The gut-skin axis in health and disease: A paradigm with therapeutic implications

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As crucial interface organs gut and skin have much in common. Therefore it is unsurprising that several gut pathologies have skin co-morbidities. Nevertheless, the reason for this remains ill explored, and neither mainstream gastroenterology nor dermatology research have systematically investigated the gut-skin axis. Here, in reviewing the field, we propose several mechanistic levels on which gut and skin may interact under physiological and pathological circumstances. We focus on the gut microbiota, with its huge metabolic capacity, and the role of dietary components as potential principle actors along the gut-skin axis. We suggest that metabolites from either the diet or the microbiota are skin accessible. After defining open key questions around the nature of these metabolites, how they are sensed, and which cutaneous changes they can induce, we propose that understanding of these pathways will lead to novel therapeutic strategies based on targeting one organ to improve the health of the other.

Keywords:
diet; gut; microbiota; probiotic; skin

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Introduction

Gut and skin share a number of important characteristics: besides being heavily vascularised, richly perfused and densely innervated, they are massively colonised with distinct microbial communities and operate as crucial contact organs through which the mammalian body communicates with its environment. Moreover, they are complex immune and neuroendocrine organs that are fully integrated into the overall immune and endocrine systems. Proper functioning of both skin and gut is essential for homeostasis and survival of the entire organism [1].

Both diet and gastrointestinal disease impact on the skin, and defined dermatoses show a strong association with selected gastrointestinal (GI) diseases. This has long been integrated into the canon of both internal medicine and dermatology textbook wisdom [2, 3], as exemplified by the clinical pointers summarised in Table 1. Whilst it is not surprising therefore that the intimate, yet often underestimated relationship between gut and skin manifests itself most overtly in certain disease states, the pathobiological basis is often not fully understood [1–3]. Several conditions that primarily affect the gut also have manifestations in the skin, while several distinct dermatological entities can point to a primary, and sometimes life-threatening, underlying gastrointestinal disorder (Table 1).

The recognition that the gut and the skin engage in intimate tri-directional connections with the brain reaches far back into the first half of the 20th century, notably to the dermatologists Stokes and Pillsbury [4, 5]. More recently, interest in dissecting the gut-skin axis has been revived by the report that feeding certain lactobacilli to mice can markedly change the overall skin phenotype [6]. Thus, it is both timely and important to systematically re-explore the potential of a gut-skin axis. Clearly, some of the overlap of gut/skin pathologies may be genetic (e.g. some polyposis syndromes) or due to shared pathobiological processes (e.g. systemic vasculitis). Because of space constraints, genetically determined overlap conditions will not be considered here. Instead, we will focus on important potential mechanisms including

Table 1. Clinical pointers to the gut-skin axis

Disease/ condition	Gastrointestinal manifestation	Cutaneous manifestation	Comments and references
Inflammatory bowel disease	Chronic relapsing inflammation	Skin ulcers, vasculitis hair loss, Erythema (reddening) folliculitis, Psoriasis	The course of chronic relapsing gut inflammation often is mirrored by the appearance and disappearance of associated skin lesions. Refs. [7, 8]
Coeliac disease	Malabsorption	Dermatitis, Psoriasis	If this specific GI disease or this dermatosis are seen, the likelihood that the 'partner disease' in the other organ system is also present is very high. Refs. [9, 10]
Rosacea	Intestinal dysplasia *H. pylori* infection, intestinal bacterial overgrowth	Papules & pustules, erythema	While long misinterpreted as an acne-like disease, this skin disease is now understood as a characteristic, stereotypic response pattern of the skin immune system and skin vasculature to the exposure to certain microbial products and antigens, seen in susceptible individuals. Refs. [11, 12]
Cutaneous paraneoplasia	Malignant GI tumor – can be pancreatic or intestinal	Acanthosis nigricans (darkened, thickened patches of skin)	The listed skin signs so strongly point to the presence of an underlying GI malignancy that they make a systematic oncological screening mandatory
		Erythema gyratum repens (reddening with a 'wood grain' appearance)	Reviewed in [13]
		Hypertrichosis lanuginosa (excess hair on the body	
		Léser-Trélat (sudden appearance of numerous warts on the trunk)	
		Comment: All of the above make oncological screening mandatory)	
Peutz-Jeghers Syndrome	GI polyposis and malignancy	Peri oral hyperpigmentation	Excessive pigmentation spots on and around the lips indicate the presence of polyps, namely in the small intestine. Reviewed in [14]

diet and the specific microbiota of gut, and immune- and central nervous system-dependent mechanisms of potential interaction (summarised in Fig. 1). Thus, we not only recall attention to the existence of a gut-skin axis in the light of recent research progress, and independent of genetics, but also a clinically relevant inter-organ communication axis that is open to therapeutic intervention.

