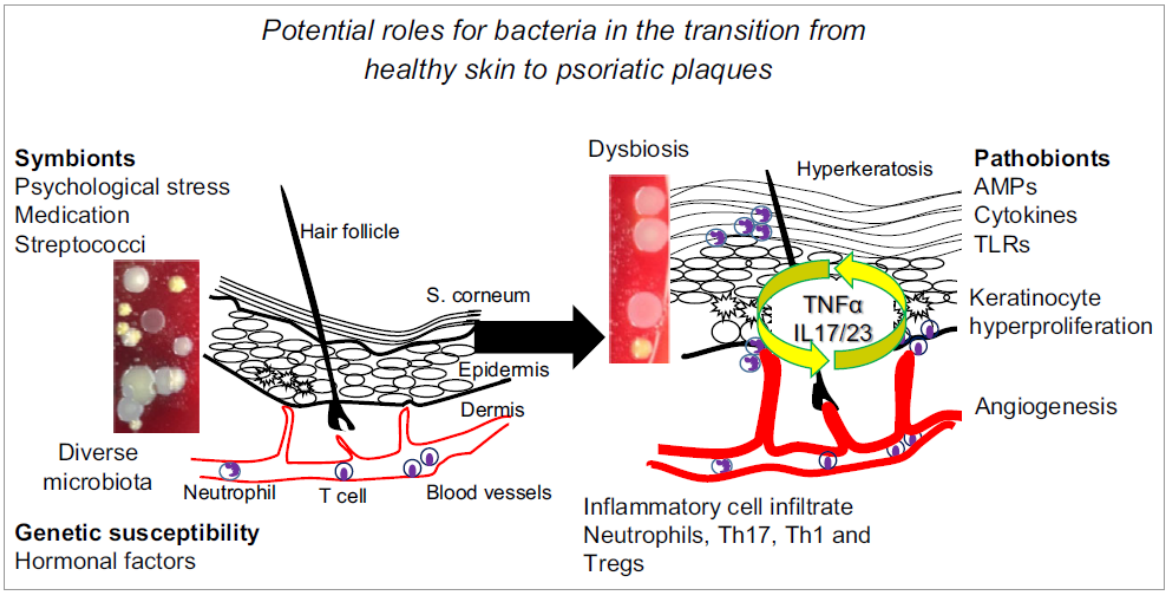

Fig. 3.10 Potential roles for bacteria in the transition from healthy skin to psoriatic plaques [270]

3.10 Skin microbiome and psoriasis

The skin serves as an immune barrier against external threats and also functions as physical barrier, and its resident microbiota plays a crucial role in regulating these processes.[296] Reduced barrier function was seen in psoriasis, an inflammatory skin condition, although the underlying processes are still unknown.[297] Skin microbiota alterations are strongly associated with psoriatic fares, and the microbiota is an important factor in the etiology of the condition.[271,298,299] Psoriasis is also closely linked to repeated skin infections.[299,300] A significant association exists between psoriasis and disruption of the skin's epidermal barrier integrity due to disturbance of resident microbial community, such as some fungal and bacterial flora that may induce Th17 cell accumulation.[301,302] Skin barrier function and structure are maintained by the skin microbiota and immune cells found within the epidermis. Inflammatory responses can be triggered by damage to this structure under pathological conditions. However, it is frequently unclear whether aberrant immunity to the microorganisms is a bystander to the inflammatory process or a cause and/or magnifier of the disease states, which is why further research is needed.

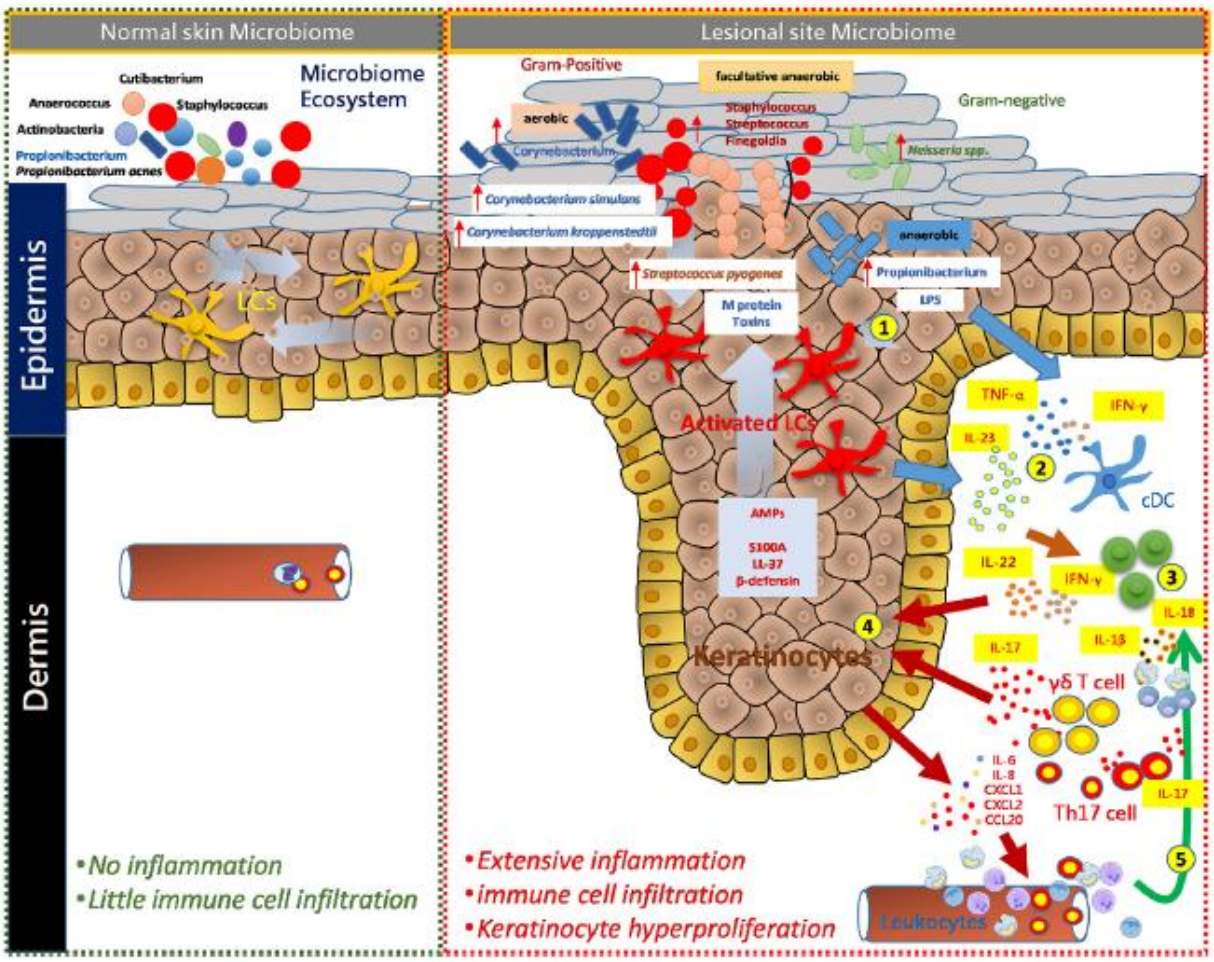

Fig. 3.11 Pathogenesis of psoriasis and interactions of the immune system, keratinocytes, and skin microbiome.[303]

