

## The gut-skin axis: a bi-directional, microbiota-driven relationship with therapeutic potential

Maira Jimenez-Sanchez , Larissa S. Celiberto , Hyungjun Yang , Ho Pan Sham , and Bruce A. Vallance 

Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, Canada

### ABSTRACT

This review explores the emerging term “gut-skin axis” (GSA), describing the bidirectional signaling that occurs between the skin and the gastrointestinal tract under both homeostatic and disease conditions. Central to GSA communication are the gut and skin microbiota, the microbial communities that colonize these barrier surfaces. By influencing diverse host pathways, including innate immune, vitamin D receptor, and Aryl hydrocarbon receptor signaling, a balanced microbiota contributes to both tissue homeostasis and host defense. In contrast, microbiota imbalance, or dysbiosis at one site, can lead to local barrier dysfunction, resulting in the activation of signaling pathways that can disrupt tissue homeostasis at the other site, potentially leading to inflammatory skin conditions such as atopic dermatitis and psoriasis, or gut diseases like Inflammatory Bowel Disease. To date, most research on the GSA has examined the impact of the gut microbiota and diet on skin health, but recent studies show that exposing the skin to ultraviolet B-light can beneficially modulate both the gut microbiome and intestinal health. Thus, despite the traditional focus of clinicians and researchers on these organ systems as distinct, the GSA offers new opportunities to better understand the pathogenesis of cutaneous and gastrointestinal diseases and promote health at both sites.

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## Introduction

The human body develops and grows while in constant contact with its external environment, primarily through two interfaces, namely the skin and the gastrointestinal (GI) tract. Both sites receive an array of environmental signals that are transduced to deeper tissues, usually eliciting beneficial and/or homeostatic responses. Unfortunately, they also represent vulnerable target sites for both biotic and abiotic threats. While their embryonic origins differ, with the skin arising from ectoderm and the gut forming from complex interactions between the endoderm and mesoderm, these organs share many fundamental structural and functional similarities.<sup>1,2</sup> Both are lined by epithelial cells that serve as protective barriers, that are supported, and strengthened by signals from underlying stromal and immune cells.<sup>3</sup> Furthermore, they are both extensively vascularized and innervated, allowing rapid communication with the immune and central nervous systems, thereby facilitating rapid responses to environmental threats.<sup>4</sup> Notably, both surfaces

host diverse communities of commensal microbes, collectively known as the microbiome.

Many studies have demonstrated significant immune cell transit and communication between distinct mucosal associated lymphoid tissues (MALT),<sup>5</sup> such as the GI tract and the lungs, potentially as a means to broadly promote mucosal immunity and defense. In recent years, a growing body of research has also revealed significant signaling/cellular crosstalk between the skin and the gut, despite being apparently unrelated organ systems.<sup>6</sup> Termed the gut-skin axis (GSA), the communication pathways connecting these two organs are mediated by an array of cytokines,<sup>7–10</sup> microbial metabolites,<sup>11,12</sup> hormones<sup>13,14</sup> and neurotransmitters.<sup>15,16</sup> These molecules have emerged as key players in maintaining tissue homeostasis and coordinating systemic responses to various stimuli. Among these molecules, hormones such as vitamin D, as well as key microbial metabolites, including Aryl hydrocarbon receptor (AhR) ligands, have been associated with modulating immune responses and metabolic

**CONTACT** Bruce A. Vallance  [bvallance@cw.bc.ca](mailto:bvallance@cw.bc.ca)  Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

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processes, thereby influencing health outcomes throughout the body. Moreover, the effects of environmental factors, such as ultraviolet B (UVB) radiation on the skin, extend beyond those tissues that are directly affected, modulating the functions of distant organs, including the gut.<sup>17</sup>

This review provides a summary of recent findings that support the concept of bidirectional communication between the skin and the gut, as well as the roles played by various molecular players, including but not limited to microbial metabolites, signaling molecules, and environmental factors. By elucidating these pathways, we seek to deepen our understanding of how diverse environmental signals promote tissue homeostasis, as well as propose that UVB light may offer a novel therapeutic approach for the human GI tract, acting via the GSA.

### Gut and skin barrier functions

The skin is composed of three layers: the hypodermis (deepest layer), dermis and epidermis.<sup>18</sup> The epidermis, along with its appendage structures (i.e. hair follicles, sebaceous and sweat glands), is the first barrier encountered by the external environment and is colonized by, and constantly stimulated by an array of skin dwelling microorganisms including bacteria, fungi, viruses, and parasites.<sup>6</sup> Likewise, the gut is protected by an epithelial barrier that safeguards the host by segregating potentially noxious factors such as pathogenic bacteria, viruses and food antigens inside the gut lumen.<sup>19</sup> Among the cells that comprise this barrier, goblet cells (a subset of intestinal epithelial cells (IEC)) synthesize mucus that forms a protective physicochemical gel that overlies and supports the epithelium, while other secretory IEC release molecules that regulate immune responses, exert antimicrobial actions and aid in epithelial repair.<sup>20</sup> The gut epithelial barrier is maintained through tight junction proteins like zonula occludens, claudins, and occludin, which play a crucial role in sealing the paracellular space and regulating IEC permeability.<sup>21</sup> Disassembly of these proteins can result in increased intestinal permeability, also known as “leaky gut”, leading to the passage of luminal factors such as bacterial and dietary components into the gut mucosa and systemic circulation, thus triggering inflammation.<sup>21</sup>

### Innate and adaptive immunity in the gut and skin

Consistent with their frequent exposure to environmental threats, the skin and gut both harbor an array of cells that can elicit protective immune and antimicrobial responses. Specifically within the dermis of the skin, several innate immune cell types are present, such as dendritic cells, macrophages, as well as  $\gamma\delta$  T lymphocytes and innate lymphoid cells (ILC).<sup>22</sup> As the largest immune organ in the body, the GI tract contains a similar array of innate immune cells, but at higher densities.<sup>23</sup> Moreover, IEC serve as an essential component of innate intestinal defense, expressing pattern-recognition receptors such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors, allowing them to rapidly respond to threats. For example, a subset of secretory IEC called “sentinel goblet cells” were recently shown to recognize pathogenic stimuli through TLRs, and respond by rapidly releasing mucus in an inflammasome dependent manner.<sup>24</sup> Additionally, IEC actively protect against pathogen colonization through the production of antimicrobial peptides (AMPs), while infected IEC can undergo inflammasome-induced pyroptosis, expelling invading pathogens back into the gut lumen.<sup>25</sup> Similarly, keratinocytes in the skin express various TLRs, enabling them to sense bacterial infections and produce AMPs that exert antimicrobial activity and chemokines that promote immune cell recruitment.<sup>26,27</sup>

Both the skin and gut also contain specialized subsets of dendritic cells that sample antigens from their surroundings and regulate immune responses. Correspondingly, diverse T cell subsets reside within these tissues, including regulatory T cells (Tregs), effector T cells, and memory T cells, which are crucial for immune regulation, surveillance, and the development of immune responses to pathogens.<sup>28</sup> Moreover, tissue macrophages, which are essential for immune surveillance, inflammation, and tissue balance, are found in abundance in both organs, along with mast cells which are best known for their roles in host defense and allergic reactions.<sup>29,30</sup>

### Microbiota in gut and skin health

The human gut and skin are colonized by diverse microbes, collectively termed the microbiota, with

the skin carrying  $10^4$ – $10^6$  microbial cells per  $\text{cm}^{231}$  while microbial density in the gut can reach  $10^{11}$  microbes per gram of fecal material.<sup>32</sup> Under healthy conditions, the host and its microbiota symbiotically co-exist, with the host's skin and gut providing a place to reside as well as nutrients for the microbes. The specific compositions of the gut and skin microbiotas, as well as their respective functions are outlined below.