How gut and skin can impact on one another – principle pathways

Does the gut microbiota have an impact on skin health?

As long ago as 1907, Metchnikoff [15] postulated that health and longevity are intimately connected to the gut microbiota. The 'virtual organ' that is the gut microbiota has huge immunological impact and metabolic capacity which may affect other organ systems including the skin. Hence, we hypothesise that the gut microbiota is central to the gut-skin axis. A recent pivotal study in mice supports this hypothesis: Erdman's group demonstrated that addition of the probiotic organism, *Lactobacillus reuteri*, to the drinking water of mice resulted in several beneficial changes to the integumentary system. *L. reuteri* supplemented mice had increased dermal thickness, increased folliculogenesis, a more acid pH of the skin and increased sebocyte production. All these changes led to shinier, thicker fur in the probiotic-supplemented mice when compared to mice not supplemented with *L. reuteri*. The mechanism underlying these positive changes was found to be immune based. Probiotic-fed mice exhibited increased serum levels of the anti-inflammatory cytokine IL-10, and decreased serum levels of the pro-inflammatory IL-17 [6, 16]. The effects of the probiotic were mediated via this pathway because IL-10 deficient mice exhibited no changes to their integumentary system when supplemented with *L. reuteri*. Many of the changes induced by IL-10 involved the induction of $CD4^+CD25^+Foxp3^+$ Treg lymphocytes [17–19]. Interestingly, purified $Fox3^+$ cells from donors fed *L. reuteri* were sufficient to produce all the probiotic induced changes to the integumentary system in recipient mice, even when these were not exposed to *L. reuteri* [16]. Thus these data add to an emerging picture that modulation of the immune system via Tregs has benefit beyond the gut.

Studies in humans also point to the potential for the gut microbiota to enhance skin health. In a human study, *L. paracasei* NCC 2461 was fed to 32 caucasian volunteers for 2 months. At the end of this time, the sensitivity of the skin to challenge with Capsacin, and transepidermal water loss (TEWL – a marker of barrier function) following tape-stripping were measured. In the *L. paracasei*-supplemented group, reduced skin sensitivity and TEWL were noted compared with the placebo-fed group [20]. The authors attributed these