3.10.1 Disruption in skin microbiome

It is possible for the microbiota of the skin to change due to a variety of factors, including the environment, host genetic variation, lifestyle, and hygiene. As a result of these changes in microbiota composition and structure, a dysbiotic state may develop, which if not recovered could lead to a dermatologic immune dysregulation state such as psoriasis. The diversity of microorganisms present on human skin varies due to the presence of different microhabitats. Sebaceous areas predominantly contain Propionibacterium spp, while moist regions like the

axilla and inguinal crease are characterized by Staphylococcus and Corynebacterium spp. Dry areas, on the other hand, harbor gram-negative microorganisms. Previous beliefs held that microbial life on healthy skin was confined to the epidermis, hair follicles, and sebaceous and sweat glands. However, recent analyses indicate that live microorganisms can also be found in deeper layers of the skin, specifically the dermis and the underlying adipose tissue. The variation among different skin sites within the same individual is typically greater than the variation observed among skin sites of different individuals in the same microhabitat.[304]

The occurrence of psoriatic attacks is strongly connected to alterations in the microbiome, known as dysbiosis, characterized by changes in the diversity and composition, as well as the proliferation of opportunistic pathogens. Specific pathogens, such as Staphylococcus aureus and Streptococcus pyogenes bacteria, human papillomavirus and endogenous retroviruses viruses, and Malassezia and Candida albicans fungi, have the potential to trigger or worsen psoriasis.[305,306]

Compared to healthy controls, Malassezia, which is the most prevalent fungal species found on normal human skin, exhibits reduced abundance.[307,308] Candida species are commonly found on the skin in areas affected by psoriasis, as well as in the feces of people with psoriasis. Additionally, interleukin-17, which is overexpressed in psoriasis patients, has a protective effect against infections, particularly those caused by Candida species.[309,310] This suggests that the heightened Th17 response could be a contributing factor to the development of psoriasis. The order of events needs to be determined: whether abnormal colonization by C. albicans precedes the onset of psoriasis or if psoriasis leads to the abnormal colonization. If it is found that abnormal colonization occurs first, specific antibiotics can be used to eliminate the pathogen and prevent the occurrence or progression of the disease. The presence of S. aureus, a frequently occurring pathogen, has the potential to be a pathogenic factor in psoriasis. This is supported

by the observation of increased Th17 polarization and intensified cutaneous inflammation during the early colonization of newborn mouse skin.[311]

3.10.2 Skin Dysbiosis in Psoriasis

Several immune-mediated skin diseases, such as psoriasis, atopic dermatitis, and acne vulgaris, are associated with disturbances in the microbiome. Distinctive skin microbiological traits are present in each disease. Extensive research has highlighted differences in the composition and role of the skin microbiome between psoriasis patients and healthy individuals. Moreover, changes in the skin microbiome have been linked to the occurrence of psoriatic flares.[295]

Using sequencing of the 16S rRNA V1-V3 variable region, Chang et al. discovered that the taxonomic composition at the phylum and genus levels can differentiate between various disease states, including healthy skin, psoriatic lesions, and non-lesional psoriatic skin.[311]Remarkably, there was no significant differentiation observed for the overall Staphylococcus genus across different skin conditions. However, the presence and abundance of specific Staphylococcus species were found to be associated with varying disease states. These findings suggest that the complex interactions between different Staphylococcus species might contribute to the formation of diverse microbial communities in both healthy and psoriatic skin. In psoriatic skin, there is a higher prevalence of the Pseudomonas genus, which comprises several opportunistic pathogens. This particular genus also plays a role in the treatment response of psoriasis patients who undergo narrowband ultraviolet B (UVB) therapy.[312] For example, the prominent bacterium causing Gram-negative toe-web infections, Pseudomonas aeruginosa, has a strong correlation with the occurrence of psoriasis.[313] Chang et al. also noted that microbial communities in psoriatic lesions demonstrate higher alpha diversity and increased heterogeneity, while exhibiting lower stability compared to the microbial communities in healthy skin. Conversely, Alekseyenko et al. reported a decrease in taxonomic

diversity within the microbiome of psoriatic lesions, along with an enrichment of Firmicutes and Actinobacteria.[299] The combination of these two taxa has the potential to serve as markers for distinguishing different skin disease states. Through RT-PCR, Gao et al. showed that psoriatic lesions exhibited an overrepresentation of the Firmicutes phylum, while the Actinobacteria phylum and Propionibacterium species were underrepresented.[314] In a larger-scale analysis, Fyhrquist et al. profiled the skin microbiota of individuals with atopic dermatitis, psoriasis, and healthy volunteers, and found that a decreased abundance of Corynebacterium members might have a regulatory role in psoriasis.[315] Corynebacterium species present in the human microbiome are often identified as opportunistic pathogens. In the case of Corynebacterium kroppenstedtii, its abundance is higher in the skin microbiota of psoriasis patients than in healthy individuals, and it has been sporadically linked to human infections, primarily involving granulomatous mastitis and breast abscesses.[302] Moreover, Quan et al. demonstrated a close relationship between increased abundance of Corynebacterium and decreased abundance of Cutibacterium in psoriatic lesions.[316] Using sequencing of the 16S rRNA V3-V4 variable region, Fahlen et al. noted a decreased level of diversity in psoriatic lesions when compared to the control group.[298] Psoriatic subjects exhibited lower levels of Staphylococci and Propionibacterium, while higher levels of Proteobacteria were observed in comparison to the control group. It is important to note that the amplification region and sampling method employed in this study differ from those used in other studies, potentially leading to distinct findings. In the study conducted by Drago et al, it was observed that psoriatic subjects exhibited higher levels of Proteobacteria and lower levels of Streptococcaceae, Rhodobacteraceae, Campylobacteraceae, Moraxellaceae, and Firmicutes compared to healthy controls.[317] The small number of participants in the study raises doubts about the reliability of the findings, even though rigorous dietary controls were applied to the individuals included. In

