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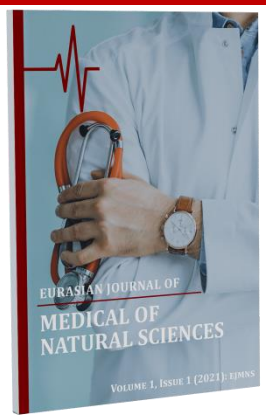

ADVANCES IN THE HUMAN SKIN MICROBIOTA AND ITS ROLES IN CUTANEOUS DISEASES

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ABSTRACT

The skin, the body's largest organ, is influenced by environmental factors and is susceptible to various diseases, including acne, psoriasis, and atopic dermatitis. Serving as the primary barrier against pathogens, the skin's health is intricately linked to its microbiota. Despite the challenging conditions it presents, the human skin hosts a diverse array of commensal microorganisms that contribute to its overall environment. Imbalances and dysbiosis in the skin microbiota can lead to the onset or exacerbation of skin diseases. This review explores recent advancements in our understanding of the skin microbiota and its interactions with the human skin. Additionally, it examines the potential roles of specific microbial species in skin health and disease. The review delves into various strategies for preventing, diagnosing, and treating microbe-related skin conditions, such as adopting healthy diets, lifestyles, and the use of probiotics and prebiotics. Furthermore, it discusses the potential of synthetic biology to modulate the skin microbiota, offering opportunities to optimize interactions between microbes and the skin. Ultimately, this review sheds light on the recovery of the human skin microbiota, its connection to skin diseases, and innovative strategies for engineering or reconstructing it.

Introduction

The human skin, serving as the body's largest and most exposed organ, acts as a physical barrier against pathogens from the environment while also providing an extensive ecological niche for a wide array of microorganisms. Despite the stringent biochemical conditions of the skin, such as low pH, high salinity, dryness, and constant exposure to environmental factors, numerous microbial species successfully inhabit it, including bacteria, fungi, and viruses, notably bacteriophages. The composition of the human skin microbiome is influenced by

genetics, environmental factors, and local microenvironmental conditions, resulting in variations across different body regions and among individuals of different races, ages, sexes, and health statuses. Skin microbiomes constitute diverse ecosystems of microorganisms that interact with host epithelial and immune cells, as well as with other microorganisms sharing the same habitat. Typically, these interactions between the skin microbiome and hosts are mutually beneficial, with hosts providing a "home" and nutrients for the microbiome while the microbiome protects hosts against pathogen invasion and modulates the immune system. However, perturbations in the human skin microbiome can lead to pathogenic outcomes closely tied to host homeostasis.

Certain skin diseases, such as acne vulgaris, psoriasis, atopic dermatitis, and chronic wounds (see Table 1), have been linked to pathogens. However, our understanding of the causal relationships between these diseases and specific species of the human microbiota remains limited. With the advent of sequencing technologies, particularly next-generation sequencing techniques and long-read sequencing technologies, identification of pathogens within the human microbiota has become feasible. In many cases, species-level information alone is insufficient to discern pathogenic strains; instead, strain-level resolution is necessary. For instance, certain strains of Staphylococcus epidermidis and Cutibacterium acnes (formerly Propionibacterium acnes) contribute to acne and other skin diseases, while others aid in promoting skin health by inhibiting pathogen growth and invasion. Insights into the molecular and immunological mechanisms governing microbiome-host interactions are crucial based on identified microbes and their microbiological pathogenesis.

Table 1

Skin microbiome and associated diseases

Disease type	**Key Points**	**Major findings**	**References**
Acne vulgaris	*P. acnes*	Although the relative abundances of *P. acnes* were similar, certain strains were highly associated with acne and healthy skin	Sorel Fitz-Gibbon et al.
	S. epidermidis	*S. epidermidis* mediates fermentation to inhibit the growth of *P. acnes,* which can be implications of probiotics in acne vulgaris	Yanhan Wang et al.
	S. epidermidis & *P. acnes*	*S. epidermidis* and *P. acnes* are thought to contribute to the disease, but they are also known to promote health by inhibiting the growth and invasion of pathogens	Alan M. O'Neill et al.
	Dysbiosis & Balance	The mere presence of disease-associated strains, as well as the balance between metagenomic elements shapes the overall virulence property of the skin microbiota. Dysbiosis is the process leading to a disturbed skin barrier and disequilibrium of the cutaneous microbiome	Emma Barnard et al. B. Dreno , Chun-xi LI et al.
	Androgen hormone activity	Increases sebum production inside the pilosebaceous follicle, adjusting the environment for *P. acnes* which triggers inflammation	M. A. Rocha et al.
Psoriasis	Diversity & Stability	Psoriasis induces physiological changes both at the lesion site and at the systemic lever, with increased diversity and reduced stability compared to the healthy skin microbiome	Alexander V Alekseyenko et al, Daniel J. Lewis et al.

	Skin microbiome	Increased abundance of *Corynebacterium, Staphylococcus*, and *Streptococcus*, and decreased abundance of *Malassezia, Propionibacterium, Cutibacterium* genera versus controls	Di Yan et al. , Hsin-Wen Chang et al.
	Gut microbiome	The gut microbiome composition in psoriasis patients has been altered markedly, and the ratio of *Firmicutes* and *Bacteroidetes* was perturbed in psoriatic individuals compared to healthy controls	Xinyue Zhang et al. , Di Yan et al.
Atopic dermatitis	*S. aureus*	AD has long been associated with *S. aureus* skin colonization or infection, and increases in *Streptococcus, Propionibacterium*, and *Corynebacterium* species were observed following therapy	Heidi H. Kong et al., Tetsuro Kobayashi et al.
Chronic wound	*S. aureus* & *P. aeruginosa*	*S. aureus* and *Pseudomonas aeruginosa* are the most common bacteria isolated from chronic wounds	Raffaele Serra et al.
Skin and soft tissue infection	*Cutibacterium acne*	*C. acnes* has the potential to directly and indirectly cause inflammation and tissue damage	Laurice Floweis et al.