The human skin is colonized at birth by an array of microorganisms such as bacteria, archaea, viruses and fungi, with the mode of delivery greatly impacting the infant's initial skin microbiota profile.<sup>33–35</sup> Neonates born vaginally initially carry a skin microbiota signature closely resembling their mother's vaginal bacteria, predominately featuring *Lactobacillus* spp. Conversely, infants delivered by cesarean section often display lower skin microbial diversity,<sup>36–38</sup> being mainly colonized by environmental microorganisms and those from their mother's skin, including *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* species.<sup>36</sup> This initial colonization by commensal bacteria appears to play an important role in establishing immune tolerance,<sup>34</sup> as the presence of skin bacteria causes Tregs to express the FOXP3 transcription factor, a critical step in developing their immunoregulatory functions.<sup>39</sup> Within four to six weeks after birth, the infant's skin microbiome increases in diversity, aligning more closely with their mother's skin microbiome.<sup>38</sup> The ability of these microbes to protect the infant's skin from external threats is particularly important as children have underdeveloped immune systems and vulnerable skin barriers. Certain bacteria such as *Staphylococcus epidermidis* and *Staphylococcus cohnii* are known to protect infants from skin conditions like atopic dermatitis (AD) or eczema (an inflammatory disorder characterized by dry and scaly skin).<sup>40</sup> While *S. epidermidis* is generally considered a beneficial commensal, its protective effects appear to be strain specific as recent studies have shown that certain strains of *S. epidermidis* can induce the expression of pro-inflammatory mediators, such as the cytokine IL-1 $\beta$ ,<sup>41</sup> which can explain the observed correlation between the higher abundance of *S. epidermidis* and the most severe cases of AD in both adults<sup>42,43</sup> and infants.<sup>44,45</sup>

Throughout the infant's development, commensal bacteria continue to influence the production of various cytokines and AMPs, thereby strengthening the skin's defenses against pathogens. For example, bacteria like *S. epidermidis* can stimulate the production of calprotectin S100A8/9 from keratinocytes via interleukin (IL)-17 producing CD8<sup>+</sup> T cells, and produce lipoteichoic acid that suppress inappropriate immune activation by inhibiting the production of the pro-inflammatory cytokines tumor necrosis factor (TNF)- $\alpha$  and IL-6.<sup>46,47</sup> During adolescence, a significant shift occurs in the skin microbiome, with *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* ( $\beta$ - and  $\gamma$ ) giving way to the more lipophilic *Actinobacteria*. This shift can lead to an imbalance in the skin microbiota known as dysbiosis, and potentially contribute to skin disorders such as acne vulgaris.<sup>48</sup> Ethnicity and geographical differences have also been described to influence skin properties, resulting in distinct skin microbiota compositions across populations.<sup>49,50</sup> The most notable differences in skin bacterial profiles are associated with body site, as reflected by their different physiologic characteristics such as humidity, temperature, pH, lipid and sebum content and AMP expression.<sup>33,51–54</sup> Interestingly, several skin sites including the forearm, palm, index finger, back of the knee, and the sole of the foot harbor microbiomes with higher phylogenetic diversity as compared to the gut microbiome.<sup>54</sup> Hygiene practices, the type of clothing worn, diet, medications, and environmental conditions, including sunlight exposure, can also modulate skin bacterial communities over time, leading to an evolving microbiome composition.<sup>54,55</sup>

The human gut is also colonized by microbes immediately after birth and is influenced by the infant's mode of delivery and subsequent diet (i.e. breastfeeding vs. formula). The GI tract, and especially the colon, harbor the largest bacterial load in the human body, with more than five million different genes carried by 1,000 to 1,500 distinct bacterial species that comprise the gut microbiota, belonging to the genera *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Cyanobacteria*, and *Verrucomicrobia*.<sup>56</sup> The gut microbiota exert an array of functions, such as aiding in the digestion of food, promoting immune

system development and defense against pathogens, vitamin biosynthesis, fat storage and angiogenesis while also producing important metabolites such as the short chain fatty acids (SCFA) acetate, propionate and butyrate.<sup>57</sup> Strikingly, the gut microbiota also influences mood and behavior, as it has been linked to the pathogenesis of several neuropsychiatric disorders and abnormal behaviors in animal models.<sup>58,59</sup>

After their initial colonization, the community of gut microorganisms gradually develops into a diverse ecosystem as the host ages and grows. Microbes and the host immune system mature together through a cooperative relationship, where the host provides food, while commensal microbiota help protect the host against enteric pathogens and other noxious stimuli.<sup>60,61</sup> Similar to the skin, gut bacteria such as *Bacteroides fragilis* and certain *Clostridium* species can trigger an increase in the local population of Foxp3+ Treg cells, thereby contributing to immune tolerance to commensal microbes.<sup>62</sup> Additionally, macrophages in the intestinal lamina propria specialize in phagocytosing pathogens, exhibiting less pronounced pro-inflammatory responses as compared to macrophages at other tissue sites.<sup>63</sup> This adaptation suggests that the host adjusts to the presence of a large population of commensal microbiota, by minimizing the risks of triggering unnecessary or exaggerated inflammatory responses.<sup>64</sup>

### Microbiota in gut and skin disease

As noted above, microbial dysbiosis refers to an imbalanced microbiota community, often characterized by reduced bacterial diversity and stability. Gut microbiota dysbiosis has been implicated in the development and progression of various conditions, including atopic asthma, mental health disorders (depression, schizophrenia, addiction), obesity, type 2 diabetes, cardiovascular diseases, and autoimmune disorders like rheumatoid arthritis and multiple sclerosis (MS).<sup>65–67</sup> Moreover, GI conditions, including inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), have been associated with an altered gut microbiota profile in comparison with healthy subjects, as microbial dysbiosis can influence gut physiology, nutrient absorption, and the host's immune system.

We suspect that in many cases, inflammation, whether originating in the intestine or the skin, may be initially triggered by a dysbiotic gut microbiota, providing a starting point for the GSA to negatively impact the skin.<sup>68</sup> Notably, intestinal microbial dysbiosis often triggers systemic inflammation, in association with alterations in microbial metabolic capacity (i.e. nutrient metabolism, lipid metabolism, vitamins B and K synthesis, detoxification and hormone metabolism) which may affect other organ systems, including the skin, thus disrupting cutaneous homeostasis.<sup>69–74</sup> Moreover, intestinal microbial dysbiosis is associated with T-cell activation as well as impaired production of immunosuppressive cytokines and Treg cells, which together, are essential for maintaining host tolerance to the microbiota.<sup>69</sup> Whether skin microbial dysbiosis can initiate similar detrimental effects at distal sites, such as the GI tract has received less attention, but should be a priority for future studies.

The transition from microbial dysbiosis to the promotion of disease is complicated and involves multiple interconnected mechanisms. Disruptions in gut microbiota can compromise intestinal barriers, increasing permeability (“leaky gut”) and triggering systemic inflammation.<sup>75</sup> This imbalance also promotes immune dysregulation, including to the overactivation of pro-inflammatory pathways (Th1, Th17), causing impaired immune tolerance.<sup>76</sup> Furthermore, shifts in the levels of microbial metabolites, such as reduced SCFAs and increased harmful byproducts, can exacerbate inflammation and tissue damage.<sup>77–79</sup> Genetic predisposition and environmental factors, such as diet, stress, and antibiotic use, can further contribute to disease progression.<sup>80,81</sup> It should be noted that further studies are required to understand these relationships, as a prerequisite to developing targeted therapies to restore microbial balance and alleviate subsequent symptoms and pathology.

Dysbiosis may also significantly impact intestinal stem cells (ISCs), which are critical for maintaining gut integrity and function, and by extension, the gut-skin axis. A healthy microbiota supports ISC proliferation and differentiation, but dysbiosis can impair these functions, compromising gut barrier integrity and increasing