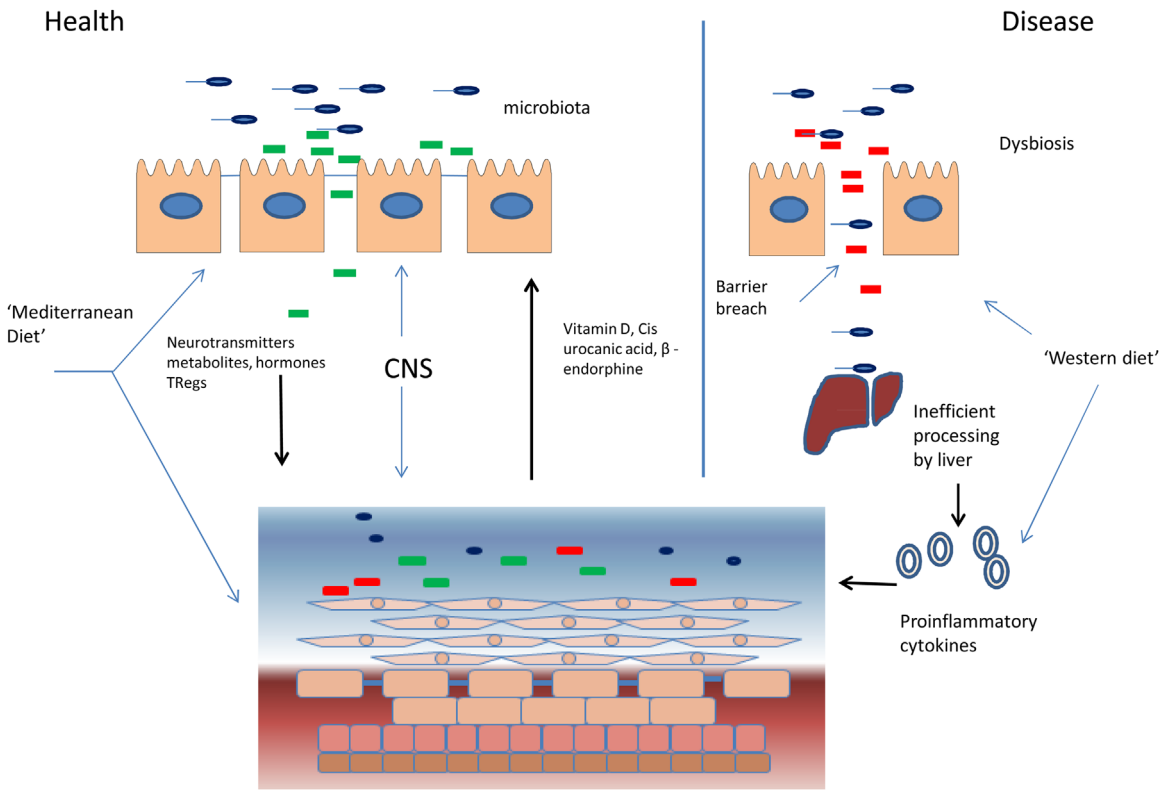

Figure 1. The gut skin axis has multiple components. In health, the gut and the microbiota produce metabolites (▬), neurotransmitters and hormones which can enter the circulation to modify the skin. Dietary components (▬) can also access the skin either directly or via processing by the micobiota. The skin also produces an array of chemicals which could modify the gut such as vitamin D. In disease, dysbiosis leads to production of toxins (▬) which can escape from the gut along with bacteria through a leaky gut barrier. Inefficient processing in the liver sets up a proinflammatory environment with consequences for the skin.

effects to an increase in circulating TGF-β levels observed in the *L. paracasei*-fed group because this cytokine is known to affect barrier integrity [21, 22]. Several other studies also point to a role for the gut microbiota in skin health largely via modification of the immune system [23–26]. Thus, all these studies support a concept whereby the skin and gut are linked via modulation of the immune environment via the microbiota. However, the resident microbiota of the skin is also vital in maintaining skin immune homeostasis. Skin is home to diverse commensal microbial communities which occupy distinct anatomical sites [27]. Microbial products from skin commensals, such as staphylococcal lipteichoic acid have been shown to have anti-inflammatory effects [28]. Furthermore, protection from cutaneous pathogens is the role of the skin, but not the gut microbiota [29]. Thus, gut and skin must work together for optimum skin health.

Is intestinal dysbiosis observed in skin disease?

The examples above suggest that gut bacteria can positively affect the skin. However, if this is true, then we hypothesise that disturbances in the gut microbiota may directly impact on the skin. Gut dysbiosis has been observed in conditions such as atopic dermatitis [30–32] and rosacea, where eradication of the associated small intestinal bacterial overgrowth leads to significant regression of the skin lesions [12]. What could be the possible mechanisms of these associations? We believe there are at least three scenarios:

(1) The gut microbiota have a huge capacity to synthesise molecules, with both beneficial or negative effects, that could then access the circulation and affect distant sites such as skin. For example, free phenol and p-cresol are metabolites of aromatic amino-acids that can be produced by gut bacteria, interestingly, most notably, *Clostridium difficile* [33]. Indeed, p-cresol is a biomarker of a disturbed gut. Recent evidence suggests that free phenol and p-cresol can access the circulation and preferentially accumulate in the skin of mice fed a diet rich in L-tyrosine [34]. In vitro data suggest that p-cresol and phenol reduce the expression of keratin 10 in cultured keratinocytes [34], and could thus impact on epidermal differentiation and epidermal barrier function. Furthermore, studies in humans suggest that restriction of probiotics results in elevated cresol levels in the serum, associated with reduced skin hydration and reduced size of corneocytes [34].
(2) As well as metabolites from gut bacteria, the gut bacteria themselves could enter the circulation, perhaps via a disturbed gut barrier, and travel to the skin. Consistent with this theory, it was recently reported that DNA of bacterial intestinal origin can be found circulating in the blood of patients with psoriasis [35]. In this context, it is

noteworthy that phagocytic Kupffer cells in the liver normally capture gut commensal bacteria and bacterial products/components thus preventing systemic inflammation. However, damage to the liver firewall leads to increased systemic exposure and systemic immune activation to intestinal commensals [36]. While the relevance of these later findings for the skin-gut axis remains to be verified, one can speculate that loss of function of Kupffer cells (e.g. that occurring in nonalcoholic steatohepatitis) allows intestinal bacteria to enter the systemic circulation and subsequently precipitate or contribute to skin pathologies.