a separate study involving 28 patients with plaque psoriasis, shotgun metagenomics was employed to examine the microbiome of both affected and unaffected skin. The findings revealed minimal differences between the microbial communities at the species level. However, there were notable variations in strain colonization and functional diversity, indicating the necessity for more detailed analyses to better understand the pathogenesis of psoriasis and identify potential therapeutic targets.[269] Paulino et al. uncovered that the Malassezia microbiota demonstrated a stable and host-specific nature over time, with no noteworthy variation observed between samples collected from healthy skin and psoriatic lesions. This conclusion was drawn based on the utilization of multiplex real-time PCR.[318] Through a comprehensive examination of numerous studies exploring the association between skin microbes and psoriasis, it was observed that the patterns of Firmicutes, Actinobacteria, and Proteobacteria abundances exhibited considerable inconsistency, resulting in conflicting outcomes. Additionally, there is ongoing debate regarding whether the microbial community on psoriatic lesional skin exhibits lower diversity than that on healthy skin. Nevertheless, it is well-established that psoriatic lesions exhibit an increased abundance of S. aureus and a decreased abundance of S. epidermis.[319] The variations in the findings can be attributed to the interplay between a range of host and environmental factors that affect skin microbes. These factors include daily hygiene habits, the use of cosmetic products, exposure to antimicrobials, friction, climatic conditions, and UV irradiation.[320–323] Therefore, it is essential to meticulously control for these confounding factors in research studies to achieve comparability of results among different samples and studies. Furthermore, factors such as variations in skin sites and types, the specific primers used for sequencing amplification, and the selection of sampling methods (such as swab, scrape, and punch biopsy) all contribute to discrepancies in experimental findings, particularly concerning the diversity of the microbial community.[156,311,324–326]

Chapter IV

The impact of diet and probiotics on psoriasis through the gut microbiome

4.1 Introduction

The gut microbiome, a complex community of microorganisms residing in the gastrointestinal tract, plays a crucial role in human health, including digestion, immune system regulation, and metabolism.[327] Recent studies have highlighted the gut-skin axis, a bidirectional communication pathway between the gut and skin, which can influence skin health and the development of various skin diseases.[328] Diet and probiotics can modulate the gut microbiome, thereby affecting skin health through this gut-skin axis.

Dietary habits can significantly influence the composition and function of the gut microbiome. For instance, diets rich in whole grains have been associated with improved health and lower risk of non-communicable diseases, potentially due to their impact on the gut microbiome. Furthermore, the consumption of certain dietary proteins, such as soy-protein concentrate, has been shown to alter the microbial community composition in fish, suggesting a similar effect in humans.[329] Skin health is closely linked to the gut microbiome, with alterations in the gut microbiota associated with the development of several dermatoses.[330] Additionally, oxidative stress, which plays a dominant role in inflammatory skin diseases, has been shown to interact closely with the gut microbiome.[331]

Probiotics, live microorganisms that provide health benefits when consumed in adequate amounts, have been shown to be effective in the prevention and treatment of various skin diseases. Studies have established a link between a disrupted gut microbiome and inflammatory skin diseases, thereby increasing the potential of oral probiotics as a treatment option for skin disorders. Topical probiotics have also been investigated, but there is limited information and clinical studies examining their effectiveness.[332] Understanding the gut-skin axis and the influence of diet and probiotics on the gut microbiome will be essential for developing novel therapeutic strategies for skin diseases and improving overall skin health.

4.2 Diet

Diet plays a crucial role in shaping the gut microbiome, which in turn influences skin health. Breastfeeding, a fiber-rich diet, and specific protein sources can have positive effects on the gut microbiome and promote skin homeostasis. Conversely, high-fat diets and certain dietary proteins can contribute to gut dysbiosis and skin-related issues.[333] Breastfeeding and formula feeding influence the gut microbiome of newborns differently. Breastfed infants show higher levels of beneficial bacteria like Lactobacillus and Bifidobacterium[334], while formula-fed babies often exhibit colonization by proinflammatory species and opportunistic bacteria.[335] On the other hand, a high intake of trans-fatty acids and refined oils can negatively affect the gut microbiome, increasing the number of harmful microbes (such as *Proteobacteria* and *Desulfovibrionaceae*) while suppressing populations of advantageous microorganisms (e.g. members of Bacteroidetes, Bacteroidales and Lachnospiraceae), leading to inflammation and skin manifestations. Moreover, High-fat diets reduce microbial diversity, compromise colonic integrity, and promote systemic inflammation.[336,337] A diet rich in protein can lead to the synthesis and release of excessive proteins and amino acids by the gut microbiome. This process results in the formation of toxins such as indoxyl sulfate (IS), trimethylamine N-oxide (TMAO), and p-cresyl sulfate, which are associated with various skin conditions like psoriasis.[338] On the other hand, a high-collagen peptide diet can have positive effects on the skin, such as preventing aging and aiding in wound healing.[339]

A fiber-rich diet has numerous benefits for the gut microbiome. Fermentation of dietary fiber by gut bacteria produces short-chain fatty acids (SCFAs) like propionate, acetate, and butyrate, which enhance gut integrity, modulate immune responses, and prevent inflammatory disorders.[340] SCFAs also play a role in regulating Tregs, promoting anti-inflammatory effects.[341,342]

According to a study conducted by Afifi et al., a high percentage (86 percent) of psoriasis patients noted that consuming specific food ingredients, such as sugar, alcohol, or gluten, resulted in experiencing psoriasis flare-ups or worsening symptoms.[343] Earlier studies have provided evidence for the impact of these food choices on altering the microbial composition, causing irritation of the intestinal lining, triggering the production of inflammatory cytokines, and disrupting the microbial balance. The researchers also reached a conclusion that a diet abundant in fiber, encompassing fruits, vegetables, and complex carbohydrates, plays a role in reducing proinflammatory cytokines and rebalancing microbial composition. Western diets commonly consist of elevated levels of animal protein, saturated fats, and added sugars, while being deficient in dietary fiber. Nonetheless, individuals who integrate a diverse range of fruits, vegetables, and complex carbohydrates into their eating habits have demonstrated reduced circulating levels of tumor necrosis alpha, C-reactive protein, and IL-6, indicating a potential link between diet and inflammation markers.[344]

4.3 Probiotics

While there are numerous factors at play in the development and progression of psoriasis, recent emphasis has been placed on nutrition and the restoration of the gut microbiome. The restoration of the gut microbiome shows promise as a preventive and therapeutic approach in various clinical conditions.[345] Existing evidence indicates that modifying of the gut microbiota, through dietary interventions and the use of probiotics and prebiotics, may offer a novel treatment avenue for autoimmune disorders such as psoriasis,[346] multiple sclerosis[347] and celiac disease.[348] Probiotics, derived from the Latin word meaning 'for life' (Ozen M, 2015) are live microorganisms recognized by the World Health Organization (WHO) as conferring health benefits when consumed in appropriate amounts. Postbiotics, unlike probiotics, are the bioactive compounds generated by bacteria or released after their breakdown that can demonstrate similar properties to the probiotic strains from which they originate.[349] The objective of postbiotics is to recapitulate the beneficial effects of probiotics without the risk associated with administering live microorganisms. A notable example is butyrate, a prominent postbiotic produced by commensal bacteria. Butyrate serves as a major energy source for the colon and plays vital roles in intestinal growth, differentiation, and the modulation of inflammation.[350,351] Prebiotics are dietary substances that cannot be digested and stimulate the growth of commensal bacteria, playing a crucial role in maintaining intestinal health. Fermented products like beer, bread, wine, kefir, kumis, and cheese have been extensively consumed for their nutritional and medicinal benefits long before the recognition of probiotic microorganisms. It is widely believed that these fermented products were likely discovered in a spontaneous manner.[352] Various medical and popular references suggest that the earliest utilization of probiotics in human history can be traced back to 2000 BC when humans discovered methods

to prolong the preservation of milk. In fact, the early food artisans transformed milk into fermented dairy products using bacteria and yeasts.[353]

