Casual Friday Presents

The Gut – Skin Axis

and a closer look at Atopic Dermatitis

A BIOGENETIX CLINICAL PRESENTATION

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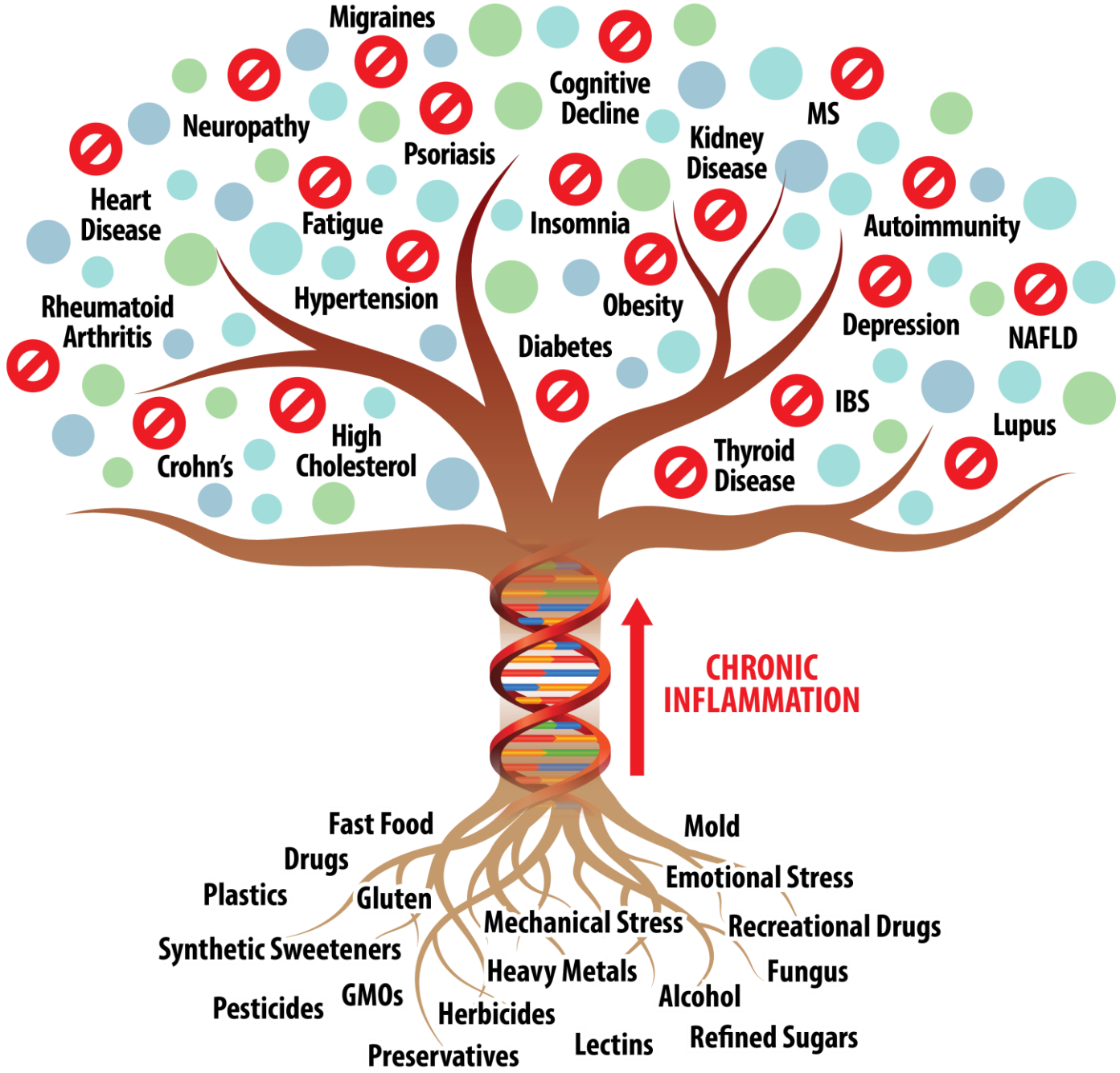
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Rheumatoid Arthritis
Hypertension
Obesity
Depression
NAFLD
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Drugs
Plastics
Gluten
Synthetic Sweeteners
Pesticides
GMOs
Herbicides
Preservatives
Lectins
Refined Sugars
Heavy Metals
Mechanical Stress
Alcohol
Mold
Emotional Stress
Recreational Drugs
Fungus