(3) Immune effects – Several studies point to intestinal dysbiosis in inflammatory skin disease. The risk of developing atopic disease is increased in children having a reduced diversity of the intestinal microbiota in early life (1 week to 18 months of age) [31, 32, 37–39]. A limited number of studies has also observed gut dysbiosis in allergic children i.e. after the onset of allergy [40–42]. However, the data are conflicting: some studies show increased diversity associated with allergic disease, and others show decreased diversity. What is becoming clear is that any intervention with probiotic bacteria on the development of eczema seems to be required during the pre- and post-natal period. To date, all the clinical trials showing efficacy have demonstrated that pre- and post-natal feeding of probiotic species to mothers significantly reduces the risk of developing atopic dermatitis in the offspring of high risk groups i.e. parents with a history of atopic disease (exemplified by [28, 30, 31, 43]). The mechanism underlying this is currently unknown, but could be due to immune programing in utero [44]. The idea that gut microbiota modify the immune system in a manner that manifests in skin has been elegantly demonstrated using the Imiquimod mouse model of psoriasis. When treated with antibiotics, adult mice developed an ameliorated psoriasiform dermatitis when challenged with imiquimod. Surprisingly, mice treated neonatally with antibiotics were shown to develop exacerbated psoriasis when challenged as adults with imiquimod [45]. The role of probiotics as a treatment for psoriasis has also been investigated. A study in 26 patients with psoriasis investigated the effects of feeding a probiotic supplement for 6–8 weeks on the levels of circulating inflammatory markers. In the probiotic-supplemented group, the levels of CRP and TNF-alpha, but not IL-6 were much reduced following the intervention. However, the study size was not sufficient for any improvement in clinical outcomes to be assessed [46].

There also exists the possibility that the resident commensals of the skin can have further modulatory effects on immune-related skin disorders that may primarily be related to the gut microbiota. In this regard, dysbiosis of the cutaneous microbiota has been observed in several inflammatory conditions of the skin including psoriasis, atopic dermatitis and rosacea where gut dysbiosis is also observed [47]. Currently, it is not clear whether modulation of the gut in these conditions can also impact upon the skin microbiota.

Diet influences skin in both health and disease

The debate about the putative link between diet and skin disease is exemplified by conditions such as acne vulgaris where opinion was conflicting until recently. However, epidemiological studies coupled with mechanistic investigations have provided good evidence that acne is fuelled by the high glycaemic load typical of a western diet [48–50]. This is associated with high intake of carbohydrates and saturated fats and mechanistic studies suggest that this leads to a defect in nutrient signalling. In particular, in the activity of the transcription factor, FoxO1 and the growth factor sensitive-kinase, mechanistic target of rapamycin complex 1 (mTORC1) are aberrant in acne patients [51, 52]. Both FoxO1 and mTORC1 control lipogenesis in the sebaceous gland via modification of the transcription factor SREBP-1 [53]. Overstimulation of SREBP-1 results in increased production of monounsaturated fatty acids and triglycerides in the sebum, leading to colonisation with *Propionibacterium acnes* (Fig. 2, [54–56]). In particular, free oleic acid increases *P. acnes* growth in keratinocytes and stimulates the production of Il-1a that is critically involved in comedogenesis [57–60].

