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REVIEW ARTICLE

# The Gut Microbiome: Human Health and Inflammatory Skin Diseases

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The human microbiome is a rich environment consisting of bacteria, fungi and other commensal microorganisms of the gut, mucosa and skin. The functional role of the gut microbiome includes facilitation in metabolism of macronutrients, maturation of the immune system, and production of pro- or anti-inflammatory signaling molecules and peptides. The identification of these resident organisms has brought about a new understanding of disease processes. Nevertheless, more questions remain regarding the interactions within the microbiome, its interactions with the host, and its contributions to the pathophysiology of disease. The purpose of this review is to examine the existing medical literature to highlight the role of the gut microbiome in human health, also paying attention to its role in several inflammatory skin diseases, namely atopic dermatitis, psoriasis, and rosacea. **(Ann Dermatol 32(4) 265～272, 2020)**

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## INTRODUCTION

Stokes and Pillsbury[1], who introduced the concept of "gut-brain-skin axis," first proposed the link between the gut microbiome and cutaneous disease in 1930. At the time, the authors theorized that bacterial products could impact the pathogenesis of various skin conditions. However, due to the technical limitations, these theories could not be tested adequately[1]. In 2007, the human microbiome project (HMP) was launched in an effort to examine the various microenvironments of the human body, characterizing resident bacteria of the oral cavity, skin, nostrils, vagina, and stool[2]. Newer techniques, such as 16S ribosomal RNA (16S rRNA) amplification[2] and metagenomic sequencing[3], have circumvented previous limitations. They differ by their scope of amplification and their depth of analysis. 16S rRNA amplification differentiates between bacterial species by focusing on variability within DNA sequences common to most bacteria leading to a more focused analysis[4]. Metagenomics, on the other hand, takes a broader "snapshot" of all genetic material available within a given bacterial microenvironment, leading to a more inclusive analysis that may not be limited to bacteria alone[5].

The HMP ultimately defined the "normal" human microbiome, supported by sampling multiple anatomic environments at various time points[2]. Although prevalence of each of these phyla depends on anatomic location[6], the study by Tap et al.[7] revealed that, generally, the most common gut microbiome phyla include Bacteroidetes and Firmicutes followed by Actinobacteria and Verrucomicrobia.

## THE ROLE OF THE GUT MICROBIOME IN OUR HEALTH

### Metabolism and obesity

The gut microbiome contributes to the basic metabolic needs of the host organism by aiding in macronutrient breakdown and homeostasis. This include catabolism of carbohydrates, proteins and fats, production of vitamins, synthesis of amino acids, and breakdown of toxins[8]. Differences in human metabolism, such as the efficiency of nutrient extraction, are largely determined by the diversity of the gut microbiome, which is shaped by diet[9].

De Filippo et al.[9] demonstrated that in children who were fed a "western" diet, there was a higher density of the phyla Firmicutes, when compared to Bacteroidetes, and an overall decrease in the diversity of the gut microbiome. Exploration of this difference, by Turnbaugh et al.[10], revealed that the gut microbiome of obese mice have a relative increase in Firmicutes and concomitant decrease in Bacteroidetes when compared to that of leaner mice. The microbiome of obese mice was also shown to be associated with a greater extraction of nutrients and calories[10]. Similarly, a study by Jumpertz et al.[11] demonstrated that increasing a dietary caloric load from baseline, while monitoring the diets of both lean and obese humans, led to an increase in Firmicutes over Bacteroidetes within the gut microbiome. Similar to results of the mouse model study, this shift was associated with a decreased caloric loss in the stool, shown by examining stool samples using 16S rRNA amplification for genetic profiling[11].

Interestingly, Turnbaugh et al.[12] showed that it is possible to transplant human fecal samples to germ free mice in order to replicate the microbial architecture of the human source and its modification with changes in diet. First, it was demonstrated that germ free mice could receive fresh or frozen fecal samples from human hosts and maintain a microbial profile similar to the source donor. Next, it was demonstrated that the microbiome of these humanized mice reacted to changes in diet with a high fat Western diet leading to increases in Firmicutes over Bacteroidetes, consistent with the observations above[12]. Third, it was demonstrated that these humanized mice consuming a westernized diet had increased adiposity, compared to those that received fecal samples from humans consuming a largely plant-based, low-fat diet[12].