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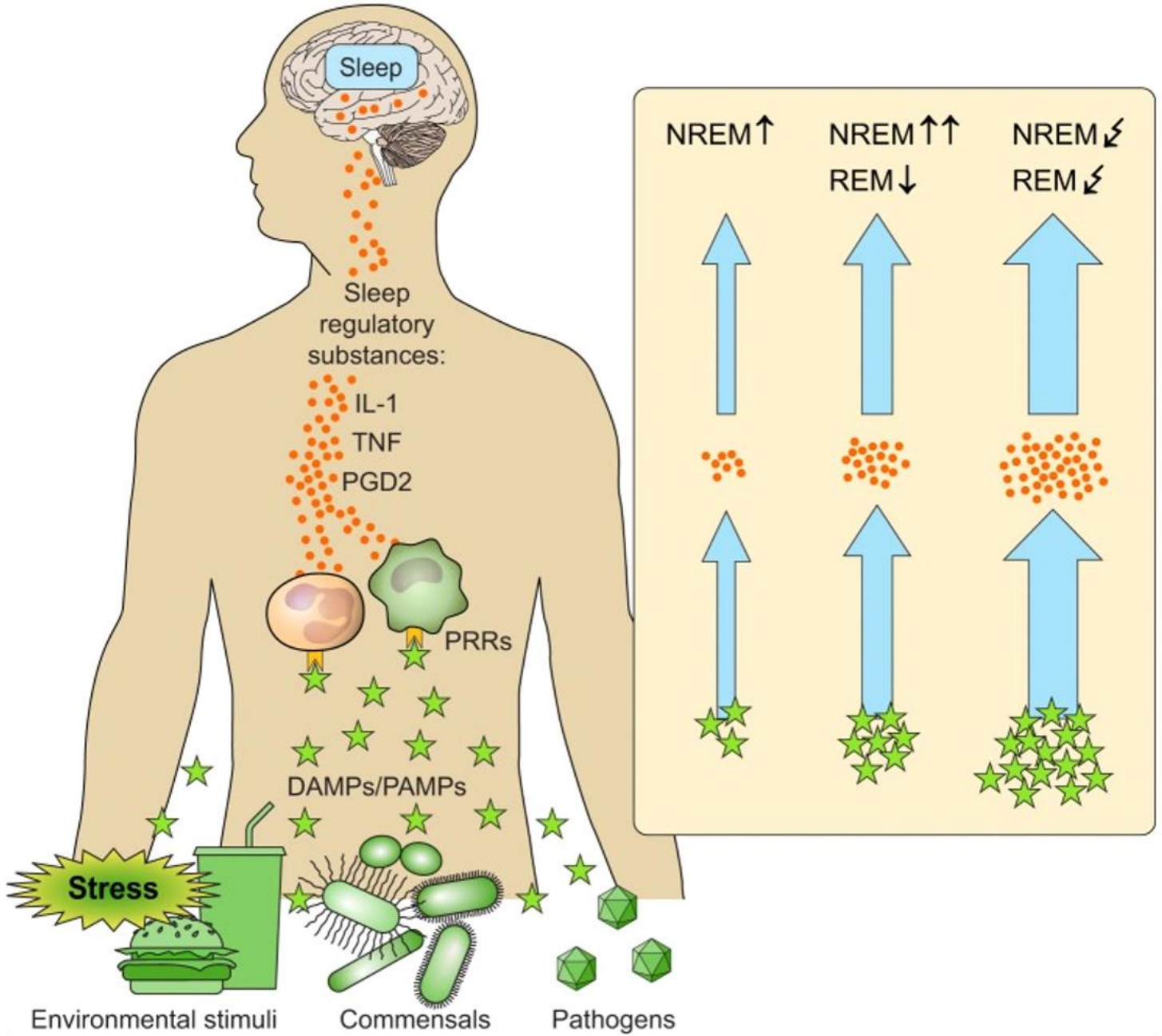