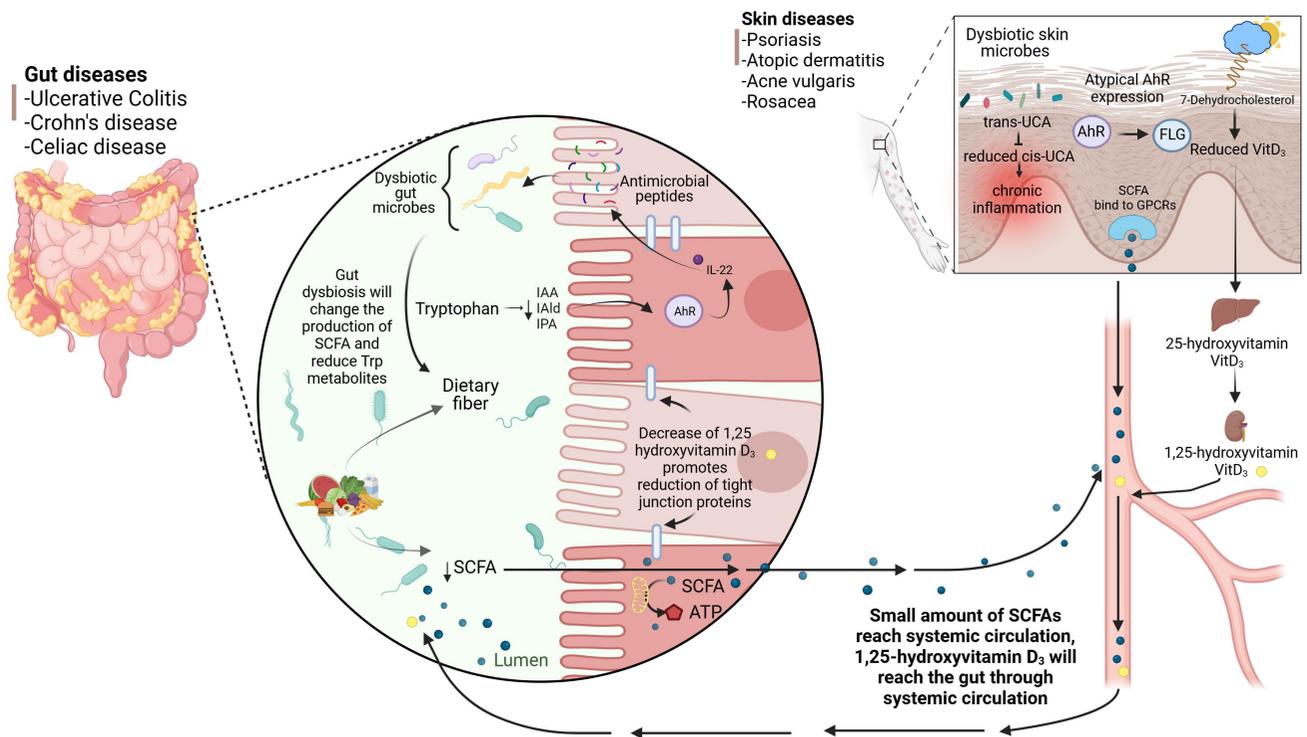
permeability.<sup>82</sup> This disruption can drive microbial translocation and subsequent systemic inflammation, which can exacerbate skin conditions.<sup>83</sup> Microbes and their metabolic products can directly and/or indirectly interact with ISCs, influencing the stem cell niche and modulating epithelial function, regeneration, and repair.<sup>84</sup> The link between dysbiosis and skin inflammation is highlighted by findings of elevated gut bacterial DNA in the bloodstream of patients with chronic skin disorders.<sup>85</sup> As already mentioned, dysbiosis reduces the production of SCFAs, which normally play a critical role in supporting ISC function, epithelial barrier integrity, and in mitigating inflammation.<sup>11,68</sup> In addition, dysbiosis can alter the regulation of ISCs through TLR and NOD pattern recognition receptors, which are influenced by the intestinal microbiota. Key microbial communities involved in these pathways include *Fusobacteria*, *Proteobacteria*, *Firmicutes*, *Lachnospiraceae*, *Coriobacteria*, *Helicobacter pylori*, and *Vibrio cholerae*. Specific bacteria, such as *Serratia marcescens*, *Erwinia carotovora carotovora-15*, and *Pseudomonas entomophila* are known to contribute to intestinal homeostasis, injury repair, and the maintenance of ISC function through these mechanisms.<sup>82</sup>

Associations between GI and cutaneous diseases are well-supported by previous studies,<sup>4</sup> as depicted in Figure 1. Notably, 10% to 25% of patients with GI diseases such as IBD and Celiac disease also experience skin pathology, including psoriasis (characterized by scaly plaques and hypertrophic skin lesions), and cutaneous ulcers.<sup>4,86</sup> Celiac disease, which is characterized by intestinal malabsorption, commonly co-presents with dermatitis and psoriasis as cutaneous manifestations, whereas patients with rosacea (a chronic inflammatory skin condition that causes reddened skin and rash) frequently exhibit small intestinal bacterial overgrowth (SIBO).<sup>87</sup> Peutz-Jeghers Syndrome, which is characterized by GI polyposis and malignancy, often features perioral hyperpigmentation as a common cutaneous manifestation.<sup>86</sup> Additionally, IBD patients frequently experience skin manifestations such as skin ulcers, vasculitis, hair loss, erythema folliculitis, and psoriasis,<sup>4,86</sup> with some of these conditions linked to the severity of the patient's GI

inflammation.<sup>88</sup> Notably, intestinal colonization with *Malassezia restricta*, a commensal fungus and frequent member of the skin microbiota, may contribute to the pathogenesis of Crohn's disease (one form of IBD), in a subset of patients, with its presence correlating with increased disease severity.<sup>89</sup> While these findings implicate a member of the skin microbiome in the pathogenesis of IBD, the underlying mechanisms have not yet been fully elucidated; but others have suggested that both the immune and endocrine systems play an important role in this interaction.<sup>69</sup>

Extensive pre-clinical research has shown that modulation of the gut microbiota can exert a positive impact on the cutaneous system, especially through the administration of beneficial microbes known as probiotics. Levkovich and colleagues<sup>90</sup> found that oral supplementation of the probiotic *Lactobacillus reuteri* ATCC 6475 to aged mice resulted in improved skin health, including increased dermal thickness, enhanced folliculogenesis, a more acidic skin pH, and heightened sebum production in comparison with aged mice not given the probiotic. These benefits appeared to be immune mediated as probiotic-fed mice showed increased serum levels of the anti-inflammatory cytokine IL-10 and decreased levels of the pro-inflammatory cytokine IL-17. Another probiotic strain (*Lactobacillus acidophilus* KBL409) orally administered to mice was shown to attenuate AD and decrease the infiltration of immune cells into skin tissues.<sup>91</sup> In addition to increasing IL-10 levels and Foxp3 expression in mice, probiotics have also been shown to modulate the gut microbiota's production of metabolites such as SCFA and amino acids. The reduced dermatitis scores found in these studies demonstrate that probiotic bacteria can exert positive effects beyond the gut, through a coordinated modulation of both the immune system and the gut microbiota. For instance, Mendelian randomization (MR) studies reveal causal links between gut microbiota and skin disorders, including eczema, acne, psoriasis, and rosacea.<sup>92</sup> For example, *Eubacterium fissicatena* is linked to psoriasis risk,<sup>93</sup> while gut bacteria may influence skin fibrosis.<sup>94</sup> These findings highlight the therapeutic potential of microbiota modulation.

Studies in humans also point to the immune system and the gut microbiota as key contributors



**Figure 1.** Links between GI disorders and cutaneous diseases. In high-latitude locations, reduced sunlight, especially during winter leads to decreased UVB light exposure and subsequently lower serum vitamin D levels. This decline leads to changes in the GI tract, including a reduction in epithelial tight junction proteins. Many patients with IBD are vitamin D insufficient or deficient, with a higher occurrence in CD than UC. Decreased UVB exposure also leads to reduced conversion of trans-urocanic acid (UCA) to cis-uca, which has been linked to chronic skin inflammation. In IBD patients, gut microbial dysbiosis leads to reduced short chain fatty acid (SCFA) levels, which is a key bacterial metabolite affecting both gut and skin health. Skin conditions such as psoriasis, acne, atopic dermatitis, and vitiligo are often associated with reduced AhR expression/activation. Several AhR ligands, including indole derivatives can impact skin health by modulating inflammation and oxidative stress. Patients with IBD exhibit decreased production of endogenous AhR ligands in their feces, likely as a result of microbial dysbiosis, which may contribute to their impaired mucosal healing. Created in [BioRender.com](https://www.biorender.com).

to the overlap seen between gut and skin conditions. For example, a recent study found an association between gut microbial dysbiosis and AD. The authors showed that clinical improvement of the skin in response to the medication dupilumab, a monoclonal antibody that blocks interleukin 4 and interleukin 13, were due to dupilumab's effects on gut bacterial function, by regulating the indole pathway of tryptophan metabolism.<sup>95</sup> This effect is likely associated with dupilumab's suppression of Th2 immune responses, leading to pleiotropic anti-inflammatory actions observed throughout the body including in both skin and gut.<sup>96,97</sup> Moreover, several clinical trials have shown beneficial effects of oral probiotic administration on skin diseases such as AD,<sup>98</sup> psoriasis<sup>99</sup> and acne vulgaris.<sup>100</sup> The potential benefits of oral probiotics have also been explored for the skin condition rosacea, with higher remission rates seen in

patients that consumed a mixture of *Bifidobacterium* species in addition to the standard antibiotic treatment.<sup>101</sup>