In addition to changes in the composition of the gut microbiome, the decreased gut microbial diversity in an obese host can lead to a low-grade inflammatory state and symptoms consistent with metabolic disease[13]. In the mouse study, Cani et al.[13] observed that feeding mice a diet resembling the western diet led to decrease in the gut microbial diversity, as well as leakage of endotoxin, such as lipopolysaccharide (LPS), into systemic circulation. These mice consequently produced symptoms consistent with metabolic disease, including insulin resistance[13]. When LPS was infused into mice that had a normal diet, similar symptoms emerged including obesity, increased visceral fat deposits, and increased liver triglycerides[13]. Moreover, the influence of LPS and inflammatory bacterial byproducts may not stay exclusively within the gastrointestinal tract. For example, Andriessen et al.[14] found an association between gut dysbiosis, release of pro-inflammatory cytokines, and angiogenesis of the eye. The culmination of these observations suggests that there exists an intricate axis of gut, systemic inflammation, and obesity.

### Inflammatory processes

Inflammation is largely known as an adaptive response to injury or infection characterized by coordination of cellular players, such as macrophages and signaling molecules, to address pathologic states[15]. This process, however, may not be entirely pathologic[15]. Recently, Franceschi et al.[16] coined the phrase "inflammaging," a contraction of "inflammation" and "aging", to describe the phenomenon of sterile chronic inflammation that appears to increase with age. The aging process in the context of "inflammaging" is thought to stem from an accumulation of damage from multiple sources[16]. One potential source of such damage is the "bystander effect", where the immune system damages host tissue as a result of fending off foreign pathogens; this can occur through direct damage or through inappropriate expression of cytokines and other signaling molecules[16]. The accumulation of these changes could lead to greater susceptibility to disease states, characteristically seen in older humans[17]. Exacerbating this situation is the loss of gut microbial diversity, as well as the changes in the composition of the gut microbiome, observed with advancing age[18,19].

Biagi et al.[19] compared the age-related gut microbiome composition between young adults and centenarians. In terms of species composition, centenarians received a significantly lower diversity score, compared to young adults[19]. Bacteroidetes and Firmicutes dominated the gut flora of both groups[19]. However, there was a significant difference in the proportion of Firmicutes subgroups. Namely, there was a decrease in *Clostridium* cluster XIVa and rearrangement of *Clostridium* cluster IV[19]. Both clusters contain butyrate, a short chain fatty acid (SCFA), producing bacteria. These butyrate producers have been implicated in inflammatory processes. In fact, pro-inflammatory status observed in centenarians, with increased levels of interleukin (IL)-6 and IL-8, was linked to the corresponding age-related de-

crease in butyrate producers[19]. This demonstrates that the gut microbiome may induce age-related inflammation.

The gut dysbiosis can also influence inflammation by decreasing production of beneficial molecules such as SCFAs[20] and tryptophan derived molecules such as indole 3-proprionic acid (IPA)[21]. SCFAs are largely produced from fermentation of dietary fiber and have a variety of downstream effects on the host including electrolyte and water reabsorption[22]. In terms of inflammatory pathways, these molecules have an anti-inflammatory functional influence on leukocytes, macrophages, and neutrophils[22]. Furthermore, IPA interacts with the pregnane X receptor (PXR), which leads to increased expression of junctional proteins in intestinal epithelial cells (IECs). Therefore, sensing of IPA by PXR decreases gut wall permeability and keeps foreign threats sequestered to the intestinal lumen, averting initiation of any inflammatory process[21].

As for the gastrointestinal tract, inflammatory bowel disease (IBD), an autoimmune condition, is characteristic of chronic inflammation leading to tissue destruction. Though the pathophysiology of IBD is largely unknown, there is growing evidence implicating a potential role of the gut microbiome in IBD. Several studies have shown an increased genetic expression of oxidative stress pathways in IBD, rather than biosynthetic pathways found in healthy controls. It is postulated that this activation of oxidative stress pathways may compromise the gut lining and cause significant perturbation in the gut microbiome leading to a greater density of Proteobacteria and decreased Firmicutes[23,24].