https://pmc.ncbi.nlm.nih.gov/articles/PMC6689741/

Volume 21, Issue 5, 31 October 2017, Pages 1160-1168

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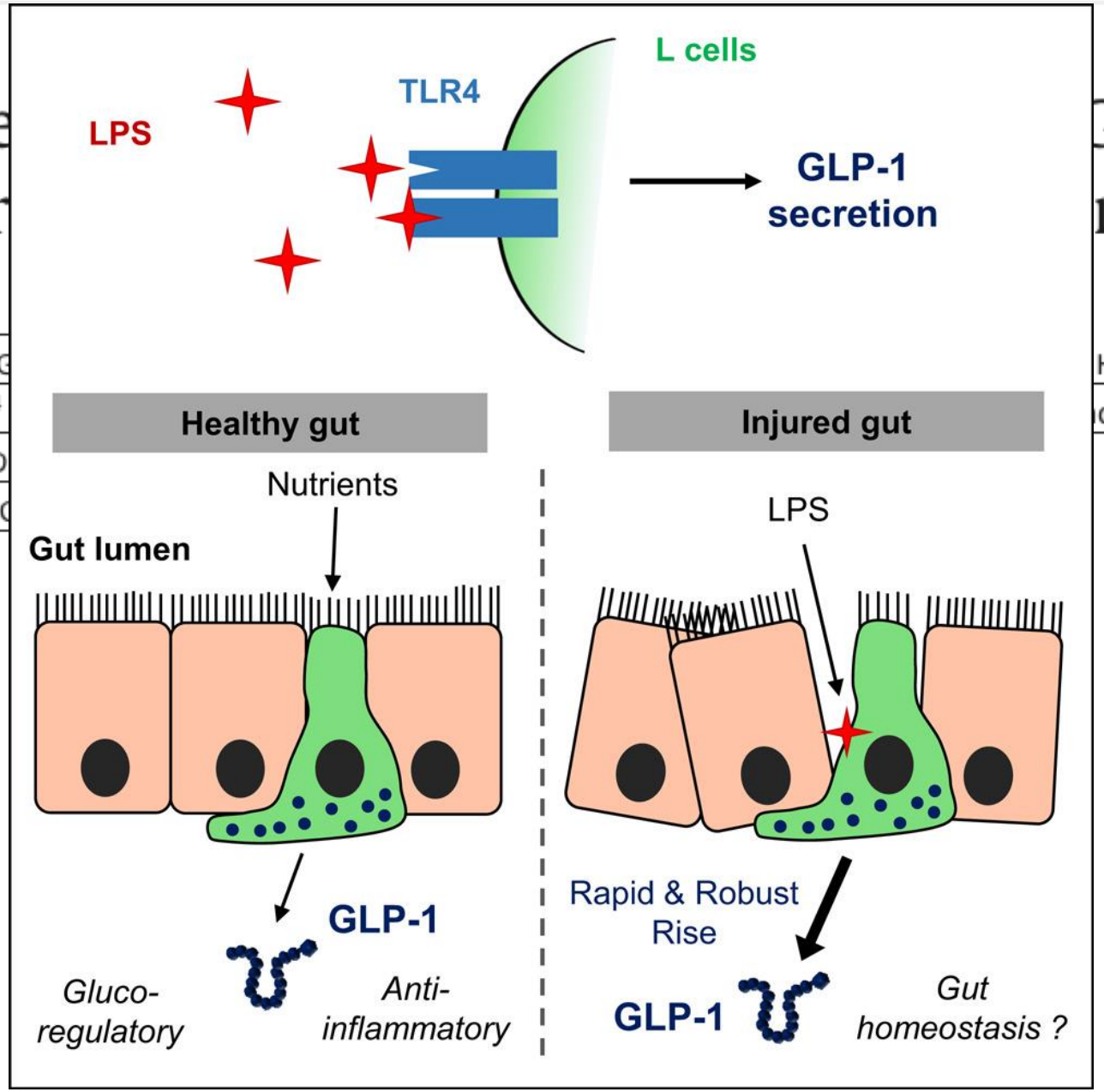