The link between diet and acne has further been exemplified via treatment regimes involving a low glycemic diet coupled with metformin, which acts as a multi-functional inhibitor of mTORC1 [61]. This regime has been shown to be effective in male subjects whose acne was resistant to other common treatments [61]. There is also well-known association between food allergy and atopic dermatitis: atopic dermatitis generally precedes food allergy [62]. In this context, an emerging important concept is that a poor skin barrier is the key driver of food allergy: the idea is that exposure to allergens via the cutaneous route and its extremely efficient antigen-presenting cells (Langerhans cells), before exposure by the oral route, causes oral tolerance to be bypassed. Thus, when the gut does get exposed to allergens such as peanut, egg, wheat, etc., this previous sensitisation by the cutaneous route leads to the symptoms associated with allergy [63]. A recent mouse model compared sensitisation via the oral versus the cutaneous route. Only mice sensitised via the skin had expansion of intestinal mast cells, raised IL-4 levels and anaphylaxis following food challenge [63]. In agreement with this observation, loss of function mutations in filaggrin (a skin barrier-related protein) are associated with peanut allergy in humans [64]. Peanut allergy is also more prevalent in homes where peanuts are consumed in significant quantities. The allergen retains activity for long periods of time [65] and can be found distributed around households in dust [66]. Therefore, it is easy to see how an individual may be exposed to peanut allergen via the skin before the gut ever has any exposure. Recently, an excellent study in humans [67] has shown that early exposure to peanuts (before 12 months) by the oral route results in fewer incidences of peanut allergy in high-risk groups, again suggesting that exposure must occur in the correct 'order' i.e. exposure by the oral route before the cutaneous route, in order to minimise the risk of allergy development (Fig. 2). However, quite how skin sensitisation promotes allergy has yet to be elucidated. Similarly, we do not know the mechanism by which, in orally sensitised patients with atopic dermatitis, cutaneous contact with food allergens