In the coming years, the approach to treating skin diseases should extend beyond the conventional methods of antibiotics, topical corticosteroids, and laser therapy. Instead, there should be a consideration for modulating the human skin and gut microbiota through healthy dietary interventions and other innovative strategies. Just as fecal microbiota transplantation has been utilized to regulate gut microbiota, combinations of probiotics, skin microbiota transplantation, and emerging techniques offer promising avenues for treating skin ailments. The construction of synthetic microbiota with specific and controllable attributes has been employed to study the fundamental principles governing skin microbial interactions and dynamics. The engineering and reconstruction of skin microbiota hold considerable potential as a formidable approach for addressing skin diseases in the future.

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Interactions Between Microbiota and the Human Skin

The surface area of human skin tissue spans approximately 1.8 m2, housing over 1010 microbes in conjunction with hair follicles, sebaceous glands, and other associated appendages, equating to around 1 million microbes per 1 cm2. Based on predominant conditions and microbiota composition, human skin can be categorized into four distinct environments: dry,

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moist, sebaceous (oily), and foot (see Fig. 1). The diversity and abundance of skin microbiota vary significantly between states of health and disease. Numerous skin ailments have been linked to dysbiosis and imbalance in the skin microbiome. Certain microbial strains and their key metabolites may serve as biomarkers for diagnosing or targeting therapies for skin diseases. Investigating the interactions between microbiota and human skin, including the microbiota of healthy skin, as well as factors disrupting the skin microbiota, and the roles of microorganisms in skin wound healing, represents an area of significant interest.

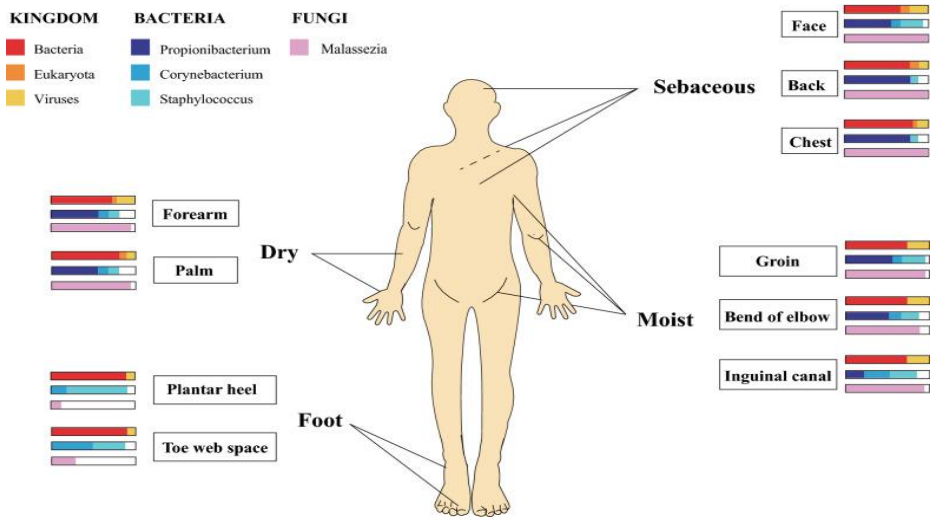

Fig. 1

Distribution of microorganisms in human skin. Human skin area can be divided into four microenvironments, including dry (forearm and palm), sebaceous (face, back and chest), moist (groin, bend of elbow, and inguinal canal) and foot (plantar heel and toe web space). The relative abundance of viral, bacterial, and fungal components of corresponding skin microbiota are indicated. Bar charts represent relative abundance of microorganism distributed in the human skin, and the white spare in the bar charts represents other bacterial or fungal categories except the described microbes in the bar chart. The front of the human body is shown

Skin Microbiota Colonization and Dynamics

The skin harbors a diverse array of microorganisms, including bacteria, eukaryotes, and viruses, with their distribution heavily influenced by environmental conditions on the skin surface (see Fig. 1). Generally, individuals without skin diseases exhibit similar compositions of skin microbiota. Bacteria reign supreme at the kingdom level, with Propionibacterium, Corynebacterium, and Staphylococcus emerging as the most predominant genera in the skin microbiota, each playing beneficial roles in human health. Sebaceous sites, owing to the secretion of lipid-rich sebum by sebaceous glands, are predominantly inhabited by P. acnes and other lipophilic Propionibacterium species. Conversely, moist areas are enriched with Staphylococcus, Corynebacterium, and other species that thrive in humid environments. Among fungi, Malassezia species dominate core-body and arm sites, while foot sites, prone to fungal infections, harbor complex fungal communities comprising Malassezia, Aspergillus, Cryptococcus, Rhodotorula, Epicoccum, and other species.