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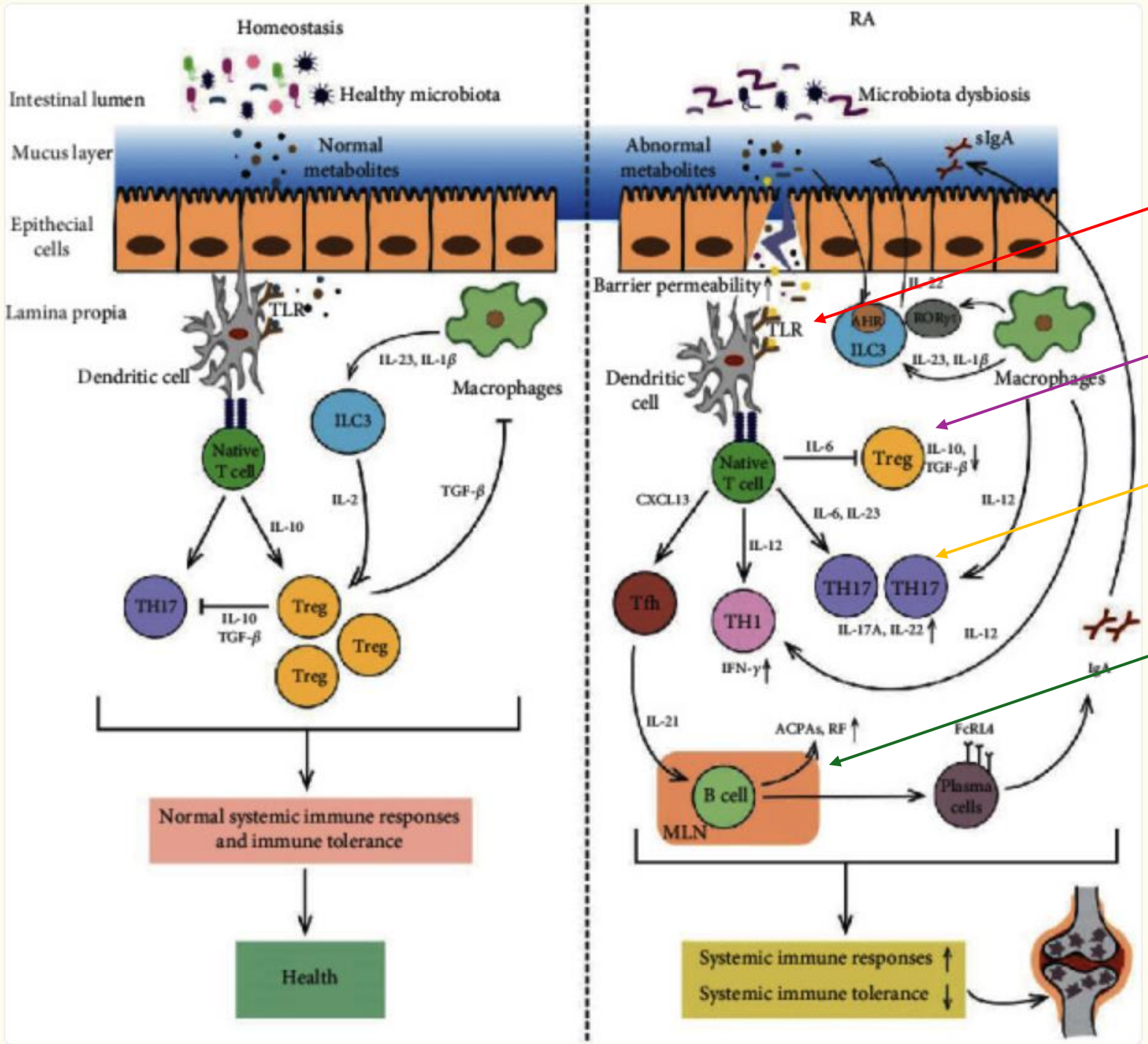
Homeostasis
Intestinal lumen
Healthy microbiota
Mucus layer
Normal metabolites
Epithecial cells
Lamina propia
TLR
Dendritic cell
IL-23, IL-1β
Macrophages
ILC3
Native T cell
IL-2
TGF-β
IL-10
TH17
IL-10 TGF-β
Treg
Treg
Treg
Normal systemic immune responses and immune tolerance
Health
RA
Microbiota dysbiosis
Abnormal metabolites
sIgA
Barrier permeability
IL-22
AHR
RORγt
ILC3
TLR
Dendritic cell
IL-23, IL-1β
Macrophages
Native T cell
IL-6
Treg
IL-10, TGF-β
CXCL13
IL-6, IL-23
IL-12
IL-12
Tfh
TH1
IFN-γ
TH17
TH17
IL-17A, IL-22
IL-12
IgA
IL-21
ACPAs, RF
FcRL4
B cell
Plasma cells
MLN
Systemic immune responses
Systemic immune tolerance