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines fermented food as "food products created through intentional growth of microorganisms and enzymatic transformations of food constituents", as stated by the organization.[354] For a probiotic to be considered optimal, it is preferable for it to originate from humans and possess qualities such as safety, absence of antibiotic resistance vectors, and lack of pathogenic or toxic factors. Additionally, a probiotic should exhibit a high level of survival capability in the harsh conditions of the intestinal tract, including acidic pH, enzymes, and biliary salts. In addition, a probiotic should demonstrate the ability to counteract pathogens and enhance immune system function, ultimately resulting in proven beneficial effects on the host.[355,356]

4.4 Application of probiotics in food industry

The correlation between human health and microbiota was initially brought up in 1907 by Elie Metchnikoff.[357]

Analysis of data covering the period from January 2001 to July 2020 indicates that fermented milk and yogurt claim the highest share as carriers of probiotics within the dairy products.[358] The families of Lactobacillus, Bifidobacterium, and Streptococcus encompass the majority of commonly found probiotic species, with the Lactobacillus and Bifidobacterium families predominantly explored in studies associated with human health.[359] During fermentation, probiotic lactic acid bacteria (LAB) generate a wide range of advantageous peptides. These peptides, which include health-promoting protein hydrolysates by-products, bioactive peptides, and ribosomally synthesized bacteriocins, have significant potential as nutraceuticals and biopreservatives.[360,361] Among non-lactic acid bacteria (LAB) groups, the genus Bifidobacterium houses the highest count of probiotics. Bifidobacteria are recognized as

important components of the colonic microbiota, constituting a major proportion (80%) of the cultivable fecal microbiota in breast-fed infants and (25%) in adults.[362] The efficacy of probiotic Bifidobacterium strains in promoting human health is highly promising, with ample clinical evidence supporting their effectiveness. One notable example is B. longum subsp. longum BB536, derived from humans, which has been extensively studied as a multifunctional probiotic and it has demonstrated positive effects on gastrointestinal well-being, alleviation of allergies, and modulation of intestinal integrity and immune homeostasis.[363] The increasing understanding of the human gut microbiota and its implications for overall health and disease has generated significant enthusiasm for exploring the probiotic qualities of commensal bacteria. This has led to the identification of novel bacteria, referred to as NGP, that play a crucial role in human health by therapeutically influencing the gut microbiota. Notably, approximately 75% of the global population experiences lactose intolerance.[364] In people with lactose intolerance, non-dairy probiotic foods are used as therapeutic treatment products.[365] Various lactic acid fermented traditional products derived from non-dairy sources are widely available and consumed worldwide. However, these traditional products have not been extensively studied as potential probiotics due to a lack of scientific research and various other factors.[366] Fruits have many nutritional benefits attributed to their diverse range of phytochemicals, antioxidant properties, vitamins, mineral content, dietary fibers, absence of cholesterol and more. Fruits such as pineapple, sweet lime, mango, blueberry, strawberry, etc. are used in making fruit-based probiotic products.[367,368] Vegetables like tomato, cabbage, ginger, carrot root, onion and others are utilized in Probiotic products. Lactic acid bacteria like L. acidophilus, L. plantarium, L. casei, and B. longum are employed in the development of probiotic foods derived from vegetables. The process of lactic acid fermentation enhances the nutritional quality of these products.[368]

4.5 Application of probiotics in treatment

The influence of probiotics on the well-being of individuals has been extensively examined and documented in numerous articles, reviews, and systematic reviews. The role of probiotics in preventing various health problems has been well-documented in these studies, including digestive disorders like diarrhea resulting from infections, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) limited to ulcerative colitis, as well as allergic conditions like atopic dermatitis (eczema) and allergic rhinitis.[369,370] The use of beneficial gastrointestinal bacteria as a supplement, known as probiotic therapy, has exhibited promising therapeutic potential for diverse skin conditions.[371–373] Probiotics can elicit beneficial effects on the skin by influencing both the innate and adaptive pathways of the host immune system. Recently, specific strains of Bifidobacteria and Lactobacilli have exhibited positive effects on skin disorders like atopic dermatitis in both animal models and humans. The underlying mechanism involves the modulation of reactive inflammation associated with the skin.[374,375] Probiotics have been extensively applied in intervention studies targeting the prevention and/or treatment of several human diseases, including notable skin disorders like atopic dermatitis (AD), allergic rhinitis, and wound healing.[376]

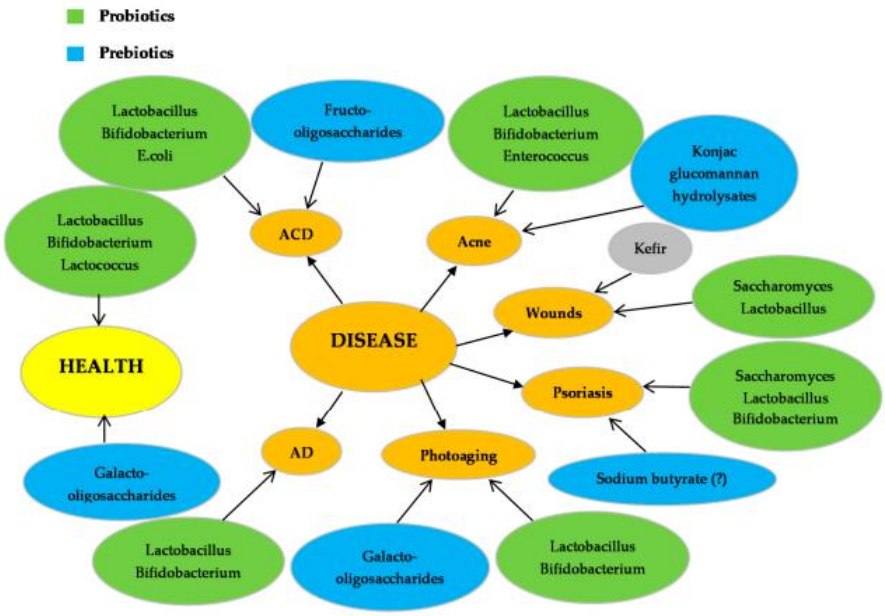

Fig. 4.1 In vitro studies have shown the capacity of probiotics, such as Streptococcus salivarius and Enterococcus faecalis, to directly inhibit P. acnes growth through antibacterial proteins' production, as detailed in this article. An example of antibacterial protein is the Bacteriocin-like inhibitory substance (BLIS), which can cause significant inhibition in the growth of P. acnes [377,378]