Similar to the gut microbiome, the skin microbiome is a dynamic entity. Whereas the human gut microbiota typically stabilizes into an adult-like profile by the age of three, with notable transient fluctuations, the skin microbiota undergoes two significant transitional

phases. The first phase is primarily influenced by the mode of delivery at birth. Babies delivered vaginally exhibit earlier maturation of skin microbiota compared to those delivered via cesarean section. Specifically, babies born via cesarean section tend to have lower alpha diversity in their skin microbiota, with elevated levels of Propionibacterium and Streptococcus species, while babies born vaginally harbor higher levels of Lactobacillus species, likely acquired from the mother's birth canal. Following birth, the skin environment experiences dynamic changes in structure and function, including alterations in pH, water content, trans-epidermal water loss, and sebum production, all of which may influence the development of the skin microbiota. The second significant transition occurs during adolescence, characterized by exuberant sebum secretion, fostering the extensive proliferation of lipophilic bacteria in the skin microbiota.

Following these developmental phases, healthy adults maintain a dynamic equilibrium within their skin microbiota, despite continual exposure to environmental factors and other individuals. Indeed, the skin microbiota undergoes subtle fluctuations during daily life, driven by changes in host biology and exposure to diverse environments. Personal care products can elicit highly individualized responses in the skin microbiome, altering steroid and pheromone levels and modifying the structure of bacterial and archaeal communities. Many skincare products incorporate antimicrobial plant-derived extracts, which may exert selective pressure, leading to the enrichment of resistant strains.

Interactions between Healthy Skin and Microbiota

The skin comprises the surface, epidermis, and dermis (see Fig. 2). A multitude of microorganisms, both resident and transient, inhabit the skin's surface, utilizing cell debris, sebum, and mineral salts found in sweat as sources of nutrients. In comparison to the gut environment, the skin poses greater challenges for environmental microorganisms to colonize. Additionally, various potential antibacterial agents, including natural antibiotics produced by pioneering microorganisms, as well as free fatty acids and antimicrobial peptides (AMPs) secreted by symbiotic microorganisms, contribute to the skin's protective barrier. Staphylococcus strains predominantly populate the skin surface, demonstrating tolerance to high salt concentrations and often utilizing components of sweat as nutrients. Certain strains of Staphylococcus have evolved mechanisms to establish mutualistic relationships with the host. On the skin surface, hairs emerge from pores originating from hair follicles, with sebaceous glands located at the base of each follicle, providing lubrication. Lipids secreted by sebaceous glands can act as a nutrient source for microbial growth. The hair follicle and sebaceous gland create a relatively anaerobic environment conducive to the colonization of anaerobic microbes. Deeper skin layers typically harbor a host indigenous microbiome characterized by a lower abundance of microorganisms.

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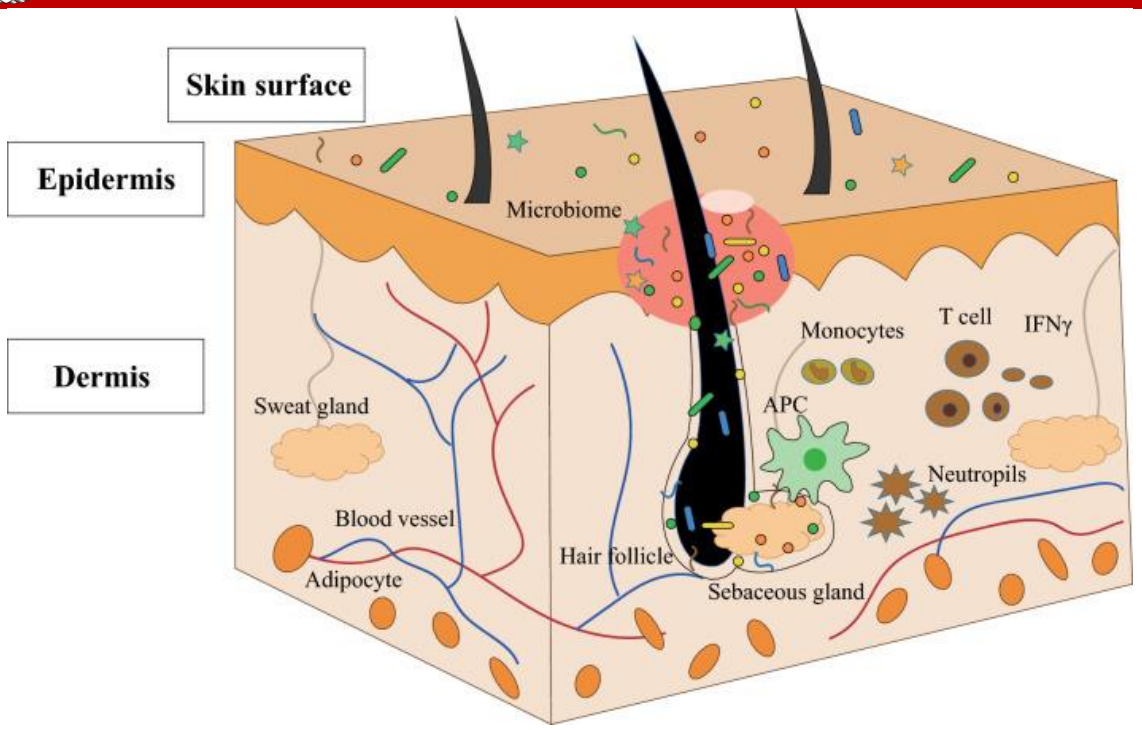

Fig. 2

Skin structure and pathogenesis of acne. The skin structure consists of epidermis and dermis. On the skin surface, there are many hair pores, and numerous microorganisms attached. Deep in the dermis, the structure is complex, and it is composed of blood vessels, sweat glands, sebaceous glands, adipocytes, hair follicles, and immune cells. The antigen-presenting cells (APC) identify the abnormalities of attached microbes and secrete lipids, presenting a signal to the T lymphocytes (T cell), which leads to the secretion of inflammatory cytokines, such as INF γ. This leads to eradication of microorganisms by recruited neutrophil and monocytes, but contributes to the redness and formation of acne in the epidermis.