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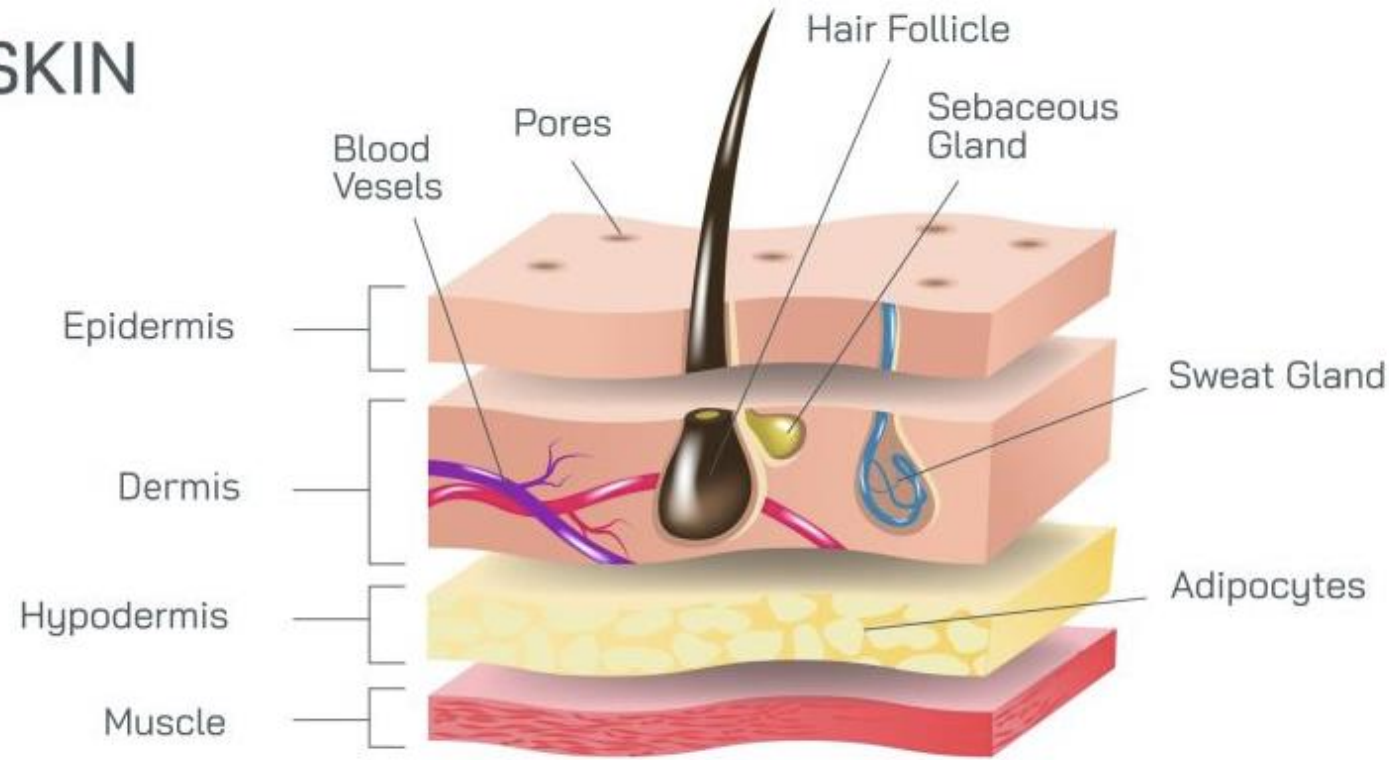
HUMAN SKIN
LAYERS