The impact of gut microbiota composition and its metabolites has also been explored in allergic skin diseases. A study by Trompette and colleagues found that administration of dietary fiber or its byproducts ie. SCFAs and in particular butyrate, attenuated allergen-induced skin barrier breach in a mouse model that mimics AD-like skin inflammation in humans.<sup>102</sup> This protection was associated with accelerated epidermal keratinocyte differentiation, which increased the production of key structural skin components such as proteins and lipids. Moreover, butyrate enhanced skin barrier function by directly shaping keratinocyte metabolism and eliciting a mitochondria-dependent differentiation program. These results support previous findings

that butyrate can modulate immune responses in the skin,<sup>103,104</sup> and that it is also reduced in children and infants diagnosed with AD,<sup>105,106</sup> as well as in children that develop allergic reactions later in childhood.<sup>107</sup>

### Communication pathways in the gut-skin axis

The relationship between the gut and skin is highlighted by the vital role of the microbiota in facilitating communication between these two systems. Further defining the communication pathways that underlie the GSA is key to understanding both its role in disease pathogenesis, and its potential therapeutic applications. Alongside the microbiome, various metabolites and micronutrients serve as essential components of the GSA dialogue, with the specifics outlined below.

#### Gut communication with the skin

The most common assumption regarding the GSA is that the communication largely occurs in only one direction, i.e. the gut communicates with, and thereby impacts the skin. This assumption stems from the crucial roles played by the gut microbiota in an array of metabolic and immune functions that can impact the entire body and thus influence skin health. Members of the gut microbiota metabolize indigestible complex polysaccharides into essential nutrients, including vitamin K and the water soluble B vitamins, which are associated with wound healing and metabolic functions such as DNA replication, repair and methylation, respectively.<sup>108,109</sup> Moreover, the gut microbiota produce their own (i.e. bacterial) metabolites such as SCFA, which have been described as important signaling factors in the GSA as they can alleviate skin inflammation.<sup>11</sup>

Diet is recognized as a major factor influencing the composition and function of the gut microbiota, highlighting the importance of dietary patterns and specific nutrients in the GSA. The western dietary pattern, which is rich in saturated fats as well as refined carbohydrates, is often associated with reduced microbial diversity and higher luminal concentrations of bacterial cell wall components such as lipopolysaccharides, which can negatively affect gut barrier function and trigger systemic inflammation.<sup>110</sup> Additionally, a diet

containing excessive levels of animal protein can favor the production of metabolites such as indoxyl sulfate, Trimethylamine-N-oxide (TMAO) and p-cresyl sulfate, that are linked to psoriatic arthritis, a chronic inflammatory disease affecting the joints and connective tissue that is commonly seen in patients with psoriasis.<sup>111,112</sup> Conversely, a high-collagen diet has been shown to be beneficial with respect to skin aging and wound healing, emphasizing that different sources of protein may exert quite divergent effects on the skin.<sup>113,114</sup> Moreover, a dietary pattern favoring oily fish and olive oil has been associated with a reduction in skin inflammation due to their high levels of omega 3 and mono-unsaturated fatty acids, respectively.<sup>115–119</sup> In addition to macronutrients, the consumption of dietary fiber is largely considered beneficial for overall health. Fibers such as inulin and resistant starch cannot be digested by the human body but instead rely on the microbiota to be fermented, in a process that increases the population of beneficial gut microbes and their metabolites, such as SCFA, which can promote skin health.<sup>120</sup>

In addition to the indirect effects of diet on skin health via modulation of the gut microbiota, different ingested nutrients can directly support skin structure and function. While most studies focus on dietary compounds as supplements, it is important to note the effects elicited by whole foods on specific aspects of the GSA as a way to explore targeted dietary recommendations for skin conditions. The Mediterranean diet, rich in plant-based and healthy fat foods, is associated with a lower incidence of several chronic inflammatory diseases, including dermatological conditions.<sup>121</sup> Plant-based foods such as vegetables, fruits, legumes and nuts are considered rich sources of bioactive compounds, including carotenoids, vitamins, and polyphenols, which play a key role in maintaining skin health.<sup>122,123</sup>

Vitamin C, which is abundant in many fruits and vegetables, plays a crucial role in collagen synthesis and acts as a potent antioxidant, protecting the skin from the damage caused by reactive oxygen species (ROS).<sup>124</sup> Moreover, vitamin C works synergistically with vitamin E, a powerful antioxidant present in fruits such as avocado, that together can reduce skin aging and increase level of moisture. The effects of specific foods rich in vitamin C have also been

studied, with mango, particularly the Ataulfo variety, reducing deep facial wrinkles in postmenopausal women after 16 weeks of intervention when consumed in moderation.<sup>125</sup> However, portion sizes are key for dietary recommendations, as individuals who ingested 250 g of mango experienced an increase in wrinkles. This result could potentially be attributed to the sugar content of the fruit, as glucose and fructose can enhance the glycation process of collagen and elastin fibers, thereby compromising the structural integrity of the subcutaneous tissue that provides support to the skin.<sup>126</sup>

Polyphenols also seem to play an important role in skin health, with a study showing that cocoa flavanol supplementation reduced facial wrinkles and improved skin elasticity after only 24 weeks in photo-aged women.<sup>127</sup> Additionally, supplementation with grape seed extract, rich in polyphenols such as anthocyanins, flavanols, and resveratrol,<sup>128–130</sup> has also shown benefits in melasma, a common skin condition characterized by dark skin patches.<sup>131</sup> Carotenoid-rich foods such as tomatoes, which are also rich in lycopene, exhibit robust antioxidant properties, offering protection against UV-induced skin erythema,<sup>132,133</sup> while daily consumption of a carotenoid-rich kale extract was found to improve collagen and elastin levels, enhancing skin health.<sup>134</sup>

Intake of nuts such as almonds have also been associated with skin health benefits by contributing to antioxidant defense and reducing wrinkles.<sup>135</sup> Additionally, legumes such as soybeans contain isoflavones, bioactive compounds that exhibits estrogen-like properties. As a result, their consumption can mitigate the reduced estrogen levels seen during menopause, thereby improving the typical skin wrinkling, dryness, and poor wound healing.<sup>136</sup> Thus, a diverse diet, rich in nutrient-dense whole foods not only benefits the gut microbiota composition profile but also directly provides the essential nutrients and antioxidants needed to promote skin health and delay signs of aging.

### **Skin communication with the gut**

In contrast to the well-studied roles that dietary components and the gut microbiome play in

affecting skin health, the inverse direction of the GSA has received much less attention. We know that an array of external environmental factors such as pollution, smoking, climate, and sun exposure impact the skin directly.<sup>137</sup> In this section, we will discuss how skin responses to specific stimuli impact the gut, highlighting the importance of vitamin D and tryptophan metabolites as key examples of the bidirectional communication between the GI tract and the skin. By focusing on these compounds, we seek to show how external factors, such as ultraviolet (UV) radiation, influence the skin and, in turn, affect gut health.