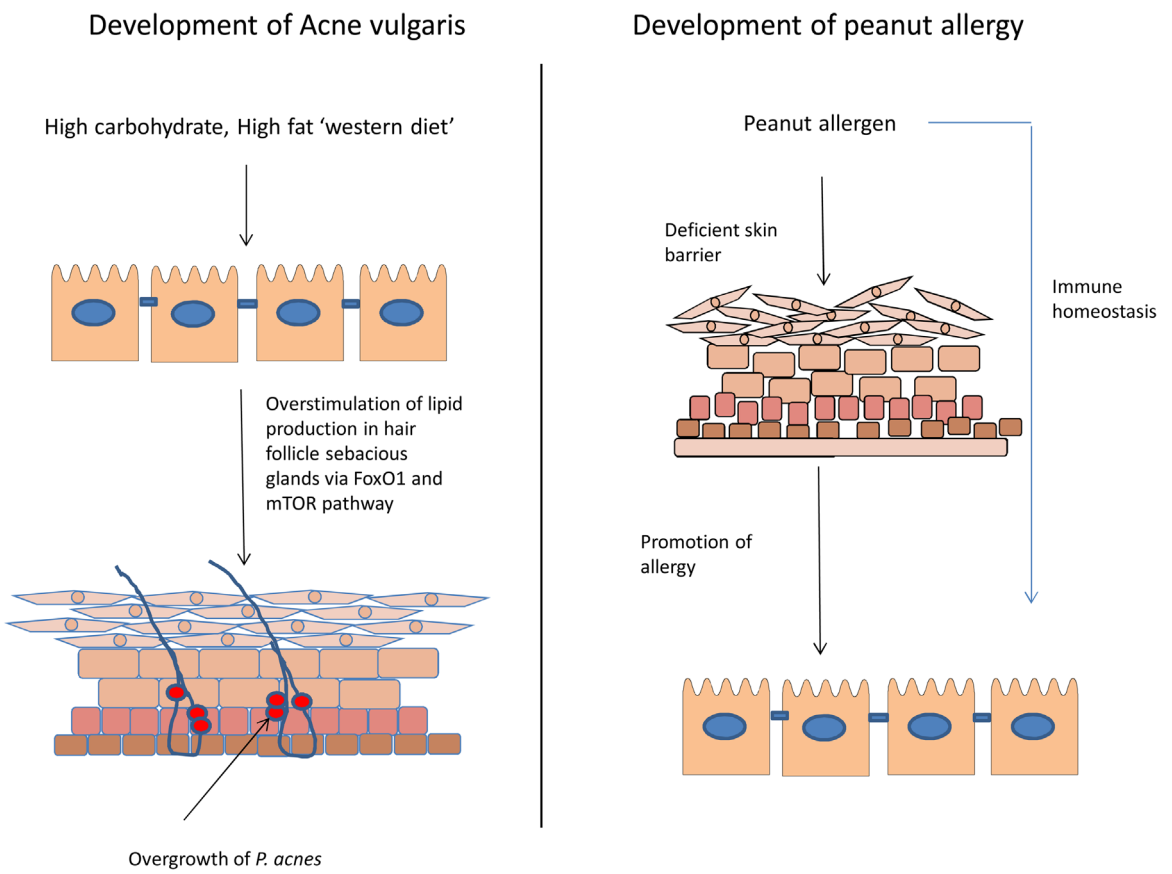

Figure 2. Diet affects the gut skin axis in disease. Left panel: acne vulgaris is known to be fuelled by the high glycaemic load typical of a western diet which stimulates lipid production in hair follicle sebaceous glands leading to overgrowth of *P. acnes* (●). Right panel: peanut allergy appears to be result of cutaneous exposure to the allergen before exposure via the oral route.

can trigger flare-ups of skin lesions. Studies in mouse models of atopic dermatitis show that antigen-specific gut-homing CD4 + α4β7 + T cells that develop in response to oral immunization can be reprogrammed in mesenteric lymph nodes following cutaneous antigen exposure to migrate to the skin and elicit allergic skin inflammation. Migration of effector T cells to the skin relies on skin-homing chemokine receptor CCR4, because allergic skin inflammation does not develop at sites of cutaneous antigen challenge in orally immunised CCR4-deficient mice [68]. Dendritic cell-derived vitamin-D3 is critical in reprogramming gut-homing antigen-specific T cells to express CCR4 and home to skin. This finding is consistent with the demonstration that mechanical injury, such as inflicted by scratching in atopic dermatitis patients, upregulates vitamin D3-metabolising enzymes [68].

Data are beginning to emerge as to the identity of dietary components with the capacity to positively modulate skin physiology. For example, metabolites of green tea catechins and polyphenols in strawberries are incorporated into the skin and can reduce the inflammation associated with ultraviolet radiation [69–71]. This is associated with reductions in the levels of particular pro-inflammatory eicosanoids. Green tea polyphenols are also showing promise as novel therapeutics for the treatment of melanoma (78). Curcumin is also reported to be chemoprotective [72]. Lycopene, a carotenoid found in tomatoes, is suggested to protect against both acute and long-term photodamage [73, 74] possibly due to its actions as an antioxidant. Dietary rice prolamin extracts are protective in mouse models of experimental atopic dermatitis perhaps due to their ability to promote T helper (Th) type1-immune response counteracting the pathogenic Th2 immunity [75]. An array of phytomolecules have also shown promise as anti-ageing products because of their abilities to scavenge free radicals, to prevent transepidermal water loss and to protect skin from wrinkle production (reviewed in [76]). For some of these molecules, it is clear that they can be incorporated into the skin [77]. However, for others, it remains possible that their mode of action may be via gut microbial metabolism [78, 79], or by altering the gut microbiota [80, 81].

If there is a true gut-skin connection mediated by diet, then we hypothesise that ethnic differences associated with dietary habits should be apparent. In agreement with this hypothesis, isolated hunter-gatherer communities have been documented to have extremely low rates of acne [82], and diets high in fibre, such as the Mediterranean diet, may have a protective role against development of atopic disease (reviewed in [83]). Whilst some of these observations might be related to genetics, the effects of diet cannot be ignored given recent evidence in inflammatory bowel disease where ethnic differences are also observed: recent studies suggest an increase in IBD prevalence in Asia, a finding that is not likely to be linked to family history. Indeed, one study involving over

300,000 participants with inflammatory bowel disease noted an association between a diet low in vegetables and disease incidence [84]. Conversely, diets high in fibre and low in carbohydrates such as the Mediterranean diet may have a protective role [83]. However, because diet also impacts upon the microbiota, the effect of diet on the skin is difficult to disentangle from its indirect effect via an influence on the gut microbiota.

Are there other possible modes of interaction between gut and skin?

Metabolic interactions may allow communication between gut and skin

While the gut has long been appreciated as a key organ of metabolism beyond its role in vitamin D synthesis [85], it is not as widely appreciated that the skin is also is a major metabolic organ whose range of enzymatic activities may rival that of gut and liver [86]. This may be particularly relevant for the metabolically most active human skin appendage, the hair follicle, which appears primarily to employ aerobic glycolysis and glutaminolysis and whose epithelium is prominently engaged in mitochondrial energy metabolism that underlies neuroendocrine controls [87, 88]. Thus, it not only remains to be systematically studied to what extent metabolites generated by the gut impact upon skin, but also whether circulating metabolites generated within the skin, including those under the influence of skin microbiota and associated xenobiotic enzymes, impact on gut metabolism and homeostasis.