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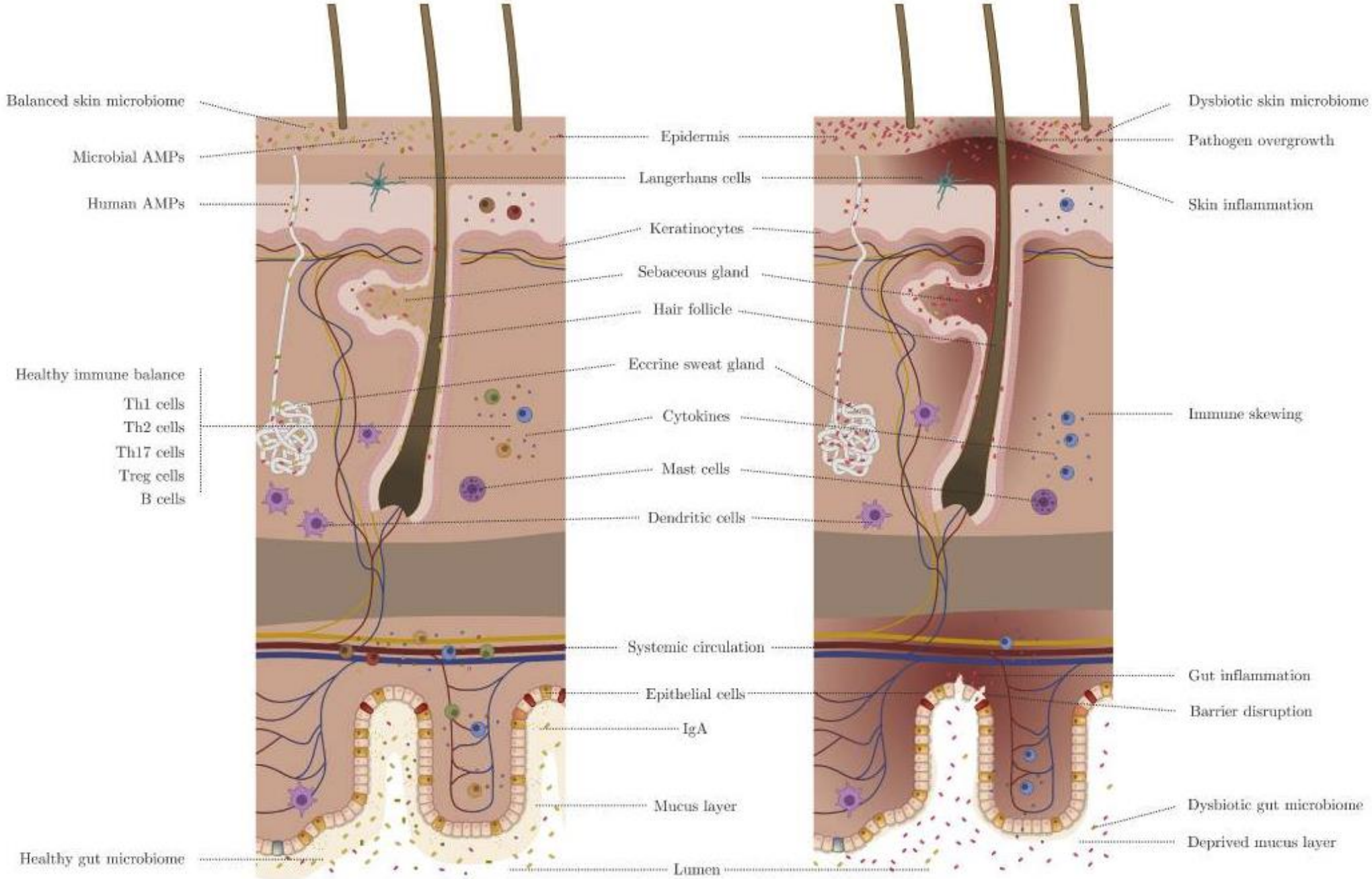
Balanced skin microbiome
Microbial AMPs
Human AMPs
Healthy immune balance
Th1 cells
Th2 cells
Th17 cells
Treg cells
B cells
Healthy gut microbiome
Epidermis
Langerhans cells
Keratinocytes
Sebaceous gland
Hair follicle
Eccrine sweat gland
Cytokines
Mast cells
Dendritic cells
Systemic circulation
Epithelial cells
IgA
Mucus layer
Lumen
Dysbiotic skin microbiome
Pathogen overgrowth
Skin inflammation
Immune skewing
Gut inflammation
Barrier disruption
Dysbiotic gut microbiome
Deprived mucus layer

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Microorganisms. 2021 Feb 11;9(2):353. doi: 10.3390/microorganisms9020353

Gut–Skin Axis: Current Knowledge of the Interrelationship between Microbial Dysbiosis and Skin Conditions

Britt… [1] … [2] … [1] … [3] …ert [1,*]