### **Vitamin D signaling**

Calciferol, also known as vitamin D, is a fat-soluble vitamin that can be obtained from the diet as it is naturally found in oily fish and eggs, while breakfast cereals and milk are often fortified with vitamin D. In addition to dietary sources, vitamin D is also produced by the human body in response to sunlight; skin exposure to UVB light can lead to the production of vitamin D within the epidermis, from the precursor chromophore 7-dehydrocholesterol.<sup>138</sup> Recently, exposing the skin to UVB light was shown to modulate the gut microbiota composition of vitamin D insufficient, but otherwise healthy women.<sup>17</sup> The exact mechanisms by which vitamin D alters gut microbiota composition are unclear, but they likely include increased innate immune signaling, the downregulation of inflammation, and strengthening of intestinal barrier function.<sup>139</sup>

In both the skin and gut, vitamin D receptor (VDR) activation plays a critical role in regulating the production of AMPs such as cathelicidin, which help maintain microbiota homeostasis and provide protection against pathogens.<sup>140,141</sup> Vitamin D itself also induces the expression of antimicrobial peptides in human keratinocytes, monocytes, and neutrophils,<sup>142–144</sup> since the promoters of the human cathelicidin antimicrobial peptide (*CAMP*) and defensin beta-2 (*DEFβ2*) genes contain vitamin D response elements that regulate their transcription. Notably, vitamin D synthesized in the skin can activate VDR signaling in the gut, enhancing Paneth cell defensin production, with defensins acting as key regulators of gut microbiota and metabolic health.<sup>145</sup> The VDR

is expressed by various immune cells within the gut, including dendritic cells, macrophages, T cells (particularly regulatory T cells), and B cells, thus highlighting its role in immune regulation.<sup>146,147</sup> Vitamin D modulates the function of regulatory T cells, which are crucial for maintaining immune tolerance and controlling inflammation.<sup>148,149</sup> Additionally, it modulates dendritic cells to promote Treg development, regulates macrophage-mediated inflammation, and affects antibody production and immune regulation in B cells. This immune modulation is particularly relevant in IBD, where vitamin D deficiency is common and associated with increased disease severity.<sup>148,149</sup>

Vitamin D also plays an important role in maintaining mucosal barrier function by upregulating the expression of tight junction and adherent junction proteins in IEC, as well as suppressing IEC apoptosis. Furthermore, fermentation products from the gut microbiota, such as the SCFA butyrate, upregulate IEC expression of the VDR and suppress inflammation in a mouse colitis model.<sup>150</sup> Together, these activities of vitamin D have potential downstream consequences for microbial composition change.<sup>139</sup>

The links between vitamin D and gut microbiota are intriguing, as vitamin D deficiency has been linked to the increasing incidence of several dysbiosis-associated inflammatory diseases like IBD and MS. These conditions are common in northern countries where sunlight exposure is limited during winter, leading to vitamin D deficiency. For example, increasing IBD incidence has been associated with low sun exposure and high latitude, with the two forms of IBD, namely ulcerative colitis and Crohn's disease being 40% and 80% higher, respectively, in northern Europe as compared to southern Europe. Additionally, regions in the United States with lower UV exposure exhibit increased incidence and severity of IBD, along with higher hospitalization rates.<sup>151</sup> Vitamin D deficiency in IBD patients ranges from 16% to 95%, and is seen more commonly in CD than in UC patients.<sup>152–154</sup>

Notably, IBD patients often develop skin lesions that mirror the appearance and disappearance of their chronic relapsing gut inflammation. There are different cutaneous signs of IBD, such as fissures and fistulae, erythema nodosum (inflammation of subcutaneous fat tissue), pyoderma gangrenosum

(an ulcerative disorder), pyostomatitis vegetans (pustular eruption of the mouth and skin folds), oral aphthous ulcers, cutaneous polyarteritis nodosa (type of vasculitis affecting medium-sized vessels in the skin), necrotizing vasculitis, and psoriasis.<sup>86</sup> It has been reported that the serum vitamin D levels of IBD patients with psoriasis are significantly lower than those of patients without psoriasis. Moreover, after these patients received vitamin D supplementation, they showed clinical improvement over that of patients not receiving this therapy.<sup>155</sup> Since vitamin D has such an important role in the immune system, it is not surprising that its deficiency has been implicated in several skin diseases beyond psoriasis, including AD (eczema),<sup>156</sup> acne<sup>157</sup> and vitiligo, a condition characterized by loss of skin pigmentation.<sup>158</sup>

### **Tryptophan metabolites and aryl hydrocarbon receptor signaling**

Tryptophan is an essential amino acid and a precursor for the neurotransmitters kynurenes, serotonin, and melatonin.<sup>159</sup> It also functions as an important chromophore when exposed to UVB light, resulting in the production of 6-formylindolo [3,2-b] carbazole (FICZ).<sup>159</sup> This molecule is a potent activator of the AhR and promotes transcriptional regulation of a variety of downstream genes, including *Il22* (which encodes IL-22, an innate immune cytokine and a key component of AhR-regulated intestinal immunity). The AhR is expressed in a variety of tissues, with very high expression seen in epithelial barriers and cells of the gut-associated immune system.<sup>160</sup> Moreover, there are other endogenous host tryptophan-derived metabolites such as kynurenine, kynurenic acid, xanthurenic acid, and cinnabaric acid, as well as a number of bacterial metabolites,<sup>161</sup> including indole-3-aldehyde (IAld), indole-3-acetic acid (IAA) and indole-3-propionic acid (IPA), skatole, and tryptamine, that can act as AhR ligands in the context of promoting intestinal immunity.<sup>162–164</sup> Thus, an array of AhR activating tryptophan metabolites can be produced by the skin in response to UVB light as well as by commensal microbes in the gut.

AhR is an important regulator of the skin barrier as it is known to control immune-mediated responses in the skin.<sup>165</sup> For example, the AhR is overexpressed in the epidermal lesions found in skin diseases, such as psoriasis, and AD.<sup>166</sup> Moreover, indole-3-lactic acid mediated activation of AhR can influence both skin and gut health by reducing inflammation and increasing barrier function of the skin and gut epithelia.<sup>167,168</sup> In patients with psoriasis and mouse models of skin disease, AhR activation has been shown to ameliorate inflammatory sequelae. For example, stimulation of affected skin zones with FICZ induces the expression of *Cyp1a1*, a gene downstream of the AhR pathway, and linked to the decreased expression of several pro-inflammatory chemokines involved in the psoriasis transcriptome.<sup>169</sup> Another skin disease regulated by AhR pathway is vitiligo, as AhR is involved in melanogenesis through the induction of melanogenic genes.<sup>170</sup> Correspondingly, two major therapies for vitiligo; psoralen (light-sensitive substance from plants that is sensitive to UVA light) and UV phototherapy, which promote the re-pigmentation of the skin<sup>171</sup> both activate AhR signaling within the human skin.

Alterations in tryptophan metabolism have also been reported in several intestinal conditions such as IBD, IBS, and colorectal cancer.<sup>172–174</sup> Studies using mouse models have determined that inflammation-induced gut microbial dysbiosis often involves the loss of tryptophan-metabolizing gut microbes such as *Lactobacillus reuteri*. This loss leads to a corresponding decrease in tryptophan metabolites, such as IAA, and a reduction in AhR activation. These microbiota changes impair activation of intestinal group 3 innate lymphoid cells (ILC3) and reduces their production of the tissue protective cytokine IL-22, a key component of AhR-regulated intestinal immunity, culminating in increased susceptibility to dextran sulfate sodium (DSS)-induced colitis.<sup>175</sup> Similarly, fecal samples from patients with IBD often show reduced AhR activity and decreased levels of IAA.<sup>175</sup> Correspondingly, studies have shown that AhR activation decreases cytokine (TNF, IFN $\gamma$ , IL-7, IL-12, IL-17, and IL-6) production in the intestine under inflammatory conditions, while also promoting T cell differentiation by controlling key transcription factors such as Foxp3 for T regs

and ROR $\gamma$ T for T helper 17 (Th17)/ILC3 cells in a ligand-specific manner.<sup>176–179</sup> These cells are crucial in promoting intestinal homeostasis as well as defending against invading pathogenic microbes, respectively.<sup>180</sup>

Despite the extensive assessments of AhR signaling in the gut or the skin, the potential for AhR signaling at one site to simultaneously modulate both organs is poorly defined. Memari et al. investigated the effects of UVB skin exposure on the induction of AhR signaling in peripheral tissues *in vivo*. They used a single 1.2 kJ/m<sup>2</sup> dose of UVB to examine the expression of several AhR target genes in the blood, liver, and intestine, at 3 and 6 hours after UVB exposure. They showed that AhR target genes, including *Il22* and *Il23a* (whose signaling lies upstream of Il-22) in the intestine, were upregulated following UVB exposure on the skin. These findings provide compelling evidence that moderate cutaneous UVB exposure induces endocrine signaling through AhR, a ligand-regulated environmental sensor.<sup>181</sup> Given the emerging role of AhR signaling in the immune system in both mice and humans, particularly in barrier organs, this data further supports a role for cutaneous UVB exposure in mediating endocrine regulation of systemic immunity.