However, recent investigations have proposed that probiotics may exert beneficial effects beyond the realm of gastrointestinal well-being, as they have displayed efficacy in ameliorating specific metabolic disorders including hypertension, hypercholesterolemia, and atherosclerosis. The suggested mechanisms through which probiotics exert their effects on metabolic disorders encompass the inhibition of pathogen adhesion to the gut mucosa, the stabilization of the microbial flora, and/or the enhancement of intestinal integrity and barrier function. These mechanisms can contribute to improved energy metabolism and insulin sensitivity. Metabolic disorders such as hypercholesterolemia can adversely affect the function of microvessels, but the use of lipid-lowering therapy like cholestyramine has demonstrated the ability to reverse this effect. Building on this evidence, incorporating suitable quantities of probiotics into the diet

could potentially yield beneficial outcomes for peripheral vascular blood flow and hair growth.[379–383]

The study analyzed a probiotic product derived from kimchi, cheonggukjang, and natural herbs, which consisted of a diverse range of probiotics and prebiotics. The findings by Choi et al indicated that the presence of ultra-high molecular weight poly-γ-glutamic acid (UHMW γ-PGA) isolated from Bacillus subtilis, the bacterium involved in the fermentation of cheonggukjang, exhibited the ability to enhance hair growth in vivo.[384]

4.6 Mechanism of action of probiotics

The mechanism of action of probiotics involves various aspects, such as modulation of the immune system, production of organic acids, enhancement of colonization resistance, interaction with gut microbiota, improvement of barrier function, synthesis of small molecules with systemic effects, generation of enzymes.[385]

4.6.1 Mechanism of action of probiotics on immune system

In humans, specific receptors named TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are associated with the outer membrane and predominantly react to bacterial surface-related PAMPs. Conversely, TLR3, TLR7, TLR8, and TLR9 are found on endosomes' surfaces, where they primarily respond to nucleic-acid-based PAMPs from viruses and bacteria. The signaling of TLR9 plays a crucial role in mediating the anti-inflammatory effect of probiotics. Figure 4.2 summarizes the interaction of probiotics with TLRs.[386]

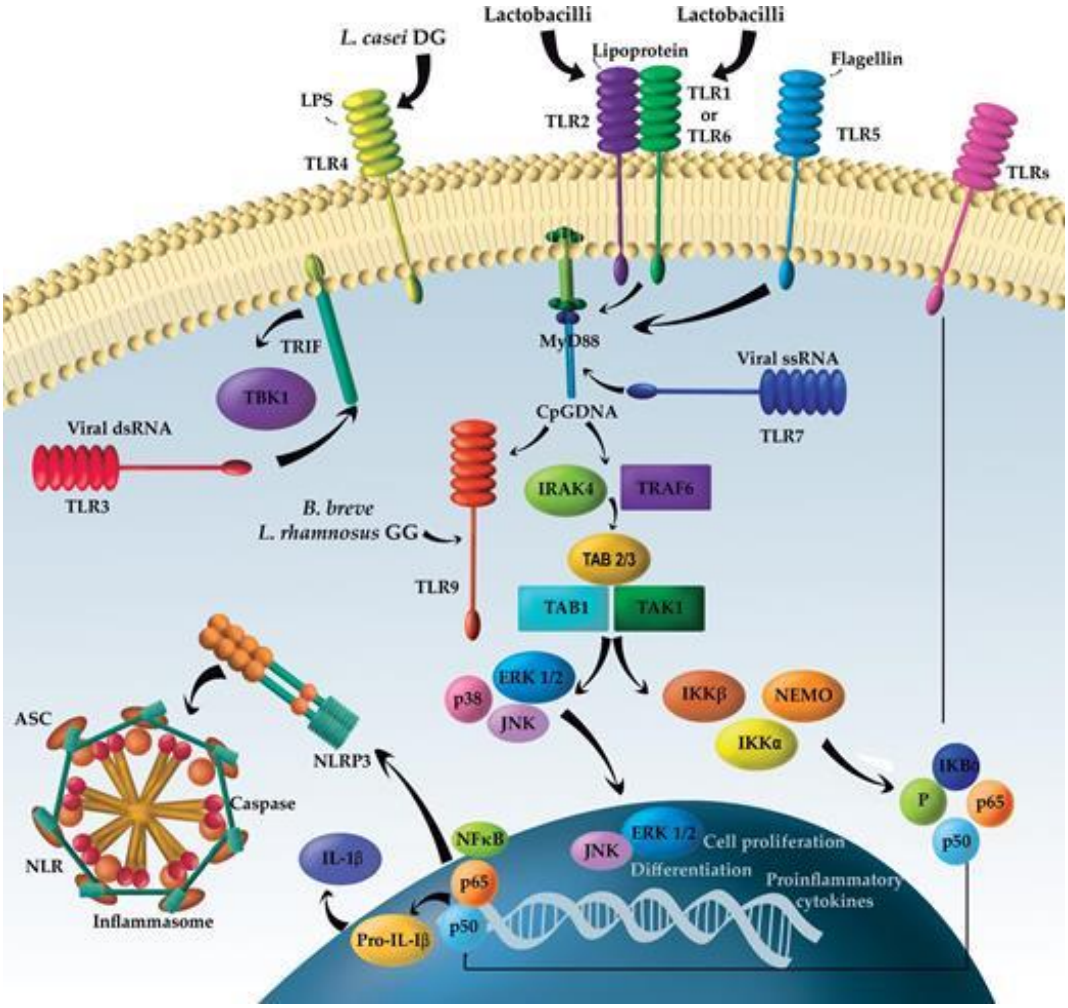

Fig. 4.2 Important effects of probiotics on body. [387]

4.6.2 Mechanism of action of probiotics on digestive system and their effects on skin

The immune response can be regulated by metabolites produced by gastrointestinal bacteria, as they have the ability to modulate the balance between inflammatory responses and immune tolerance. This modulation is achieved by influencing the differentiation of naïve T cells into either Treg or Th17 cells.[272] An abundance of pro-inflammatory Th17 cells and their specific cytokines can be observed in both the intestine and the skin, and their impact on the development of chronic inflammatory skin disorders, such as skin hypersensitivity, and psoriasis, is considered to be substantial.[176,179,388] The composition of commensal

gastrointestinal flora can influence the differentiation of T cells in response to immune system stimulants, ultimately contributing to the regulation of skin allostasis. Studies have demonstrated that the intake of probiotic Lactobacillus casei (L. casei) orally can impede the differentiation of CD8+ T cells into cytotoxic T cells in the skin and inhibit their migration to the skin. Moreover, this probiotic enhances the recruitment of FoxP3+ Treg cells to the skin, leading to decreased skin inflammation mediated through apoptosis. These findings highlight the potential of L. casei in modulating immune responses and restoring homeostasis.[374,389] By acting as a key modulator of the gastrointestinal-skin axis, the gastrointestinal microbiota establishes a communication link between the two systems. It exerts its influence on skin hemostasis by modulating systemic immune responses. Commensal clostridia, Faecalibacterium prausnitzii, and Bacteroides fragilis produce certain microbial metabolites such as retinoic acid and polysaccharide A. These metabolites stimulate the accumulation of regulatory T (Treg) cells, which contribute to the inhibition of inflammation. Conversely, spore-forming bacteria like Clostridia have potential to induce the accumulation of Th1 and Th17 cells that possess pro-inflammatory properties. Furthermore, SCFAs, particularly butyrate, play a role in restraining inflammatory reactions mediated by pro-inflammatory cells through the suppression of cytokine production, cellular proliferation, and migration. Furthermore, SCFAs exert control over the activation and apoptosis of immune cells through the inhibition of NF-kB signaling cascades and histone deacetylase. Inhibiting histone deacetylase promotes the proliferation of Treg cells, which play a role in various physiological processes of the skin, including the regulation of skin wound healing and the differentiation of hair follicle stem cells.[154,170–172,390]