Central nervous system and neuroendocrine interaction along the gut-skin axis

To simplify the discussion, for the purpose of this treatise, we do not discuss in-depth the interactions of the gut-skin axis with the central nervous system. (For background, see Arck et al. [89], Bowe and Logan [5].) An example of the importance of the GI-CNS-skin axis is the so-called 'zones of referred pain' (Head's zones), i.e. the projection of pain into defined skin regions induced by pathological changes in visceral organs [90]. More recently, it was reported that feeding mice one strain of lactobacilli greatly reduced neurogenic skin inflammation and associated hair growth inhibition induced by perceived stress [91]. This landmark observation may be related to several studies clearly demonstrating the production of neurotransmitters by the gut microbiota. These include dopamine, serotonin and GABA (Table 2). Experimental changes to the gut microbiota have been demonstrated to increase levels of substance P [92] and conversely, probiotics can reduce substance P release [93, 94]. Studies also suggest that the production of lipids by sebocytes is controlled at least in part by the cannabinoid receptor 2 (CB-2) [95]. This is of interest given that probiotics are capable of modulating cannabinoid receptor expression [96]. Obviously, it will be interesting and important to investigate whether this neural gut-skin axis also works in the reverse direction, i.e. can chronic skin inflammation impact on gut neurogenic inflammation that depends on sensory nerve fibres, mast cells, and spinal processing?

It is conceivable that neuroendocrine circuits that constitute an integral component of the gut-brain axis, i.e. afferent and efferent sensory and autonomic nerve fibres secreting neuropeptides or neurotransmitters also modulate biological responses outside the gut, e.g. in the skin. After ingesting nutrients, gut endocrine cells release a panel of peptides and amines that principally signal via the vagus nerves to the brainstem, eliciting a range of reflexes that control digestion and further food intake, but also exert systemic anti-inflammatory effects: these may be part of the physiological defence system installed against the antigenic load associated with a meal [97, 98]. It is possible that some of these anti-inflammatory secreted agents that are not immediately metabolised/inactivated in loco may also impact upon the skin. There is also good evidence that gut endocrine cells and their function are abnormal in gut infections [99, 100], in both coeliac and Crohn's diseases [101], and also with changing gut function during ageing [102, 103]. Given that human skin and its appendages are prominent target organs of a wide variety of neuroendocrine stimuli (besides producing most of these themselves) (reviewed in [104]), GI-disease-associated abnormalities in the serum level of selected neurohormones and neuropeptides are almost certain to impact also on skin health and dermatoses. However, this aspect of the gut-skin axis represents an as yet entirely unexplored frontier of translational skin and gut research.

Major open questions and future perspectives

For the reasons outlined above, we hypothesise the existence of a gut-skin axis that communicates via the metabolites, the neuroendocrine system, diet and the central nervous system. However, the gut-skin connection may well be largely influenced, either directly by the gut microbiota, and their products, or indirectly via the diet and/or secretory responses of GI epithelium to changes in gut microbiota or diet. Gut microbes synthesise a wide range of molecules that potentially have the capacity to influence the skin (see Table 2). The nature of these molecules may change with diet. Currently, much attention has focused on the nature of the microbial communities present in the gut; in contrast, much less is known regarding their functions for GI physiology, namely for GI epithelial biology. Hence we do not know key pieces of information such as the nature of the molecules produced by bacteria, which bacteria make them, whether we can alter the production of skin accessible molecules within the gut to make more or less of them depending on their effects. The skin, with its high lipid content may be a reservoir for accumulation of such compounds, which might explain the intimate and lasting relationship between the gut and the skin that clinicians have so long been aware of (Table 1), but whose molecular basis has mostly remained unexplored.