### **Skin wounding**

Dermal injuries have been shown to initiate a complex interplay between the skin and gut, leading to significant disruptions in the intestinal microbiome and in immune balance. This phenomenon is particularly evident in mouse models, where skin injuries exacerbate gut microbial dysbiosis and alter immune responses. One mechanism by which skin injury impacts gut health is through the systemic circulation of inflammatory mediators. For example, Yokoyama et al. demonstrated that skin disruption induced by indomethacin treatment in mice resulted in elevated plasma levels of inflammatory mediators such as IgE and TNF- $\alpha$ .<sup>182</sup> These mediators migrated to the gut, where they aggravated intestinal inflammation. Additionally, Gallo et al. highlight that localized skin injuries can compromise intestinal antimicrobial defenses and alter the gut microbiome, increasing susceptibility to DSS-induced colitis.<sup>183</sup> Using

a hyaluronan (HA) digestion model, they replicated the local release of HA fragments from the dermis, a process that occurs during skin wounding or in conditions like psoriasis.<sup>184</sup> This model controlled for confounding factors commonly associated with skin inflammation. The study revealed that HA fragments disrupt the gut microbiome, resulting in heightened colitis susceptibility. Experiments further demonstrated that HA fragments enhanced Reg3 production in the mouse colon as well as in cultured human colonic epithelial cells, linking dermal inflammation to gut dysfunction.<sup>183</sup>

These findings demonstrate the close relationship between the skin and gut. Dermal injuries can disrupt the delicate balance of the intestinal microbiome and immune homeostasis, highlighting the need for further exploration into therapeutic strategies targeting this interplay when it becomes maladaptive.

### Ultraviolet radiation – local and systemic effects

Building on the insights from the previous section, we know that UVB light/radiation can significantly affect both the skin and gut. UVB stimulates the production of vitamin D in the skin, which, among its many roles, helps sustain a healthy gut microbiome, as deficiencies have been linked to microbial dysbiosis and IBD.<sup>154</sup> Moreover, UVB exposure influences the tryptophan pathway by promoting the synthesis of AhR ligands, which play a vital role in the GSA. In this section we will focus on the multifaceted impact of UVB radiation (largely from the sun) on both skin and gut health.

Sunlight is defined as a continuous spectrum of electromagnetic radiation divided into different wavelength ranges: Ultraviolet (UV), visible, and infrared. Specifically, the UV spectrum (200–400 nm) can be further subdivided into three wavelength ranges: UVC (200–290 nm), UVB (290–320 nm), and UVA (320–400 nm).<sup>185</sup> Only UVA and UVB can penetrate the skin since UVC is absorbed by the atmosphere's ozone layer.<sup>186</sup> UV radiation can yield both beneficial and adverse effects on human health. Sunburns, immune suppression, cataracts, photo-aging and DNA damage that can lead to non-melanoma and melanoma skin cancers are some of the examples of unwanted

UV effects. Among the positive aspects, a widely recognized outcome of UV radiation is the synthesis of vitamin D upon skin exposure.<sup>187</sup> Moreover, specific skin pathologies such as vitiligo have been treated with phototherapy (sunlight) since 2000 B. C. in Egypt, Greece, and India. Starting in the 20th century, the UVA spectrum of light began to be frequently utilized in the treatment of morphea and eczema, while UVB is currently applied to address conditions such as psoriasis, vitiligo, and mycosis fungoides (the most common type of cutaneous T cell lymphoma).<sup>185,188–190</sup>

### UV radiation as skin therapy

The effects of phototherapy depend on the depth of the light penetration into the skin. UVB light is typically absorbed in the epidermis and upper dermis, whereas UVA, due to its longer wavelengths, effectively penetrates the dermis and it can vasodilate arterial vasculature and lowers blood pressure.<sup>191–193</sup> When UV light penetrates the skin, it interacts with molecules called chromophores, which absorb the light and undergo chemical reactions. UVB primarily targets nuclear DNA as its main chromophore,<sup>194</sup> rapidly leading to the formation of DNA photoproducts as well as DNA damage, and the apoptosis of keratinocytes, immune cells, fibroblasts, and endothelial cells residing within the various layers of the skin.<sup>194</sup> Delayed effects on skin health include the release of anti-inflammatory prostaglandins and cytokines. The overall outcome of UV light involves both localized and systemic immune suppression, changes in cytokine expression, and cell-cycle arrest, all contributing to the suppression of disease activity.

Studies have shown that certain wavelengths of UV light administered at specific doses can exhibit immunosuppressive effects. For example, treatment with the longer, non-erythemic and deepest penetrating wavelengths of UVA light, specifically the subclassification UVA1 (340–400 nm) can improve the symptoms suffered by patients with systemic lupus erythematosus (SLE). This benefit was attributed to UVA1 light reaching the deep dermal – epidermal junction, where it reduced systemic B cell and T cell activity, causing a decrease in the numbers of

IFN $\gamma$ -producing Th1 cells and cytotoxic T cells.<sup>195,196</sup> In the case of psoriasis, UV radiation can exert divergent effects, either exacerbating or improving disease symptoms.<sup>190</sup> Although excessive sun exposure can worsen existing psoriasis plaques, treatments such as narrow-band UVB and UVA combined with a plant substance called psoralen that increases skin photosensitization, have proven effective in treating moderate to severe cases of psoriasis.<sup>185</sup> Psoriasis is believed to be triggered by elevated levels of Th1 and Th17 cell derived cytokines. UV radiation treatment modifies this cytokine profile by tilting the balance toward Th2 cell-associated cytokines, such as IL-4 and IL-13, thereby reducing the pro-inflammatory response and suppressing the IL-23–IL-17 axis<sup>197,198</sup>

Filaggrin is an important skin barrier protein, with AD often linked to loss of function mutations in the filaggrin gene (FLG), and thus AD may be caused by impaired epidermal barrier function.<sup>156</sup> Even when normally expressed, filaggrin can be degraded by several “natural moisturizing factors” in the skin, including *trans*-urocanic acid (*trans*-UCA), a major UVB photon-absorbing chromophore.<sup>199</sup> UVB phototherapy is commonly used to treat AD since it has been shown to increase filaggrin levels in patients after 12 weeks of treatment.<sup>200</sup> This may reflect that upon absorption of UVB radiation, *trans*-UCA is converted to *cis*-urocanic acid (*cis*-UCA) which may initiate immunosuppression.<sup>201</sup> Correspondingly, narrow-band UVB treatment in patients with AD has been shown to reduce skin-infiltrating lymphocytes, dendritic cells (DCs), and eosinophils, along with significant suppression of the Th2 and Th22 immune axes, along with a milder suppression of the Th1 axis.<sup>202</sup> Clinical improvement is associated with a decrease in IL-22 levels,<sup>202</sup> as well as the suppression of Th2-related cytokines such as IL-5, IL-13, and IL-31,<sup>203</sup> and a reduction in IgE binding cell numbers.<sup>204</sup>

### **UV radiation has systemic effects**

Localized beneficial effects of UV light on the human skin have been extensively studied<sup>185</sup>; however, beyond the skin, UV radiation can exert diverse systemic effects. Aside from inducing

vitamin D synthesis, it also promotes immune system regulation,<sup>205</sup> and metabolic processes such as the regulation of insulin levels and hepatic steatosis; moreover, it triggers the release of endorphins – natural pain-relievers and mood enhancers and helps regulate the body’s internal clock (circadian rhythm), affecting sleep patterns and hormonal release.<sup>206</sup> Additionally, some studies suggest that UVA exposure may help regulate blood pressure through the release of nitric oxide, which can relax blood vessels.<sup>193</sup> Likewise, there is emerging research suggesting that UV radiation might impact certain neurological processes, potentially affecting mood and cognitive function.<sup>207</sup> While skin exposure to UV radiation is known to affect the resident skin microbiota, an exciting new area of research is the potential influence that UV radiation may exert on microbiota members at distant sites, such as those in the gut.