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The skin epidermis, along with its appendage structures, such as sweat and sebaceous glands, provide a total skin surface of about 25 m^2 and is one of the largest epithelial surfaces for interaction with microbes [1]. The skin is a first-line barrier from the outer environment, continuously interacting with it. The gastrointestinal (GI) tract is one of the largest interfaces (30 m^2) between the host and its environment [2]. About 60 tons of food is estimated to pass through the gut in a lifetime, all of which have a big impact on human health [3]. Both the gut and skin are immensely immersed with microbiota as it is estimated that the skin has about 10^{12} microbial cells while the gut accounts for 10^{14} microbial cells [4,5]. The microbiota point to the assemblage of specific microorganisms that are present within a defined environment. The emergence of next-generation sequencing in the past decade has provided unprecedented insights into microbiome composition, both on skin and in the gut. The microbiome refers to the genomes present in a certain environment, meaning the accumulation of all their genetic material (i.e., DNA and RNA). Both organs are characterized by a low microbial diversity at the phylum level but high diversity at the species level [6]. The microbiome provides a multitude of benefits to the host, such as shaping the immune system, protecting against pathogens, breaking down metabolites, and maintaining a healthy barrier [3].

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Britta aert [1,*]

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The gut and skin barrier share surprisingly many features. The gut and skin are highly analogous to each other in purpose and functionality. Both organs are highly innervated and vascularized, as they are both essential for immune and neuroendocrine function [11]. The gut–skin axis results from this resemblance [11]. The inner surface of the gut and the outer surface of the skin are both covered by epithelial cells (ECs) which have direct contact with the exogenous environment [12]. This way, the immune system is continuously primed to distinguish between harmful and beneficial compounds. Immune cell priming starts early on in life and forms the basis of tolerance, a crucial concept hypothesized to be flawed in several autoimmune disorders [13]. ECs maintain an important link between the internal body and the external environment. They act as a first line of defense, preventing the entry of microorganisms [12]. Keratin, which is present in the stratified squamous epithelium of the skin, presents a formidable physical barrier to most microorganisms [14]. In addition, this compound makes the skin resistant to weak acids and bases, bacterial enzymes, and toxins [15]. Mucosae provide similar mechanical barriers, as it comprises a glycoprotein layer on top of the epithelium in which commensal bacteria reside [16,17]. The epithelial membranes produce protective chemicals that eliminate microorganisms [18]. The skin acidity (pH of 5.4 to 5.9) creates an inhospitable environment for potential pathogens and inhibits bacterial growth [19]. Sebum produced by the sebaceous glands acts as a seal for hair follicles and contains several antimicrobial molecules as well as specific nutritional lipids for beneficial microorganisms [20,21]. Meanwhile, in the digestive system, saliva and lacrimal fluid contain lysozyme, followed by the stomach mucosae that secrete strong acid and protein-digesting enzymes [22]. In addition, mucus traps microorganisms that enter the digestive and respiratory tract [23].

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Gut–Skin Axis: Current Knowledge of the Interrelationship between

The second line of defense are the antimicrobial peptides (AMPs), phagocytes, and innate lymphoid cells (ILCs) [24]. These two first lines of defense form the innate immune system [23]. AMPs produced by keratinocytes, such as cathelicidin and psorasin, provide an effective barrier function to the skin [25,26]. The serine protease Kallikrein 5 (KLK5) cleaves cathelicidin into active peptides, such as LL-37 [27]. Compared to the skin, the composition of the intestinal epithelial barrier varies throughout the gastrointestinal tract. The proximal part of the gastrointestinal tract, the mouth and esophagus, is analogous to the skin, covered by multiple layers of squamous epithelium, which is cleansed by mucus from salivary and other glands [28]. The remaining part of the digestive tract includes a single layer of active cells, e.g., goblet cells (mucus secretion), enteroendocrine cells (hormone secretion), enterocytes or colonocytes (absorption), etc. [29,30]. The intestinal epithelium constitutes a single layer of enterocytes or colonocytes, and its barrier integrity is protected by the immune system. The absorptive functionality of the enterocytes in the small intestine ensues a discontinuous layer of mucus with fewer goblet cells [31]. Paneth cells are enriched in the crypts of the small intestine that secrete AMPs, which integrate in the complex mucus layer [32].