The array of microbial species present in skin environments plays multifaceted roles, including promoting immune tolerance, eliciting pro-inflammatory responses, and contributing to overall skin health. Concurrently, the host provides nutrients to these microbes, thereby influencing the composition of the microbiota. S. epidermidis serves as a prime example of the intricate relationship between microbiota and the host. Commonly found on healthy human skin, S. epidermidis is generally considered benign. Certain strains of S. epidermidis exert protective effects through the secretion of specific chemicals, while also playing a role in promoting wound healing, bolstering skin immunity, and inhibiting pathogen colonization. This symbiotic interaction between microbiota and the host contributes significantly to the stability of the microbiota and the integrity of the skin. Other species such as Roseomonas mucosa and Malassezia species have the capacity to modulate keratinocytes and host immune responses in an environment-dependent manner. P. acnes, an anaerobic bacterium, stands out as one of the most prevalent and vital symbiotic bacteria on human skin. P. acnes metabolizes sebum secretions into fatty acids for sustenance and aids in maintaining the skin's acidic pH, creating a favorable environment for specific microorganisms. The skin microbiota represents a complex network of interactions among various microorganisms and with our skin. Therefore, comprehending and preserving the delicate equilibrium between the skin and its microbiota

are crucial steps in gaining insights into the mechanisms responsible for maintaining healthy skin.

Roles of Skin Microbiota in Acne

Acne vulgaris, a chronic inflammatory skin condition, predominantly affects teenagers, with approximately 85% of young individuals experiencing its effects, of which 15–20% suffer from severe cases. Besides causing permanent scarring, acne obstructs and damages hair follicles, manifesting as pimples, pustules, and nodular cystic lesions due to bacterial infiltration into the follicles. The presence of acne significantly impacts both the physical and psychological well-being of teenagers, leading to various discomforts and feelings of inadequacy. Typically, excessive sebum production from sebaceous glands, colonization by P. acnes, and alterations in follicular keratinocytes are considered the three primary contributors to acne development. Initially, overproduction of sebum obstructs hair follicles, creating a relatively enclosed and anaerobic environment conducive to inflammation, thereby facilitating the proliferation of P. acnes. Increased levels of androgen and sebum further foster the growth of P. acnes within hair follicles. Additionally, certain Malassezia species have also been implicated in refractory acne cases.

S. epidermidis, often considered a beneficial skin bacterium, can engage in glycerol fermentation, producing short-chain fatty acids (SCFAs) with antimicrobial properties that suppress P. acnes growth. The incidence of acne has been linked to dysbiosis of the skin microbiota, particularly an imbalance between P. acnes and S. epidermidis. The microbiota composition of acne lesions varies across different body zones, and omics technologies have identified specific strains of P. acnes and S. epidermidis associated with acne development in the skin cuticle. Consequently, certain S. epidermidis strains and other microbiota strains present in acne lesions hold potential as biomarkers for predicting and targeting acne development, aiding in precise diagnosis and treatment. While patients with grade 1–3 acne share similar skin microbiomes, those with grade 4 acne exhibit significant differences, including increased alpha diversity and a higher prevalence of Gram-negative bacteria.

Understanding the pathophysiology of acne remains limited, with host-microbiome interactions playing a pivotal role in immune homeostasis, affecting both innate and adaptive immunity. Additionally, acne is influenced by immune-mediated mechanisms, as well as genetic, dietary, and hygiene factors. Presently, antibiotics are commonly employed to curb P. acnes growth. However, given the escalating concern of antibiotic resistance in clinical practice, it is imperative to delve into the skin microbiome's association with acne and explore alternative treatment strategies.

Roles of Skin Microbiota in Psoriasis, Atopic Dermatitis, Rosacea, and Other Skin Diseases

Psoriasis stands as a prevalent dermatological condition with a multifaceted etiology encompassing genetic and non-genetic factors such as diet, medication, smoking, infections, and psychological stress. Its pathogenesis is believed to be driven by interactions among innate and adaptive immune cells and keratinocytes, mediated by cytokines such as interleukins IL-6, IL-17, and IL-22, interferon, and tumor necrosis factor, along with other signaling molecules. Patients with psoriasis often exhibit significant dysbiosis in both skin and gut microbiota, characterized by reduced alpha diversity in affected skin areas. Notably, psoriasis-affected skin

microbiota mirrors that of adjacent skin, with psoriatic lesions associated with increased Firmicutes, Bacteroidetes, and Streptococcus, and decreased Actinobacteria and Propionibacterium. Xanthomonadaceae, classified under Proteobacteria and known for its keratolytic properties, has been linked to clinical improvement following balneotherapy treatment. Furthermore, orally administered probiotics demonstrate positive effects on psoriasis progression, suggesting the potential for developing molecular signatures for psoriasis diagnosis from skin microbiome data. Strain-level analyses reveal psoriatic niche-specific strain adaptations or selections, indicating strain heterogeneity colonization and functional variability associated with psoriasis .

Atopic dermatitis (AD), on the other hand, involves various interconnected factors, with the impaired barrier function of AD patients' skin differing significantly from healthy skin. Dysbiosis of the skin microbiota is linked to increased colonization by pathogens and a reduction in beneficial commensals. Although the role of dysbiosis in AD pathogenesis remains unclear, AD patients typically exhibit low-diversity skin microbiota, with a prevalence of S. aureus. In some cases, S. aureus overgrowth precedes AD development, warranting further investigation into the association between Staphylococci abundance and AD symptoms.