**Immune system**

The human immune system develops and is maintained in response to environmental sources of microorganisms even prior to birth. A normal, innate immune system of the host gastrointestinal tract consists of mucous-producing goblet cells and anti-microbial peptides such as defensins, cathelicidins, and lysozymes, which keep the commensal bacteria under control[25]. In addition, the IECs and dendritic cells (DCs) of the gut contribute to acquired immunity, sensing foreign threats and coordinating appropriate immunologic responses with lymphocytes found in Peyer's patches within the intestinal lining[25]. A fine balance exists between host immune system and the potentially pathogenic commensals that live within the gastrointestinal tract. If this balance becomes unstable, illness and autoimmunity can arise.

The development of the gut microbiome starts early in life. Though the newborn gut was once thought to be sterile at birth, there is emerging evidence that infants are exposed to microorganisms *in utero*. For example, Jiménez et al.[26] demonstrated that genetically labeled bacteria could be found in the meconium of the pups delivered by C-section after pregnant mice consumed milk containing the bacteria. In humans, studies found that the microbiome inhabiting placental tissue, amniotic fluid, and meconium was found within the intestine of the infant[27] and that maternal diet influenced the microbiome of the amniotic fluid as well as the fetal gut[28]. The mode of delivery can also shape the gut microbiome in the first year of an infant's life. In contrast to infants delivered via C-section, infants delivered vaginally more closely resembled the gut microbiome of their mothers[29].

After birth, the development of the infantile gut microbiome is influenced by environmental exposures. Indeed, infant's diet can alter the colonization of the gut[30,31]. The prevalence and counts of *Clostridioides difficile* and *Escherichia coli* were significantly lower in the gut microbiome of breast-fed infants, compared to that of formula-fed infants. In fact, breast milk has been shown to contain microorganisms, immunoglobulin A (IgA), cytokines and other immune cells that help to foster the nascent microbiome and favors the growth of Bifidobacteria[32]. This family of bacteria has been shown to aid in maturation of DCs and T-cells in the nascent thymus and to induce proliferation of signaling molecules to further develop the acquired immune system[33].

By the age of 1 year, the infantile gut microbiome resembles that of the adults. Palmer et al.[34] followed 14 full-term healthy infants from their first stool to 1 year of age, studying their gut microbiomes using 16S rRNA amplification techniques. The investigators also took vaginal and breast milk samples to investigate the influence of microorganisms in these environments on the gut microbiome of the children. It was shown that by the age of 1 year, the infantile microbiome, though highly variable, still had converged towards a microbial profile similar to what is found in adults[34]. This early establishment of the gut microbiome plays a key role in developing the immune system of the host[35]. Hansen et al.[35] demonstrated that there exists a critical window early in the postnatal period of mice that allowed permanent changes in the gut microbiome via inoculation of cecal content. These changes permanently altered the immune phenotype of the host, as in the levels of regulatory T-cells, natural killer (NK) and NKT cells, and cytokines[35].

Other studies have further delineated the role of the gut microbiome in host immunity. Smith et al.[36] has shown that germ free mice tend to have fewer IgA-secreting plasma cells and lymphatic follicles, as well as demonstrate a decrease in the mass of Peyer's patches. In addition, the epithelial lining of these mice expresses different enzymes, surface receptors, cell signaling peptides, and T-cell mod-

ulating factors leading to a different immune response, compared to that of wild type mice[36]. Moreover, the gut microbiome has been shown to induce IgA class switching. He et al.[37] demonstrated that IECs detect the microbiome via the toll-like receptor cascade. This, in turn, results in release of signaling ligands that influence DCs to induce B-cells to switch production from $IgA_1$ to $IgA_2$. $IgA_2$ is resistant to bacterial enzymes, which suggests that this signaling pathway could be a response of the immune system to pathogenic bacteria[37]. Similarly, Suzuki et al.[38] observed that bacterial retinoic acid (RA) stimulates RA receptors in follicular DCs in Peyer's patches, which leads to release of key cytokines, such as transforming growth factor-$\beta$1. This signaling is crucial in B-cell migration, survival, class switching of IgA. This suggests that gut microbiome has a deeply rooted and intricate role in maturation and development of the host immune system.