### **Gut and skin microbiota communication: modulation by UV radiation**

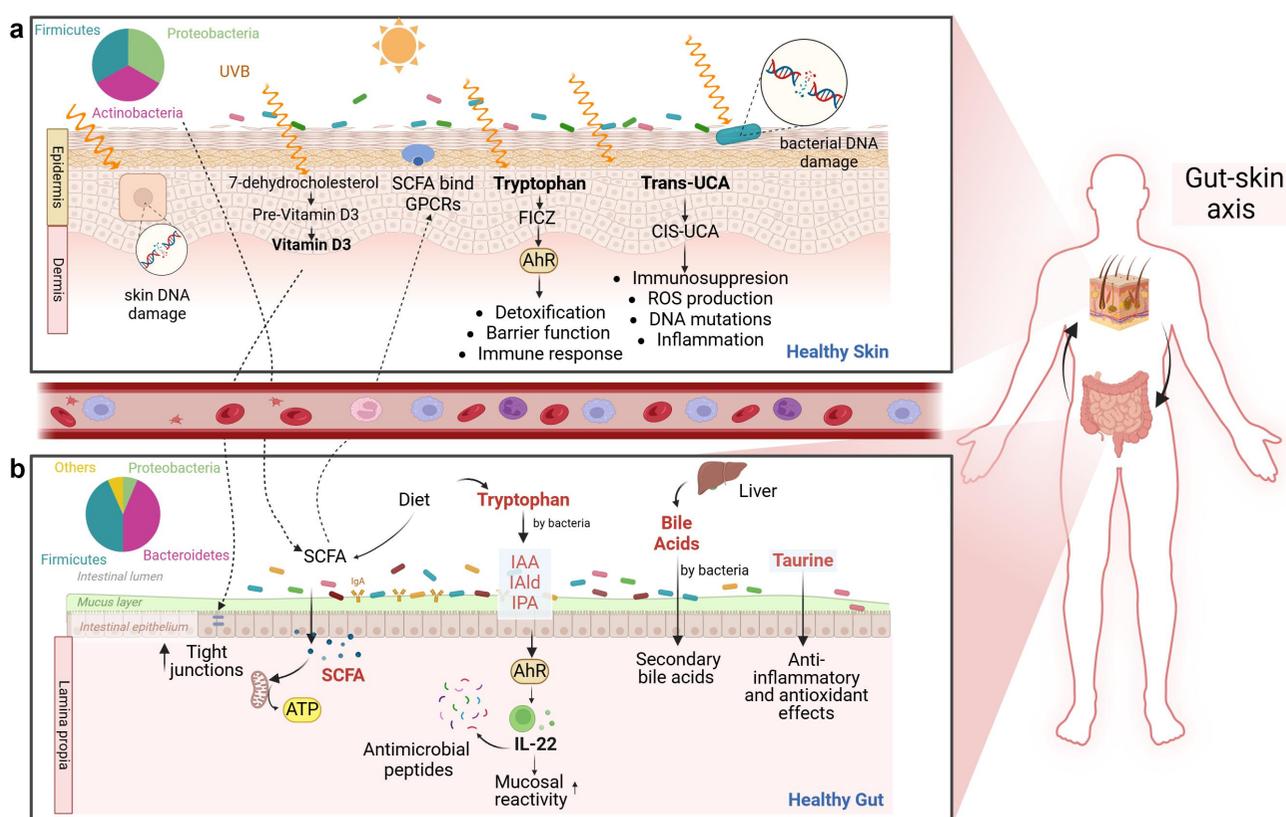
As previously noted, many studies have linked a dysbiotic skin microbiota to cutaneous pathologies such as acne, AD, and psoriasis.<sup>208</sup> Moreover, these conditions are often associated with concurrent GI diseases such as IBD, IBS and celiac disease. This raises the question of whether the ameliorative effects of UV radiation on these diseases may in part reflect UV driven-modification of the skin and gut microbiota. We suspect that exposure to UV radiation, depending on the exposure time and intensity, can directly modify skin microbial communities.<sup>205</sup> One of the major effects of UV radiation on microbes is DNA damage. However, some bacteria and fungi show a selective tolerance to UV radiation at specific stages of their life cycles, but are often susceptible during sporulation, diffusion and infection.<sup>205</sup> Thus, UV radiation could cause the loss of more susceptible microbes.<sup>209</sup> Wang et al. revealed that porphyrins produced by *Propionibacterium acnes* (*P. acnes*) were decreased following UV treatment, providing evidence that skin bacteria are sensitive to UV exposure in patients with acne.<sup>210</sup> AD patients have also been shown to carry increased *S. aureus* burdens on their skin, which were reduced after UVB treatment.<sup>211</sup> In concert with any UV-induced

changes in microbial composition, microbial metabolites should also be altered. In this section we describe some mediators that may underlie communication between the gut and skin microbiotas and their potential to being influenced by UV exposure (see Figure 2).

The importance of metabolites from the tryptophan pathway to both gut and skin health was previously addressed, but to what degree the production of these metabolites requires the microbiota is unclear. Recently, Patra et al. exposed germ-free (lacking a microbiota), disinfected mice (partially devoid of skin microbiota) and control mice with

an intact microbiota to UVB radiation (one time exposure). Assaying skin biopsies from these mice, the authors showed that UVB exposure increased tryptophan metabolism, but only in control mice that possessed an intact microbiota.<sup>212</sup> The authors highlight the difficulty in determining whether the increase in tryptophan metabolites caused by UV radiation was due to production by the microbiota or the host skin cells. Nevertheless, these results emphasize the importance of the skin microbiota in promoting a distinct metabolomics profile.

Another well-known product of gut bacteria are SCFA, which are produced through the fermentation



**Figure 2.** Effects of UVB on the skin and its potential impacts a) cutaneous exposure to UVB light can lead to the production of vitamin D from 7-dehydrocholesterol in the epidermis. Vitamin D also influences gut health by targeting three key components of the GI tract: the intestinal epithelial barrier, gut immunity, and gut microbiota. UVB light can cause DNA damage in skin cells and skin bacteria. UVB light also converts trans-uca to cis-uca in the skin, which generates ROS, resulting in immunosuppression, DNA mutations, and inflammation. Tryptophan acts as a chromophore when exposed to UVB light, leading to the production of 6-formylindolo [3,2-b] carbazole (FICZ), a potent activator of the AhR. AhR is involved in detoxification, barrier function, and immunity. b) exposing the skin to UVB light may impact distal organs such as the gut. UVB is reported to alter the gut microbiome composition and influence SCFA production. SCFA can be transported from the intestine to the skin, where they bind to G protein-coupled receptors (GPCRs) on skin cells, directly influencing tissue metabolism and function. In the gut, tryptophan can be metabolized by bacteria, producing AhR ligands that activate cells, such as ILC3 to produce IL-22. IL-22 regulates the release of antimicrobial peptides, thereby modulating microbial composition and affecting the balance between immunity and the microbiota. BAs, initially produced in the liver as primary BAs, can be metabolized in the colon by gut microbiota (e.g., *Clostridium* and eubacterium) into secondary BAs. BAs play fundamental roles in metabolism and immunological processes. Lastly, taurine can be degraded by sulfur-derived bacteria like *Bilophila* and *Escherichia*. Taurine plays roles in bile acid conjugation, osmoregulation, membrane stabilization, antioxidation, and modulation of calcium signaling. Created in Biorender.com

of indigestible polysaccharides.<sup>213</sup> Among the SCFA, butyrate is especially critical for gut homeostasis as it fuels colonocyte metabolism and acts on immune cells to reduce inflammation.<sup>214</sup> SCFA have been shown to travel from the gut to distant organs and tissues via the peripheral circulation.<sup>215,216</sup> SCFA bind to G protein-coupled receptors (GPCRs) expressed by skin cells, leukocytes, neutrophils, and other cell types, thereby directly impacting tissue metabolism and function.<sup>217,218</sup> For example, many patients with AD exhibit low levels of fecal SCFAs, in keeping with a low abundance of SCFA-producing bacteria,<sup>219</sup> a pattern also seen in animal models.<sup>220</sup> Acne, an inflammatory skin condition caused by the overgrowth of *P. acnes*, can be alleviated by the probiotic *Staphylococcus epidermidis*.<sup>221,222</sup> This probiotic inhibits *P. acnes* colonization and its ability to induce inflammation by producing SCFAs.<sup>223</sup> In terms of GI diseases, IBD patients often carry lower levels of SCFA in their feces as compared to healthy controls.<sup>81</sup> Human and murine studies indicate that multiple exposures to sub-erythemal UV radiation can enhance the diversity of the gut microbiota, potentially increasing the presence of SCFA-producing bacteria. It remains untested however, whether this results in a measurable increase in SCFA levels.<sup>17,224</sup> In a recent study, mice were exposed to UVB radiation (75 mJ/cm<sup>2</sup>) three times per week for eight weeks to analyze the effects on the cecal microbiome. The study surprisingly found that UVB irradiation reduced bacteria involved in SCFA production such as *Prevotella*, *Roseburia*, *Ruminococcus*, and *Akkermansia*.<sup>225</sup> These results contradict previous studies, but it is important to consider the intensity of the UVB light and the frequency of exposure. The longer exposure period of eight weeks in this study suggests that long-term UVB exposure may have a detrimental effect on SCFA-producing bacteria.