Rosacea's relationship with skin microbiota has not been extensively explored, as research has primarily focused on Demodex mites. However, antibiotics, while effective in treating most rosacea patients, have no impact on Demodex, suggesting the potential involvement of microbes as significant pathogenic factors. Systemic antibiotics are commonly used to control rosacea-associated pustules and papules, with the comparison of skin microbiota before and after oral antibiotic intake revealing that naturally occurring S. aureus and Corynebacterium bovis colonization exacerbates inflammation in eczematous dermatitis.

The Host Barrier and Microbial Infection

An intact skin barrier typically presents a formidable challenge for pathogens seeking invasion. Chronic leg ulcers and various other persistent wounds affect approximately 1–2% of the population, leading to heightened morbidity and healthcare costs. The skin microbiota, particularly specific pathogens, significantly contribute to microbial infections in chronic wounds. While S. aureus often serves as the culprit in atopic dermatitis (AD), it also functions as a commensal in the skin microbiome on other occasions. Given its possession of antibiotic resistance genes, S. aureus can instigate severe skin and soft tissue infections. Moreover, S. aureus strains exhibit high diversity, with different patients potentially colonized by distinct strains. In a diabetic foot ulcer cohort study, non-healing wounds showed significant enrichment of S. aureus, with certain strains correlating with elevated morbidity. R. mucosa, via the promotion of IL-6 production, inhibited S. aureus growth in murine models and human skin, underscoring the potential for identifying novel strains within the skin microbiome for the amelioration of dermatological diseases.

S. aureus and P. aeruginosa stand out as the most commonly isolated bacteria from chronic wounds. They possess surface proteins and virulence factors capable of hindering and delaying wound healing. Co-infection with S. aureus and P. aeruginosa typically results in heightened virulence compared to single infections. S. aureus strains have been observed to compromise the skin barrier and trigger detrimental host immune responses. Dysbiosis of the human skin microbiota has been implicated in immune dysregulation, subsequently

precipitating an inflammatory response. Thus, the human skin microbiota plays a pivotal role in shaping clinical manifestations.

The Gut-Brain-Skin Axis

The gut microbiome exerts influence over distant organ systems, including the skin. This interconnectedness between the gut microbiome and distant organs is conceptualized through various axes such as the gut-brain axis, gut-lung axis, gut-skin axis, and other gut-X axes. Notably, the skin and gut barriers exhibit remarkable similarity and share numerous features. Both the gut and skin surfaces are lined with epithelial cells (ECs) and come into direct contact with the external environment. Despite their high cellular turnover rate, the gut and skin present formidable challenges for microbial adherence and infection. The association between the skin and gut is largely mediated by the host immune system, with allergic food ingredients typically compromising the intestinal barrier and triggering food allergies, which may manifest as gut and skin symptoms.

A bidirectional link exists between gut and skin dysbiosis, with gut microbiota dysbiosis often responding to the pathophysiology of various inflammatory skin conditions. Notably, the gut microbiota composition in psoriasis patients differs significantly from that of healthy individuals, with variations observed in the Firmicutes and Bacteroidetes ratios [17, 19]. Exposure of the skin to ultraviolet B light (UVB) indirectly enhances serum vitamin D levels, correlating with increased alpha and beta diversities of the Proteobacteria phylum in the gut microbiota. Additionally, gastrointestinal disorders are frequently associated with certain dermatoses, with 7–11% of patients with inflammatory bowel disease (IBD) also suffering from psoriasis. Strategies aimed at augmenting or repairing a leaky gut barrier are often employed as adjuvant therapies in the treatment of inflammatory skin diseases, thereby enhancing the efficacy of standard dermatotherapy.

In the future, treatment strategies for skin diseases utilizing the gut microbiota may involve modulating the gut microbiota through dietary agents or selected natural/synthetic microbiota. The gut-skin axis is proposed as an integral component of the broader gut-brain-skin axis. For instance, chronic wound conditions and depression share common pathological features, including altered microbiome composition and dysregulated inflammation. Viewing the intestine and skin as part of a single system, the gut-skin axis could offer novel avenues for treating skin diseases. Traditional Chinese medicine (TCM) has accumulated clinical experience in modulating the intestinal tract and treating skin diseases. However, evidence supporting the gut-skin axis is primarily based on limited cohort studies, and a comprehensive multi-systematic study involving a large cohort would provide deeper insights into the relationships between skin and gut microbiota. Adopting this approach to study the gut-skin axis could unveil the mechanisms underlying the efficacy of TCM in treating skin diseases.

Approaches to Treating Skin Diseases

Imbalances in microbiota and the presence of specific strains can instigate or exacerbate various skin conditions. Numerous lifestyle factors are intertwined with skin health (Fig. 3). Engaging in regular exercise is conducive to maintaining healthy skin. While consistent physical activity can shield the skin from free radicals, intense or prolonged exercise, or a sedentary lifestyle, may induce oxidative stress and potentially contribute to skin carcinogenesis. Residing in polluted environments can diminish skin moisture levels, elevate sebum excretion rates, and

exacerbate symptoms of chronic inflammatory skin disorders. The "hygiene hypothesis" posits that insufficient exposure to a diverse array of microbiota during childhood may hamper the immune system's development. This deficiency could potentially reduce resistance to microbial pathogens and heighten susceptibility to infections and other maladies. Conditions like atopic dermatitis (AD) and other skin atopic diseases may be linked to an excessively sterile (abiotic) environment.