The microbiome may also be involved in autoimmune disease development and the host immune system's failure to differentiate foreign threats from self[39]. Miyake et al.[40] found that differences in the gut microbiome were associated with relapsing multiple sclerosis (MS). Fecal samples of those affected by MS demonstrated a significant degree of dysbiosis, with a loss of 19 different *Clostridia* species and a reduction of the phylum Bacteroidetes, when compared to those of healthy controls[40]. This difference was conserved over the study period of several months. The authors further commented that this might be consistent with a prior finding by Farrokhi et al.[41] that bacterial byproducts of Bacteroidetes are reduced in the sera of patients with MS. However, these observations suggest correlation, not causation; more study is necessary to elucidate the finer intricacies of the disease pathogenesis[39].

## THE ROLE OF THE GUT MICROBIOME IN INFLAMMATORY SKIN DISEASES

### Atopic dermatitis

Atopic dermatitis (AD) is an inflammatory condition, often associated with a history of atopy, that manifests as a pruritic rash. There are several studies of AD in infants that propose a pathogenic role of the gut microbiome in this disease[42]. The KOALA Birth Cohort Study with 957 infants demonstrated a higher risk of developing eczema with the presence and the increasing number of *E. coli* in the gut[43]. The study also highlighted an increased risk of developing all atopic outcomes (i.e. eczema, recurrent wheeze, and allergic sensitization) with the presence of *C. difficile* in the gut[43]. Other studies have also shown similar findings; for instance, the fecal presence of *C. difficile* is associated with eczema and asthma in the first 6 years of life[42]. However, in the KOALA study, it is noteworthy to emphasize that the colonization of the gut with *E. coli* and/or *C. difficile* preceded the development of atopy, implying the causal link between the gut microbiome and AD.

However, the human gut microbiome continues to evolve from infancy to the age of 2 to 3 years, at which time, the microbiome resembles that of the adult[44]. In children (mean age of $7.6 \pm 5.0$ years), *Bifidobacterium* count was significantly lower in AD, compared to in healthy controls; even more significant, the decrease correlated with severity of the AD symptoms[45]. In direct contrast, the abundance of *Staphylococcus* was significantly higher in AD patients compared to healthy controls[45]. Moreover, certain gut microbiota, such as *Bifidobacterium pseudocatenulatum* and *E. coli* and less *Bifidobacterium adolesecentis*, *Bifidobacterium breve*, *Faecalibacterium breve*, *Faecalibacterium prausnitzii*, and *Akkermansia muciniphila*, emerged as enriched in AD children with food allergy[46].

Several studies have suggested the role of these microorganisms in the pathogenesis of AD. First, the authors of the KOALA hypothesized that the presence of *E. coli* and/or *C. difficile* may disrupt the beneficial gut microbiome, normally involved in expansion of T regulatory cells (T reg cells) and maturation of the immune system[43]. In fact, *Bifidobacterium*, *Lactobacillus*, *Clostridium*, *Bacteroides*, and *Streptococcus* are known to induce T reg cells[47]. Moreover, bacterial metabolic products such as butyric acid and propionic acid are known for their ability to induce T reg cells[48]. Alternatively, certain pathogenic bacterial species may promote gut wall permeability leading to leakage of toxic and pro-inflammatory molecules[43]. In two metagenomic studies, presence of *F. prausnitzii* in the fecal samples of AD patients and concurrent decrease of SCFA, which is important in keeping the integrity of the epithelial barrier, have been suggested to lead to the 'leaky gut' in AD patients[49,50]. Others argued that it is a lack of bacterial diversity in the gut, rather than a presence of causative bacterial species, that impairs maturation of the immune system[51,52]. This view is predicated on the diversity of the gut microbiome educating and improving the immune system. In turn, it protects the host against hypersensitivity of the immune system observed in AD[51]. However, the studies to date are mostly correlative; as such, the exact functional role of these microorganisms in AD is to be further delineated.