In this study, we assessed numerous experimental and human studies that provide evidence for the protective effects of the gut microbiome on the skin's appearance and overall well-being. A

laboratory study demonstrated that the treatment of human epidermal keratinocytes with fermented milk whey by Lactobacillus helveticus resulted in increased expression of differentiation markers, such as involucrin and keratin 10, suggesting that L. helveticus has the ability to promote the differentiation of epidermal cells. In a dose-dependent manner, the expression of profilaggrin, a protein involved in the differentiation of keratinocytes, was observed to increase. Profilaggrin ultimately matures into filaggrin, which contributes to the normal hydration and flexibility of the epidermal layer, suggesting that L. helveticus might possess moisturizing properties.[391]

4.6.3 Mechanism of action of probiotics in the treatment of psoriasis

Human subjects who received oral supplementation of L. brevis SBC8803 for a duration of 3 months experienced significant reductions in transepidermal water loss (TEWL) and improvements in epidermal hydration. [392]Another clinical investigation revealed that individuals who consumed a supplement containing Lactobacillus paracasei NCC2461 for a period of 2 months experienced reductions in TEWL and improved skin sensitivity. These improvements were linked to elevated plasma levels of transforming growth factor-β and anti-inflammatory mediators, which played a beneficial role in enhancing barrier function.[172]

Furthermore, a separate investigation provided further support by demonstrating that oral supplementation of L. casei DN-114 001 successfully alleviated T cell-mediated skin inflammation without exerting immune-suppressive effects. This was achieved through immune-modulatory mechanisms involving the modulation of cytotoxic CD8+ T cells and the active participation of CD4+ Treg cells. Therefore, L casei might be an effective probiotic that can help treat psoriatic skin disorders caused by T cells.[389]

In a double-blind study conducted by Drago et al, 38 adult patients diagnosed with moderate to severe atopic dermatitis were divided into two groups. The first group was administered a

treatment comprising probiotic Lactobacillus salivarius in maltodextrin, with a dosage of 1.9 x 10^9 CFU/g, while the second group received a placebo composed exclusively of maltodextrin. The treatment regimen included consuming sachets twice daily for a duration of 16 weeks. All participants successfully finished the study, and at the beginning, there were no discrepancies in the severity of eczema between the groups. However, after four months, a notable reduction in SCORAD score was observed solely in the probiotic-treated group, with no reported adverse effects throughout the duration of the study. The evaluation of cytokine production by peripheral blood mononuclear cells was conducted before and after the treatment. Patients who received probiotics displayed no changes in cytokine production, whereas those in the placebo group exhibited a significant increase in IL-4 production, coupled with a reduction in IFN-c levels.[393–395] mportantly, patients with psoriasis have demonstrated dysbiosis patterns that are reminiscent of those found in patients diagnosed with inflammatory bowel disease (IBD).[396] Psoriasis and IBD have some overlap in their etiopathogenesis, including genetic factors and environmental influences. This is supported by evidence showing that Th17 cells and their cytokines, known to play a crucial role in the progression of psoriasis, are also implicated in the pathophysiology of IBD.[177]

Extensive studies highlight a significant association between potential mediators of T cell activation and the progression of the condition. Notably, the development of psoriatic arthritis is closely tied to CD4+ T cells, whereas probiotics exert a regulatory influence on T cells, resulting in reduced skin inflammation and improved skin moisture.[304] S. epidermidis is the second most prevalent staphylococcal species in the human microbiota, after S. aureus, according to studies of the human epidermal microbiome in psoriasis.[269] Recent research findings indicate that diseased skin displayed significantly higher levels of S. aureus compared to healthy skin, and a substantial presence of P. acnes was also observed on healthy skin. These

results imply a strong association between the microbial load of the skin and the development of psoriasis.[311] A different study indicated a decrease in the abundance of [specific microbial species] in patients with psoriasis, which was effectively restored by treatment with dimethylfumarate (DMF).[279] The depletion of beneficial bacteria in the gastrointestinal system can lead to dysregulated immune responses, potentially affecting other organs. Psoriatic patients were found to have a reduction in F. prausnitzii, a significant commensal bacterium found in the large intestine. By acting as a key provider of butyrate, F. prausnitzii plays a crucial role in offering numerous benefits to the host. Butyrate, an SCFA, exhibits anti-inflammatory effects by inducing the development of Treg cells, thereby contributing to immune tolerance that extends to organs beyond the gastrointestinal system.[396–399]

Sodium butyrate, produced by the gut microflora, has known effects on cell cycle regulation, tumor growth factors (TGF-β), and protease enzymes. In various studies using human keratinocyte (HaCaT) cells, it has been observed that exposure to sodium butyrate leads to a 50% increase in apoptosis by upregulating the death receptor Fas and activating caspases 8 and 3. Additionally, increased levels of p52 and TGF-β expression were detected, suggesting a potential role in cell proliferation and terminal differentiation.

Ultimately, a combined treatment regimen utilizing sodium butyrate and PD153035, an inhibitor of the epidermal growth factor receptor, was found to enhance keratinocyte differentiation. Overall, the data indicates that sodium butyrate has the potential to serve as an additional therapeutic approach for controlling hyperproliferative skin conditions, such as psoriasis. It achieves this by modulating crucial cellular processes like apoptosis, proliferation, and differentiation. A recent study investigating the gut microbiota of people with psoriasis unveiled a decline in the population of butyrate-producing microbes. This decrease potentially affects the well-established anti-inflammatory role played by butyrate, shedding light on its

potential preventive effects in psoriasis and similar disorders to some extent. F. prausnitzii, a prevalent microorganism found in the large intestine, plays a crucial role as a significant source of butyrate. This essential short-chain fatty acid serves multiple purposes, including providing energy for colonocytes, reducing oxidative stress, and exerting anti-inflammatory effects. Furthermore, it promotes the activation of regulatory T cells, thus establishing immune tolerance that extends beyond the gastrointestinal system. Lastly, another research study provided evidence of a marked reduction in the presence of F. prausnitzii among people with psoriasis when compared to the control group of healthy peoples.[286,397–404]