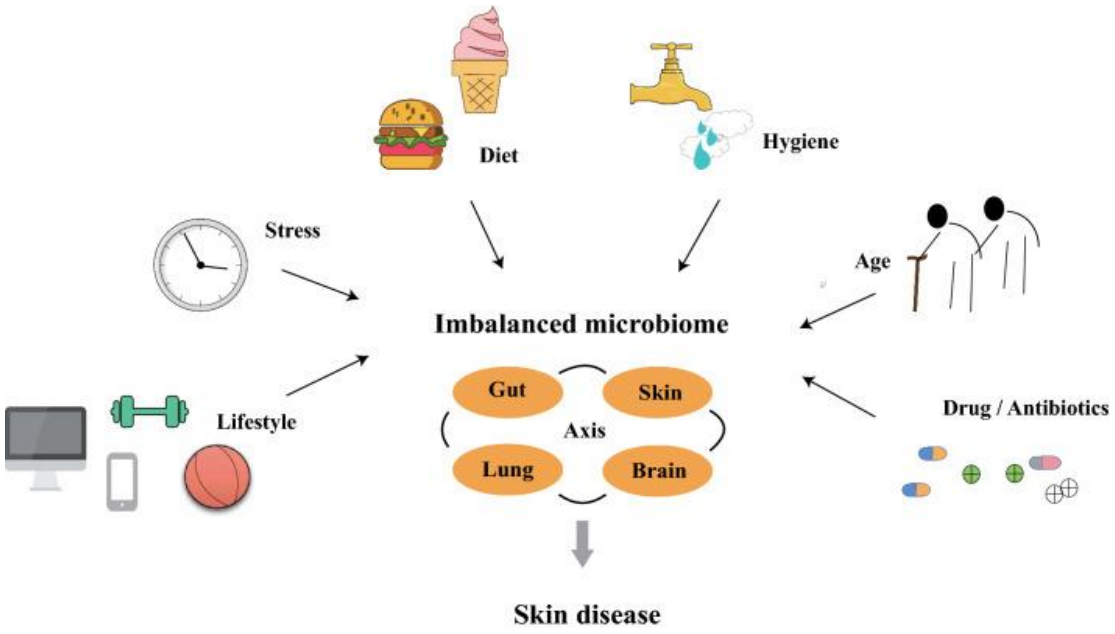

Fig. 3

Factors associated with skin diseases. Lifestyle, stress, diet, hygiene, age, and drug (antibiotics) application are closely related to skin diseases through the links between gut, skin, lung and brain axis

Conventional Approaches to Treating Acne and Other Skin Disorders

For over four decades, the prevalent treatment modality for inflammatory or mixed acne has involved the topical application of antibiotics. These antibiotics not only exhibit antimicrobial properties targeting P. acnes but also exert anti-inflammatory effects by modulating host immune responses. Topical ofloxacin, with its potent antimicrobial activity against Propionibacterium and Staphylococci strains isolated from acne patients, stands out as an effective therapeutic agent for acne vulgaris. Leveraging their anti-inflammatory properties, topical retinoids have demonstrated efficacy in addressing inflammatory lesions. Various treatment guidelines and expert consensus documents advocate for macrolides, clindamycin, and tetracyclines as the first-line therapy drugs during the acute inflammatory phase of acne.

In contemporary medical practice, nucleic acids (NAs) have emerged as pivotal agents in treating diverse diseases. Utilizing topical NAs or NAs-based drug delivery offers distinct advantages in treating skin disorders, facilitating efficient NA transfer and targeted delivery to affected skin sites. A plethora of NA-based therapeutics, encompassing genes, siRNA, aptamers, antisense oligodeoxynucleotides (ODNs), and CpG oligonucleotides, have been employed for disease management. Transdermal drug delivery systems (TDDS) have garnered significant attention, leveraging advantages such as specialized tissue targeting, enhanced drug release, avoidance of presystemic metabolism, high patient tolerance, and reduced hepatotoxicity.

Presently, various nanoparticles and nanoemulsions are harnessed in TDDS for conditions like psoriasis, wound healing, melanoma, and other dermatological disorders.

Low-level laser (light) therapy (LLLT) has emerged as a rapidly evolving technology for treating ailments requiring pain and inflammation relief, functional restoration, or stimulation of healing processes. LLLT demonstrates positive outcomes in addressing wrinkles, acne scars, hypertrophic scars, burn healing, psoriasis, acne, and other inflammatory conditions. Moreover, LLLT can mitigate UV damage both as a treatment approach and prophylactic measure. Its non-invasive nature and minimal side-effects underscore its potential for further exploration and application in dermatological practice.

Healthy Dietary Habits and Lifestyles Influence Skin Microbiota

Contrary to prevailing beliefs that diet plays a minor role in acne development, an increasing number of self-reported cases suggest a link between adolescent acne and the regular consumption of milk and milk-containing products (such as instant breakfast drinks, cottage cheese, and cream cheese). Notably, the nonfat portion of milk appears to have a stronger association with acne compared to whole or low-fat milk. Skimmed milk, enriched with hormones and bioactive molecules, may exacerbate acne due to its content of androgens, progesterone, and insulin-like growth factor-1 (IGF-1). Western diets, characterized by their high glycemic load (HGL), have been implicated in chronically or acutely elevating IGF-1 and blood insulin levels, consequently increasing sebum production and the likelihood of acne development. Positive correlations have been observed between acne severity and the consumption of high glycemic load foods, prompting dermatologists to advise acne patients to limit their intake of high glycemic index foods.