Probiotics are known to enhance host defenses by stimulating production of mucus[53], modulating tight junctions between IECs to reduce gut permeability[54], and outcompeting potentially pathogenic species for resources[55]. One study sought to determine the role of probiotics in the development of the AD by randomizing 39 infants

with AD into two groups, where the treatment arm received formula fortified with probiotics[56]. The authors found that disease severity was reduced faster in the treatment group, though this result was not statistically significant[56]. On a molecular scale, the immune system matured at a faster rate in the treatment group compared to the control group[56].

## Psoriasis

Psoriasis typically manifests as erythematous, thick, scaly plaques on the skin with or without systemic symptoms. It is another common inflammatory skin condition that is thought to be associated with the gut microbiome[57]. Zákostelská et al.[57] observed three groups of mice in their response to imiquimod (IMQ): mice reared in a germ free environment, mice made germ free with antibiotics prior to the study, and wild type mice. IMQ was applied topically to induce psoriasis-like dermatitis on the mouse skin. Currently, the IMQ induction is one of the standard approach in psoriasis research[58]. The group found that induction of psoriasis-like dermatitis was more severe in wild type mice, compared to that in the two germ free groups[57]. The robust response to IMQ observed in wild type mice correlated with increased number of Th17 cells, suggesting that the gut microbiome played a role in modulating the inflammatory response[57]. Furthermore, the group concluded that Clostridiales and Erysipelotrichales could potentially be involved in the pathophysiology of psoriasis, as these taxonomic orders were largely absent in the two germ free groups[57].

Although the pathogenesis of psoriasis is not fully understood, we do understand the critical role that Th17 cells and its associated cytokines play in the pathogenesis. The mice study does suggest that certain gut microbiota may play a role in enhancing the Th17 cell immune response in psoriasis. Using 16S rRNA sequencing, Tan et al.[59] found that the level of *A. muciniphila* in the gut was significantly reduced in patients with psoriasis, compared to that in healthy controls. Subsequent studies also demonstrated that there is gut dysbiosis present in patients with psoriasis. Hidalgo-Cantabrana et al.[60] demonstrated a severe dysbiosis with respect to lower diversity and altered relative abundance with a reduction in *Bacteroides* and Proteobacteria, but increased proportions of Actinobacteria and Firmicutes. The reduction in *Bacteroides* was also recapitulated in patients with psoriatic arthritis[60]. Similarly, Shapiro et al.[61] demonstrated a significant increase in the Firmicutes and Actinobacteria in psoriasis patients, as compared to healthy controls. According to PICRUSt analysis (http://picrust.github.io/picrust/), this difference in the gut microbiota translated to increased metabolic pathways involving LPS function[61]. Indeed, Codoñer et al.[62] was also able to demonstrate that "psoriatic core intestinal microbiome" has functional significance with an increased incidence of bacterial translocation into peripheral blood as well as higher inflammatory status observed in psoriatic patients. However, none of these studies sheds much insight into any correlation between the dysbiosis and clin-

**Table 1.** The gut microbiome in inflammatory skin diseases

| Inflammatory skin diseases | Reference |
|---|---|
| Atopic dermatitis (AD) | |
| • *Escherichia coli* in the gut increases the risk of developing eczema. | Penders et al.[43] |
| • *Clostridioides difficile* in the gut increases the risk of all atopic outcomes. | Penders et al.[43] |
| • *Bifidobacterium* in the gut is decreased in AD and the decrease is correlated with severity of AD symptoms. | Watanabe et al.[45] |
| • Certain gut microbiota are enriched in AD children with food allergy. | Fieten et al.[46] |
| Psoriasis | |
| • Clostridiales and Erysipelotrichales in the gut are necessary for induction of imiquimod-induced psoriasis-like dermatitis. | Zákostelská et al.[57] |
| • *Akkermansia muciniphila* is decreased in the gut of psoriasis patients. | Tan et al.[59] |
| • *Bacteroides* and Proteobacteria are decreased and Actinobacteria and Firmicutes are increased in the gut of psoriasis patients. | Hidalgo-Cantabrana et al.[60] |
| • Actinobacteria and Firmicutes are increased in the gut of psoriasis patients. | Shapiro et al.[61] |
| • "Psoriatic core intestinal microbiome" is associated with increased lipopolysaccharides function and bacterial translocation into peripheral blood. | Shapiro et al.[61] |
| Rosacea | |
| • SIBO treatment with rifaximin in rosacea patients demonstrated resolution of skin symptoms. | Parodi et al.[67] |
| • Gut dysbiosis was demonstrated in a group of Korean female rosacea patients. | Nam et al.[69] |