Bile acids (BAs) are crucial metabolites that also impact both the gut and skin and may play a role in communication between these two organs. Originating from cholesterol, these natural surfactants are produced in the liver and released into the small intestine, where they aid in digestion and absorption of fats.<sup>71</sup> These primary BAs are not fully absorbed in the small intestine, so a portion reaches the colon,

where the gut microbiota metabolizes these primary BAs through a process called deconjugation and dehydroxylation. This microbial conversion transforms primary BAs, such as chenodeoxycholic acid (CDCA) and cholic acid (CA), into secondary BAs like lithocholic acid (LCA) and deoxycholic acid (DCA). In this process, bacterial enzymes, specifically bile salt hydrolases (BSH), hydrolyze bile salts, releasing free bile acids. Subsequently, certain gut bacteria, predominantly from the *Clostridium* and *Bacteroides* genera, catalyze the removal of the hydroxyl group at the 7<sup>th</sup> position of the bile acid molecule, leading to the formation of secondary bile acids such as LCA and DCA.<sup>226–228</sup>

Beyond their primary functions in lipid digestion and cholesterol regulation, BAs play a role in innate immune regulation.<sup>229</sup> Disruptions in BA balance, observed in conditions like psoriatic arthritis and IBD, can indicate an imbalance in the gut microbiota as well as abnormal immunity, leading to increased cytokine production.<sup>230,231</sup> The amino acid taurine is essential for BA conjugation and has been shown to have therapeutic potential in treating UC and other diseases,<sup>232</sup> for example taurine (0.05–0.15 g/day) effectively addresses psoriasis,<sup>233</sup> eczema, and prevents irritative dermatitis.<sup>234</sup> Studies in mice have shown that supplementing with BAs or using engineered bacteria that produce BAs will boost the numbers of colonic Tregs and decrease susceptibility to colitis.<sup>235,235</sup> Patients with psoriasis often display dysfunctional BA profiles, with lower levels of conjugated primary and secondary BAs.<sup>236</sup> Early clinical studies have indicated that oral supplements of dehydrocholic acid or ursodeoxycholic acid can treat psoriasis, likely by influencing gut microbiota or by inhibiting cutaneous phospholipase A2 activity.<sup>237,238</sup> Moreover, *in vitro* studies have shown that BAs can directly suppress IL-17A production by T cells, suggesting a mechanistic link between BAs and their anti-psoriatic effects.<sup>239</sup> Dietary changes and antimicrobial agents may help modulate the microbiota-BA axis,<sup>240</sup> potentially treating various disease of the GI tract as well as skin conditions. Since studies have not yet addressed whether UVB exposure on the skin can alter BA

metabolism, more research is needed to explore the potential connection between UV radiation-induced microbial shifts and BA metabolism.

Trimethylamine N-oxide (TMAO) is another gut microbial metabolite that can affect gut and skin health. Derived from dietary sources such as choline, betaine, and carnitine, increased levels of TMAO have been implicated in the pathogenesis of IBD and Hidradenitis suppurativa (HS),<sup>241</sup> a highly disabling inflammatory skin disease associated with several cardiovascular and metabolic diseases such as metabolic syndrome, hypertriglyceridemia, diabetes mellitus, ischemic stroke and myocardial infarction.<sup>242</sup> There is also an association between HS and IBD, indicating shared genetic susceptibility and immunological features between the two conditions,<sup>243</sup> but TMAO was not studied as part of this association. The relationship between HS and IBD is influenced by shared risk factors like smoking, genetics, and common disease features like fistula formation. A study revealed that IBD (CD (0.8%) and UC (1.3%)) is significantly more prevalent among HS patients than in the general population (0.3%), with a higher risk of developing new-onset IBD.<sup>244</sup> Additionally, a 2018 cohort study found that HS patients with IBD were predominantly younger African American females, more likely to be smokers, obese, and diabetic, with longer hospital stays and higher healthcare costs.<sup>245</sup> This connection can be explained through the GSA. Both HS and IBD involve immune dysregulation, driven by key cytokines such as IL-1 $\beta$ , IL-17, and TNF- $\alpha$ , contributing to chronic inflammation in both the gut and skin.<sup>244,246,247</sup> Disruptions in the gut microbiota in IBD may exacerbate systemic inflammation, affecting skin conditions like HS. The shared inflammatory environment in both diseases also explains common features like fistula formation due to the chronic, dysregulated immune responses that affect both the skin and gut. Targeted treatments, including TNF alpha inhibitors, have proven effective in both HS and IBD, showing their interconnected inflammatory pathways.<sup>244,246,247</sup> Thus, acknowledging the GSA in HS patients with GI symptoms may warrant further evaluation for IBD, highlighting the importance of integrated care for both conditions. Interestingly, Vitamin D supplementation has shown promise in reducing TMAO levels, suggesting a novel therapeutic approach for both IBD and

HS.<sup>248</sup> Considering this, we suggest that exposure to UVB radiation, and its induction of Vitamin D should be studied for its potential to lower TMAO levels.

### UV radiation as a possible therapy for conditions linked to the GSA

The GSA has emerged as a significant area of research in recent years, attracting growing interest for its focus on defining mechanisms of communication between organs in the human body, as well as its potential for developing therapies for both skin and gut disorders. Researchers have studied several therapies to modulate the gut microbiota, such as probiotics and prebiotics,<sup>249</sup> dietary modifications,<sup>250,251</sup> topical therapies,<sup>252</sup> and fecal microbiota transplantation (FMT).<sup>253</sup> In contrast, phototherapy has been primarily studied in the context of skin diseases.<sup>185,188–190</sup> UV radiation has been investigated for its potential therapeutic effects on the skin, with studies suggesting that it can impact the cutaneous immune system through the GSA.<sup>205</sup> An exciting concept is that sunlight, particularly UVB light, may offer protective properties against a range of immune-mediated disorders, extending beyond the conventional role of vitamin D.<sup>254</sup> This discovery has sparked new discussions among scientists and reshaped our understanding of potential treatment approaches.

Phototherapy, a promising intervention, could provide benefits far beyond vitamin D regulation. Observations of SCFA production by the gut microbiome<sup>17,225</sup> and activation of targeted AhR genes<sup>181</sup> in the gut after UVB exposure to the skin suggest that this effect may extend to bile acids, TMAO, and other metabolites regulated by the microbiota. Evidence indicates that exposing the skin to UV radiation can promote changes in gut microbiota,<sup>17,225</sup> although more studies are needed to confirm that these changes can yield gut health benefits. By further exploring the complex interactions within the GSA, future studies can pave the way for personalized and effective treatments that leverage the power of the microbiota to promote gut-skin health.

## Conclusions

In conclusion, our review highlights the dynamic communication in the skin and gut axis. While the various organs interact, these two organs are uniquely exposed to the environment, and play a crucial role in maintaining homeostasis, and balancing between beneficial and detrimental effects of environmental factors. We have shown that the GSA involves both microbiota-dependent and independent mediators, emphasizing the complexity of this communication. By understanding these interactions, we can anticipate advancements in therapeutic approaches and precision medicine. Ultimately, further research will help to clarify how environmental stimuli such as UV treatment can control the complex signaling networks that control human health and disease, offering prospects for improved patient outcomes and enhanced healthcare practices.

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## ORCID

Maira Jimenez-Sanchez  <http://orcid.org/0009-0002-6541-5226>

Larissa S. Celiberto  <http://orcid.org/0000-0001-9057-9041>

Hyungjun Yang  <http://orcid.org/0000-0002-3213-7568>

Ho Pan Sham  <http://orcid.org/0009-0002-8615-2197>

Bruce A. Vallance  <http://orcid.org/0000-0003-1345-6747>

## Data availability statement

Data sharing not applicable – no new data generated.

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