Personal hygiene practices are closely intertwined with acne, with excessive washing potentially exacerbating the condition. Generally, washing twice daily is recommended as optimal. Studies conducted among young students have suggested a correlation between acne severity and stress levels during examination periods. Engaging in regular exercise, particularly high-intensity aerobic exercise for a duration of 4 hours per week, has been shown to reduce the thinning of the stratum corneum compared to sedentary controls engaging in only 1 hour per week of high-intensity aerobic exercise. Exercise has also been found to upregulate the expression level of Pgc-1, the master regulator of mitochondrial biogenesis, thereby potentially slowing down the aging of skin cells. Furthermore, vigorous exercise, notably calisthenics and aerobic exercise, has been independently associated with a reduced risk of psoriasis in women in the Uzbekistan. Consequently, adopting proper dietary habits, maintaining appropriate hygiene practices, moisturizing, and engaging in regular exercise should complement other therapeutic strategies in managing skin diseases.

Tailored Combination of Probiotics and Prebiotics

The initial wave of microbiota therapies introduced a blend of probiotics and prebiotics, meticulously crafted to sustain, rejuvenate, and optimize the skin microbiota through various mechanisms. Probiotics administered topically play a pivotal role in bolstering cutaneous immune responses and combatting pathogens by fortifying the skin's innate defense mechanisms or by generating antimicrobial peptides. Prebiotics, on the other hand, encompass non-digestible foods or metabolites that serve as substrates for gut bacteria. In cosmetic formulations, prebiotics are directly incorporated to foster the proliferation and vitality of

beneficial skin microbiota. Among prebiotics, plants, particularly traditional Chinese medicinal plants, offer a rich array of natural products conducive to skin microbiota health. Delving into traditional Chinese medicinal plants has unveiled a plethora of bioactive components; however, given the prolonged growth period of plants and the challenges in extracting bioactive natural products, engineered yeasts have emerged as efficient vehicles for their synthesis. Engineered yeasts have successfully synthesized various bioactive natural products derived from traditional Chinese medicinal plants, including ginsenosides, monoterpenoids, and glycyrrhetinic acids.

Drawing inspiration from the gut and skin microbiomes, novel probiotic and prebiotic formulations tailored for addressing diverse skin conditions are poised for development (Fig. 4A). Probiotics sourced from S. epidermidis exhibit potential in reinstating a harmoniously balanced microbiota and modulating the host's antimicrobial peptide (AMP) mediators. Coagulase-negative Staphylococci (CoNS) strains, abundantly present on the skin of healthy individuals but conspicuously lacking in those with atopic dermatitis (AD), showcase antimicrobial activity chiefly through the production of AMPs. Notably, the absence of CoNS strains in AD patients may pave the way for unchecked colonization by S. aureus. The strain-specific and potent nature of these AMPs enables selective eradication of S. aureus and synergistic action with human AMP LL-37

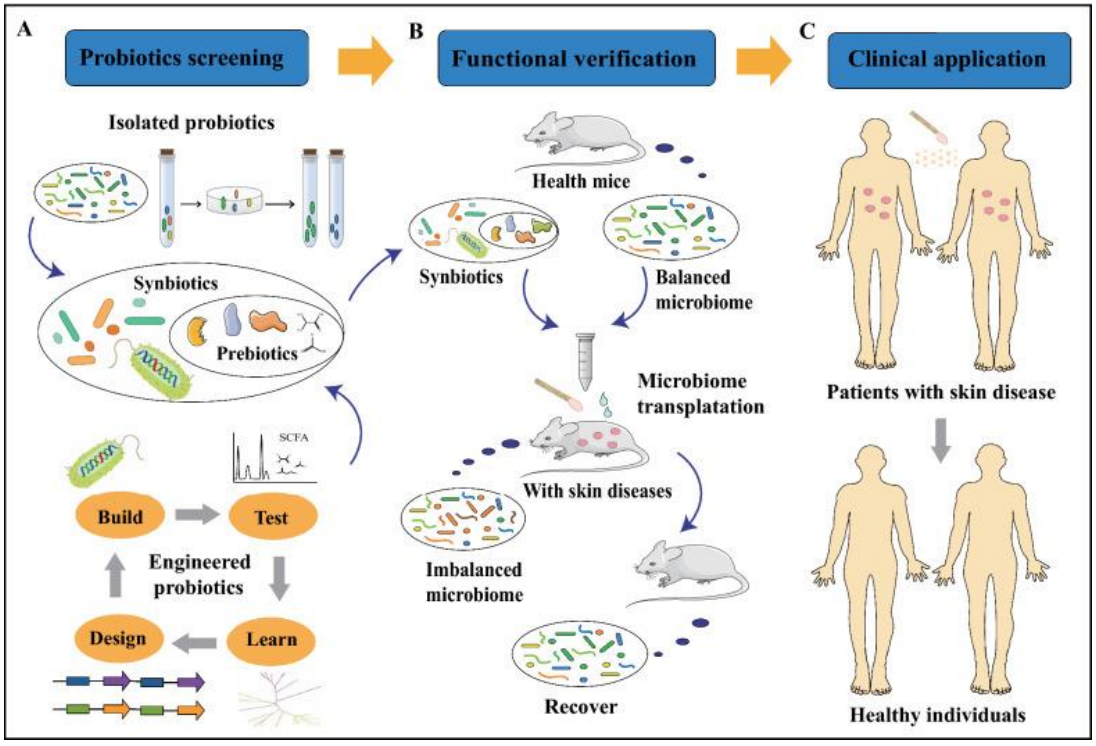

Fig. 4

Microbiome strategies used to modulate skin microbiome in a balanced state. **A** Methods to discover/build new probiotics, prebiotics and synbiotics. Isolating and identifying bacteria from healthy gut or skin microbiome to discover new probiotics would lead to discover of functional probiotics. Probiotics with beneficial functions to skin health can be engineered or built using synthetic biology strategies. Combination of these probiotics and functional prebiotics form synbiotics. **B** Functional verification of synbiotics and healthy microbiome in

vivo. Designed synbiotics (**A**) and balanced microbiome from the healthy mice to the mice with skin diseases can revert their imbalanced microbiome. **C** Microbiome transplantation to balance skin microbiota in clinical applications. Transplantation of healthy microbiome from healthy persons' skin as a whole or specifically isolated probiotics and engineered probiotics, can revert the imbalance.