A recent report showcased the successful utilization of the probiotic microorganism L. sporogenes for alleviating pustular psoriasis, resulting in a significant amelioration of lesion appearance and the patient's overall health. One year later, Groeger et al., conducted research on the immune-modulating impacts of B. infantis in patients diagnosed with ulcerative colitis, chronic fatigue syndrome, and psoriasis. In the case of psoriasis, they noticed decreased levels of C-reactive protein (CRP) and TNF-α in the blood plasma, indicating the potential of B. infantis to lower systemic markers of inflammation and serve as a promising therapeutic strategy for managing psoriatic conditions.[405,406]

In a particular case study, the effectiveness of Lactobacillus sporogenes, a probiotic, was explored as a treatment for pustular psoriasis in a 47-year-old female patient. The individual had been suffering from psoriasis for 15 years and had undergone various medical interventions, including topical and systemic treatments. Following admission, the patient underwent treatment involving the administration of steroids, dapsone, and methotrexate. However, the patient did not exhibit any positive response to conventional treatments, and her lesions continued to worsen, accompanied by indications of steroid toxicity. Hence, medical practitioners had to explore alternative medicinal options. Consequently, all medications were

halted, and the patient underwent treatment with the probiotic L. sporogenes. After a period of 15 days, the fever subsided, the lesions displayed improvement, and the absence of new lesions was noted. Moreover, there was an improvement in the patient's general condition. The probiotic treatment was continued, and during the 6-month follow-up, there was a decrease in plaque psoriasis.[407]

To evaluate the potential positive impact of probiotics on psoriasis, a randomized, double-blind, placebo-controlled trial was conducted. The trial focused on 26 male and female patients aged 18 to 60 years, who were suffering from mild to moderate chronic plaques, with a psoriasis area severity index (PASI) score less than 16. The treatment involved administering sachets containing 1 × 1010 CFU of live Bifidobacterium infantis 35,264 to each patient. Patients with psoriasis presented elevated levels of pro-inflammatory cytokines in their plasma. C-reactive protein (CRP) is an indicator of acute inflammation, primarily synthesized by liver cells in response to heightened serum levels of inflammatory mediators like IL-6 and TNF-α. A study reported that oral supplementation of B. infantis 35,624 for 6-8 weeks resulted in a notable reduction in psoriatic skin inflammation among patients. This improvement was correlated with a significant decrease in plasma levels of inflammatory markers, such as IL-6, TNF-α, and CRP.[406,408–410]

The use of probiotics as a supplement is believed to help prevent the colonization of pathological intestinal flora, enhance the mechanisms of the intestinal barrier, regulate the immune system towards an anti-inflammatory response, and produce beneficial anti-inflammatory metabolites.[411] Mice that were given probiotics in their diet exhibited improvements in dermal thickness, folliculogenesis, and sebocyte production, leading to thicker and glossier fur.[388] Furthermore, other studies demonstrated that probiotic supplementation reduced cutaneous arterial sympathetic nerve activity and transepidermal water loss, while

increasing cutaneous blood flow, skin hydration, and TGF-b levels.[155,173,232,388] The positive effects of Lactobacillus johnsonii have also been observed in repairing skin damaged by UV radiation.[412] The correlation between psoriasis and impaired intestinal barrier function has been established by researchers, and probiotics have been shown to provide a protective effect on the intestinal barrier. Therefore, regular probiotic supplementation is a cost-effective and safe method to improve skin health.[413]

In a study conducted by Chen et al., it was found that administering Lactobacillus pentosus GMNL-77, a potential probiotic strain, orally to mice treated with imiquimod resulted in a significant reduction in erythaematous scaling lesions. The treatment led to decreased levels of tumor necrosis factor-alpha (TNF-a), interleukin (IL)-6, and cytokines associated with the IL-23/IL-17A axis (IL-23, IL-17A/F, and IL-22) in the skin, along with a reduction in IL-17- and IL-22-producing CD4C T cells in the spleen. The protective effect of the ethanol extract (SEL001) obtained from Lactobacillus sakei proBio-65, a potent probiotic strain, was observed in a mouse model with psoriasis-like skin inflammation induced by imiquimod. The extract led to decreased gene expression levels of IL-19, IL-17A, and IL-23 in the affected skin.[414] As a result of Lactobacillus sporogenes supplementation three times a day, clinical improvement was observed after two weeks of initiation in a case of severe pustular psoriasis that had not responded to steroids, dapathon, and methotrexate, and almost complete resolution was observed at four weeks (Sikora M, 2019). In a separate placebo-controlled investigation focusing on psoriasis patients, the intake of Bifidobacterium infantis 35624 resulted in significant reductions in TNF a, IL-6, and C-reactive protein (CRP) levels in the group receiving the probiotic treatment. While the exact mechanism behind the decrease in T-cell activity was not fully understood, the authors postulated that this effect might be mediated by the inhibition of CD103+ dendritic cells. These specialized cells act as antigen-presenting cells in the

gastrointestinal (GI) tract and are involved in modulating the function of regulatory T cells.[406] Moreover, a placebo-controlled study conducted on psoriasis patients demonstrated that administration of Bifidobacterium infantis 35624 supplements resulted in a notable reduction in TNF-α levels compared to the placebo group. By orally administering poly-γ-glutamate, a naturally occurring substance produced by certain Gram-positive bacteria like Staphylococcus and Bacillus species, the AD-like dermatitis in Nc/Nga mice was improved. This improvement was achieved by suppressing the Th2-biased immune response and the production of IL-17A. Consequently, poly-γ-glutamate may hold promise as a beneficial prebiotic treatment for targeting hyperactive Th17 cells associated with psoriasis.[415] The consumption of orally supplemented milk fermented with Lactobacillus casei or the administration of L. casei alone has been found to reduce skin inflammation by regulating the population of cytotoxic CD8C T cells.[374] Further research indicated that the administration of Lactobacillus casei DN-114 001 effectively mitigated T cell-mediated skin inflammation by influencing the activity of cytotoxic CD8C T cells and the participation of CD4C Treg cells.[389] The therapeutic potential of Lactobacillus paracasei CNCM-I 2116 (ST11) in mitigating skin inflammation has been demonstrated in vitro, where it effectively prevents the release of TNF-a, mast cell degranulation, vasodilation, and edema, leading to improved barrier function recovery.[375] The available data on the use of probiotics in the treatment of psoriasis is limited. However, there are overlapping genetic and environmental factors and immune pathways shared between psoriasis and obesity. Th17 cells and the cytokines they produce play a crucial role in both psoriasis progression and the pathophysiology of obesity. Considering the effectiveness of probiotics in managing obesity, there is a possibility that they may also prove beneficial in the treatment of psoriasis. Obese individuals exhibit a less diverse gut microbiota compared to non-obese individuals, showing a decline in Gram-negative bacteria, particularly those from the