Another major open question is the identity of the possible mechanisms through which bacterial metabolites could be sensed in the skin. Of note is the observation that in the gut and other tissues, many bacterial metabolites are directly sensed by G-protein coupled receptors (GPCRs). Some of these

Table 2. Molecules synthesised by gut bacteria with the potential to modify skin either directly or indirectly

Molecule	Bacterial producer	Documented/ possible effects on skin	Example reference
Short chain fatty acids, e.g. butyrate, acetate, proprionate	Bacteroides, Bifidobacterium, Propionibacterium, Eubaterium, lactobacillus, Prevotella (McFarlane and McFarlane [111])	Anti-inflammatory effects	[113]
Tryptamine	*Lactobacillus*/*Bacillus* species (Jin et al. [112])	Itch	[113]
Trimethylamine	*Bacillus* species (Tang et al. [114])	Prevention of keratinocyte fragility	[115]
Acetylcholine	*Lactobacillus*/*Bifidobacterium* species (reviewed in Cryan and Dinan [116])	Barrier function	[117]
GABA	*Lactobacillus*/*Bifidoba*cterium species (reviewed in [116]).	Inhibition of itch	[118]
Dopamine	*Eschericia*/*Baci*llus species (reviewed in [116])	Inhibition of hair growth	[119]
Serotonin	*Eschericia*/*Streptococcus*/*Enterococcus* species (reviewed in [116])	Melatonin synthesis	[120]

GPCR-linked pathways are anti-inflammatory via inhibition of NF-kβ [105]). Currently, there are relatively little data as to whether skin expresses receptors for bacterial metabolites, but this is an area worthy of investigation in the future.

Another major area that has currently received little research attention is the response of the skin microbiota to changes in the gut. It is possible that components from the gut may be modulating the skin commensal microflora in therapeutically beneficial or detrimental ways. For example, garlic is readily broken down to allyl methyl sulphide which is bioavailable and is secreted through the skin, kidneys and lungs following ingestion [106]. Allyl methyl sulphide is also known to be moderately antibacterial [106]. The question then arises, does ingestion of garlic affect the microbial composition of the skin and if so, what are the consequences of this? Clearly there will be other molecules that may also reach the skins surface to modulate the microbiota. This is clearly a new area and one that in this era of 'omics' technologies, may be ripe for therapeutic exploitation.

Moreover, robust evidence is needed in the human system on whether the gut-skin axis acts uni- or bi-directionally. Irradiation of the skin with ultraviolet B induces expression of the β-endorphins [107] which have analgesic and pigmentary effects [108]. Synthesis of vitamin D (low in IBD, [109]) and urocanic acid which has been shown to suppress inflammation in models of IBD, also occurs in response to irradiation of the skin [110]. Thus, selective manipulation of the skin by topically applied agents or UV-irradiation, with its often underappreciated secretory and metabolic capacity, may offer new adjunctive therapies in GI diseases.

Conclusions and outlook

Here, we have explored the current evidence for the existence of a translationally relevant gut-skin axis. Figures 1 and 2 summarise this discussion by highlighting potential levels at which the future management of dermatoses and GI diseases may profit from targeting the gut-skin axis. The management of skin disease in the future may include manipulation of gut function. Treatments that augment or repair a leaky gut barrier could become important as adjuvant therapy in the management of inflammatory skin diseases and may help to increase the efficacy of standard dermatotherapy. Such treatments could work through manipulation of the gut microbiota or through direct effects on the gut epithelium using dietary agents or selected natural/synthetic components. All this would be geared towards modifying the secretory, metabolic and hormonal activity of gut epithelium in order to impact cutaneous inflammation.

Vice versa, augmenting the vitamin D status by enhancing intracutaneous vitamin D production via phototherapy, could become a future adjuvant treatment for inflammatory bowel disease. This, in theory, might also profit from the mild systemic immunosuppressive effects of skin UV irradiation. Just as gut microbiota impact on skin physiology and can aggravate or ameliorate some dermatoses (see above), it is possible that the therapeutic modulation of skin microbiota (e.g. via AMPs, antibiotics, antiseptics) will modify the secretory, metabolic and hormonal activity of the skin epithelium. Whether this can impact on gut inflammation is an intriguing, novel hypothesis which awaits 'proof of principle' studies.

The ability to modify the function of one organ by manipulation of the other is within reach, but now depends on concerted interdisciplinary efforts focused on better understanding of targetable pathways by which gut and skin communicate with each other. It is hoped that this rediscovery of the gut-skin axis will offer clinicians attractive, novel, well-tolerated treatment options thus overcoming the historically grown conceptual divide between dermatology and gastroenterology.

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