Mixtures of various skin microorganisms in precise proportions have the capacity to alter the composition of the recipients' skin microbiomes. Following sequential applications of a donor microbiome, the recipients' microbiota gradually aligns with that of the donors, demonstrating the feasibility of using live bacteria to modulate skin microbiome composition (Fig. 4B). Furthermore, transferring probiotic solutions derived from facial skin microbes of healthy volunteers to the faces of acne patients has shown promise in improving skin health (Fig. 4C). The application of natural bacteria onto the skin not only enhances moisture retention and reduces skin pH but also lays the groundwork for developing probiotic solutions aimed at restoring diseased skin microbiota to a healthy state.

Manipulating the skin microbiota to augment the abundance of beneficial species may mitigate the presence of undesirable pathogens and directly promote skin health. Certain microorganisms within the skin microbiome exhibit the ability to curtail the colonization and proliferation of P. acnes through glycerol fermentation, creating inhibition zones. Clinical isolates of CoNS species inhabiting the normal skin microbiota produce autoinducing peptides that disrupt the quorum sensing system of S. aureus, thereby diminishing phenol-soluble modulin (PSM) expression and hindering biofilm attachment and regrowth. An example is a clinical isolate of S. hominis synthesizing an autoinducing peptide (SYNVCGGYF), a potent inhibitor of S. aureus Agr-mediated quorum sensing, which could mitigate S. aureus-mediated epithelial damage and inflammation on murine skin. While oral probiotic interventions have been explored for various diseases, the use of external skin commensals for treating skin diseases is scarcely reported. Further exploration of probiotic functions within the skin microbiota holds promise for future skin disease treatments. Synbiotics, comprising both prebiotics and probiotics, are poised to expand the therapeutic possibilities for effectively managing skin diseases (Fig. 4).

Engineering and reconstructing the skin microbiota through synthetic biology strategies offer avenues for elucidating the underlying roles of skin microbiota in disease development and for developing innovative diagnostic and therapeutic approaches for skin diseases. Various omics techniques such as metagenomics, metatranscriptomics, metaproteomics, and metabolomics provide comprehensive insights into the skin microbiota. Tools like biosensors, memory arrays, engineered bacteria, among others, can be employed to reconfigure the microbiome. The ability to swiftly sense stimuli in situ and promptly initiate precise therapeutic interventions could restore the dysbiosis of the skin microbiome and aid in curing skin diseases.

Despite advancements, significant gaps persist in our understanding of the relationship between the skin microbiota and skin diseases, and the practical application of probiotics in modulating the skin microbiota remains unrealized. Determining the optimal dosage and formulation of probiotics poses a challenge. Moreover, identifying skin probiotics is hindered by genetic variations among strains. Therefore, there is a need to develop engineered strains with desired beneficial functions, for which synthetic biology strategies offer gene-editing and

other tools for strain reprogramming (Fig. 4A). Engineered probiotics and the functional prebiotics they produce could be directly utilized for treating skin diseases. Gene-editing tools can be delivered via phages to eliminate specific pathogenic strains, illustrating the potential for future skin disease treatments based on targeted microbiota modulation. In summary, advanced synthetic biology facilitates novel approaches to design and reprogram multispecies microbiota, presenting an exciting opportunity to deliberately engineer or reconstruct the skin microbiota for the treatment of skin diseases.

Future perspectives and conclusion

The skin microbiota plays pivotal roles in the onset and progression of skin diseases, making modulation of the skin microbiota a promising strategy for treating such conditions. Currently, a range of microbiota modulation strategies are available, including prebiotics and probiotics. Some skincare products now incorporate herbal ingredients and other prebiotics to promote skin health. While oral probiotics are commonly used to enhance intestinal flora and alleviate digestive issues and intestinal inflammation, their application in modulating skin microbiota remains limited, largely due to the constrained understanding of skin microbiota.

Omics technologies offer valuable insights into the interplay between skin microbiota and skin diseases, facilitating the identification of microbial markers for diagnosing and treating skin conditions. It is imperative to uncover species-level and strain-level information regarding microbiota associated with various skin diseases. Clinical isolation of pathogenic strains and probiotics will aid in elucidating the causal links between skin microbiota and skin diseases.

In the future, real-time monitoring of skin microbiota at disease sites and identification of pathogenic strains will furnish crucial preliminary data for treating skin diseases. More refined treatment strategies, such as the incorporation of prebiotics and probiotics, as well as the engineering or reconstruction of synthetic microbiota with specific attributes, will be deployed in clinical settings. The envisioned treatment paradigm will involve recovering an individual's unique skin microbiota, isolating key pathogenic bacteria, unraveling pathogenic mechanisms, and developing effective prebiotic/probiotic agents tailored to combat specific pathogens. This strategy not only holds promise for alleviating the incidence and progression of skin diseases but also for enhancing appearance and promoting physical and mental well-being.

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