Bacteroidetes family, and an elevation in Gram-positive Firmicutes. These microbial alterations are also evident in people with psoriasis.[416,417] Several specific strains of Lactobacillus, including L. casei strain Shirota (LAB13), L. gasseri, L. rhamnosus, and L. plantarum, along with Bifidobacterium species like B. infantis, B. longum, and B. breve B3, have demonstrated anti-obesogenic effects in animals. Additionally, microorganisms like Pediococcus pentosaceus LP28, Bacteroides uniformis CECT 7771, Akkermansia muciniphila, and Saccharomyces boulardii Biocodex have also shown similar properties.[418–423] The effects of L. casei and B. infantis strains have been validated among these. The long-term impacts of probiotics, whether used as dietary supplements or adjunctive therapy, remain unverified. Consequently, a thorough evaluation of the safety of these bacteria is essential before their application in the treatment of diverse ailments. Moreover, particular gut microbes have the capacity to recruit regulatory T cells and lymphocytes, promoting an anti-inflammatory reaction through the generation of specific metabolites like retinoic acid and polysaccharide A.[170]

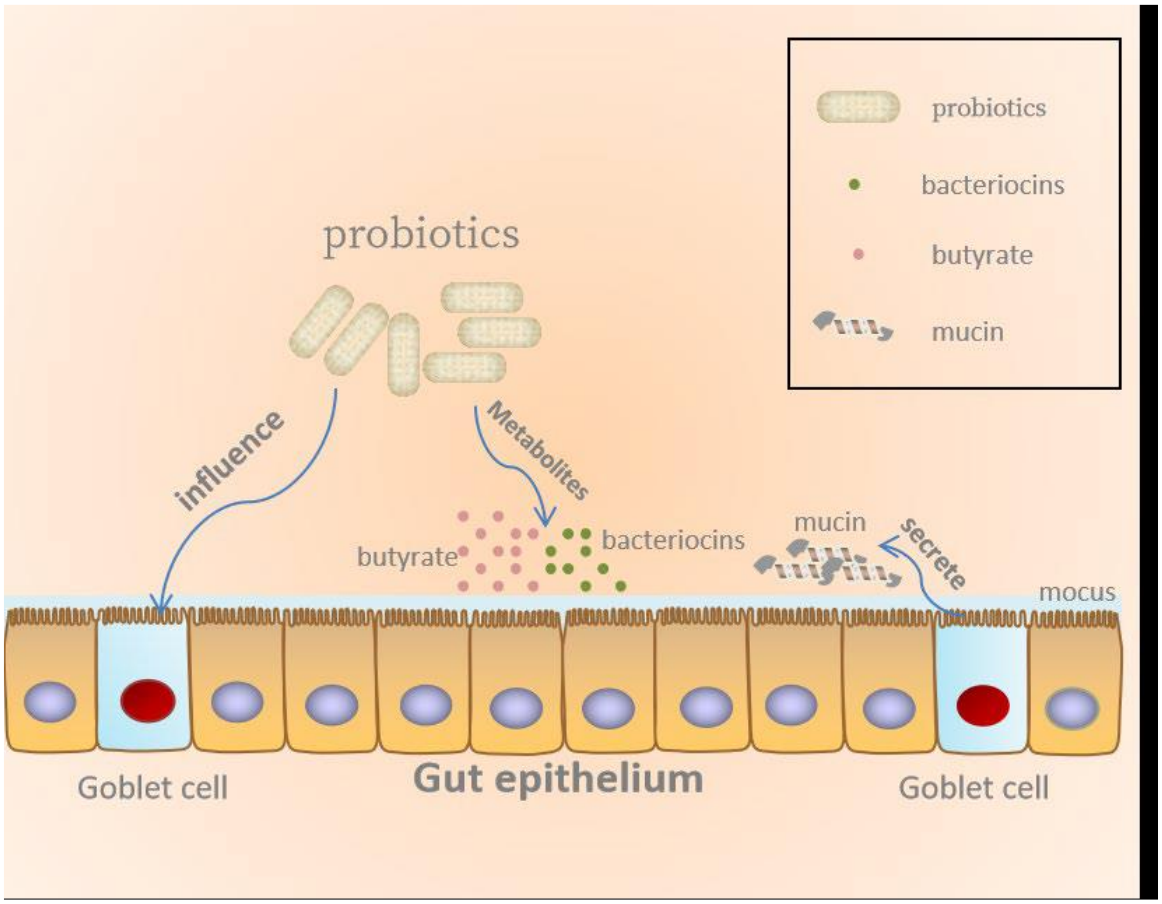

Fig. 4.3 Probiotics maintain gut epithelial barrier [424]

Chapter V

Discussion

Psoriasis is a chronic inflammatory skin disease that affects millions of people worldwide. The etiology of psoriasis is complex and multifactorial. The combination of immunological, genetic, and environmental factors (mainly emotional stress, smoking habits, lifestyle, diet, physical activity, and infections) plays a key role in its etiology. Recent research has shown that the gut-skin axis may play a role in the pathogenesis of psoriasis. The gut-skin axis refers to the bidirectional relationship between the gut microbiome and skin health, which is regulated through several mechanisms such as inflammatory mediators and the immune system. The gut microbiota, a diverse community of microorganisms residing in the GI tract, heavily influences gut function, immune function, and nutrient absorption. The exact mechanisms of influencing skin by intestinal microorganisms are yet to be elucidated. However, research suggests that catabolic products of diet and microbial compounds can impact the gut epithelium by altering gut physiology, leading to a variety of secretory products that circulate throughout the body and enter the skin. Besides acting through the immune system, microbial compounds can also impact the skin by altering the skin barrier function and modulating the skin's immune response.

Another line of research having many promising prospects on the gut-skin axis is dietary supplements promoting the health of the gut microbiome, including pre and probiotics. Research in this area has been massively studied in the past due to many beneficial health effects of fermented foods. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Probiotics can modulate the gut microbiota by increasing the abundance of beneficial microorganisms and decreasing the abundance of harmful ones. They can also increase the production of short-chain fatty acids, which are negatively correlated with the levels of inflammatory cytokines. The use of probiotics can improve gut health by reducing inflammation, improving gut barrier function, and enhancing immune function.

In recent years, the use of probiotics as an adjuvant therapy in the treatment of chronic inflammatory diseases, including psoriasis, has been gaining importance. Preliminary experiments have found that oral consumption of probiotics improves the clinical symptoms in patients with psoriasis, perhaps correlated with the gut microbiome-mediated crosstalk between the immune system and the nervous system by secreting neurotransmitters in Psoriasis.

Future research should focus on elucidating the mechanisms of influence of the gut microbiome on skin health and the development of skin diseases, investigating the role of dietary supplements and probiotics in modulating the gut microbiome and their effects on skin health. Also, further research is needed to determine the proper selection of probiotic strains, their prebiotic counterparts, and delivery systems to avoid suppression of their synergistic or complementary effect on human health. Clinical trials with both topical and oral probiotics are scarce, although they have shown positive results, especially with oral probiotics through the modulation of the intestinal microbiota, generating an anti-inflammatory response and restoring intestinal integrity, or through metabolic pathways.

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