SIBO: small intestinal bacterial overgrowth.

ical phenotypes as in the severity of the skin disease, duration of the disease, or co-morbidities, given a small cohort size. Certainly, further studies are necessary to determine if the psoriatic gut microbiome has any meaningful clinical implications.

### Rosacea

Lastly, rosacea is another common chronic inflammatory skin condition, characterized by facial flushing, telangiectasia, and inflammatory papular and pustular lesions[63]. The pathophysiology of the disease is currently unknown, though there are several theories. Many experts agree that the etiology is multi-factorial and may include the following: pathologic overabundance of the *Demodex folliculorum* mite on the face of rosacea patients[63,64], increased production of various proteinaceous materials by the skin microbiome of rosacea patients[65], or elevated level of cathelicidins in the skin of rosacea patients, an anti-microbial peptide known to defend against gram-positive bacteria[66]. In addition, both bacterial and fungal overgrowth in the gut has been implicated in the pathogenesis of rosacea[67,68].

In 1978, Baran[68] found that the gut mycobiome of rosacea patients may be altered when compared to controls. The study suggested that fungal overgrowth may be involved in the disease process, but was limited by using only cultures to identify species. Similarly, Parodi et al.[67] found a correlation between rosacea and small intestinal bacterial overgrowth (SIBO)[67]. In this study, patients with SIBO and coexisting rosacea were randomized into two groups, a placebo group and a group treated with oral rifaximin[67]. The treatment arm showed resolution of symptoms for up to 9 months, while 75% of the placebo arm, after crossing over and receiving treatment, experienced relief of their symptoms as well[67]. Patients with rosacea who tested negative for SIBO, however, did not respond to rifaximin[67]. The authors of this study argue that SIBO increases gut permeability, leading to the systemic circulation of colonic bacterial byproducts and pro-inflammatory cytokines[67].

There is only one cross-sectional study to date investigating rosacea and its association with the gut microbiome in Korean females[69]. A total of 12 rosacea patients and 251 healthy controls were recruited to this study and stool samples were collected from each subject at baseline. Using the 16S rRNA amplification and metagenomic sequencing, they were able to identify several changes in the gut microbiota including reduced abundance of Peptococcaceae family, *Methanobrevibacter*, *Slackia*, *Coprobacillus*, *Citrobacter*, and *Desulfovibrio* and increased abundance of *Acidaminococcus*, *Megasphaera*, and Lactobacillales order. At this time, however, we still do not understand how these changes potentially contribute to the pathogenesis of rosacea.

## FUTURE DIRECTIONS

Our understanding of the role of the microbiome in metabolism, inflammation, and immunity has evolved over time with the availability of new, more sensitive, and more specific microbiome profiling techniques along with advanced bioinformatics. Now, there is an overwhelming evidence that establishes the intricate link between the microbiome and human health. However, many questions still remain as to the nature of the relationship between the gut and the skin. In dermatology, past studies have mainly focused on the important relationship between the skin microbiome and various skin diseases (Table 1)[43,45,46,57,59-61,67,69]. The premise of these studies is that the microbiome of healthy skin differs in composition and diversity from that of pathologic skin. From these seminal works, we have learned a great deal about the role of the skin microbiome in the pathogenesis of skin diseases. Now, it is time for us to take a step further and explore deeper into the relationship between the gut and the skin. Furthermore, it remains to be seen if this relationship can be targeted for therapeutic purposes.

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