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Gut–Skin Axis: Current Knowledge of the Interrelationship between Microbial Dysbiosis and Skin Conditions

Britta De Pessemier [1], Lynda Grine [2], Melanie Debaere [1], Aglaya Maes [1], Bernhard Paetzold [3], Chris Callewaert [1,*]

Editor: Lionel Breton

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The skin is the largest and most external barrier of the body with the outer environment. It is richly perfused with immune cells and heavily colonized by microbial cells, which in turn train the immune cells and determine the well-being of the host [49]. The skin microbiome has gained significant attention in recent years in dermatology, skin disorders, and its connection and influence on the immune system. Many skin conditions are associated with an imbalance in the skin microbiome (Table 1). More and more studies have shown enriched pathogens and microbiota that are associated with skin conditions, some of which are obvious and others more surprising. It is nonetheless difficult to determine whether the altered skin microbiome is a cause or consequence of the skin disorder.

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Table 1.

Skin microbiota associated with nine common skin disorders.

Disease	Associated Skin Microbiota	Additional Remarks	Reference
1. Acne vulgaris	Particular *C. acnes* strains	Administered probiotic bacteria could play a protective role.	[71,72,73,74,75,76,77,78,79]
2. Atopic Dermatitis	Decreased bacterial diversity. Increased abundance of *S. aureus*.	Herpes simplex virus and coxsackie virus can infect AD * skin.	[55,80,81,82,83]
3. Psoriasis	Higher abundance of *Staphylococcus* and *Streptococcus*.	Anti-psoriasis treatments lead to skin microbial changes.	[84,85,86,87,88]
4. Hidradenitis suppurativa	*Saccharomyces cerevisiae*(yeast), *Prevotella*, and *Porphyromonas* (bacteria)	Anaerobic species in lesions.	[89,90]

5. Rosacea	*Demodex folliculorum* (mites)	*C. acnes* decreased and *Snodgrassella alvi* increased. *Geobacillus* and *Gordonia*.	[91,92]
6. Dandruff and Seborrheic dermatitis	*Malassezia* spp. (yeast)	Potential bacterial imbalance.	[93,94,95,96]
7. Alopecia areata	Limited data. Possible imbalance *C. acnes/ S. epidermidis*.	Potential role of cytomegalovirus and/or *Alternaria* fungi.	[97,98,99]
8. Skin cancer	Merkel bell Polyomavirus, *Fusobacterium*, and *Trueperella*, *S. aureus*.	Increase in certain strains of *S. aureus* in combination with a decrease in skin commensals can be associated to SCC * or BCC *, and that in MCPyV * can be associated to MCC *.	[100,101,102,103]
9. Wound healing	*S. aureus* and biofilm-forming bacteria.	Lactobacilli and fermented products can be beneficial.	[104,105]

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Dysbiosis in the gastrointestinal system is quite often linked to inflammatory diseases (Table 2) [8,9,10]. Gastrointestinal disorders are associated with certain dermatoses, for instance, 7–11% of patients with IBD also suffer from psoriasis [65]. The connection between the skin and gut seems to be mediated by the host immune system. The interaction of the microorganisms and the host immune system is important to maintain the skin homeostasis. The gut–skin axis may be viewed as an integral part of the gut–brain–skin axis, elegantly described by Arck et al. and by Bowe and Logan [7,66]. Table 3 lists neurotransmitters that are produced by intestinal microbiota that might cross the intestinal barrier, enter the bloodstream, and instigate systemic effects (Figure 1) [67,68]. In addition, SCFAs, such as butyrate, acetate, and propionate, are fermentation products derived from undigested polysaccharides by intestinal bacteria (e.g., *Bacteroides*, *Bifidobacterium*, *Cutibacterium*, *Eubacterium*, *Lactobacillus*, and *Prevotella*) [69]. These SCFAs, especially butyrate, enhance epithelial barrier function and decrease the permeability of the intestinal barrier [70]. However, the SCFA quantity that enters the bloodstream is dependent on the individual fiber intake, the microbial fermentation rate, and the amount of colon absorption. All these compounds, which are derived from the gut, could all interact with skin receptors and could directly affect the skin or modify the skin's commensal bacteria. Further research is needed to reveal if a clinical significant amount of SCFAs is reached in the bloodstream to affect the skin [11]. The studies from Table 3 support that the gut and skin interact with one another via the diet, microbial metabolites, the neuroendocrine pathways, and the central nervous system.

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Gut microbiota associated with nine common skin disorders.

Disease	Associated Gut Microbiota	Additional Remarks	Reference
1. Acne vulgaris	Decrease in Firmicutes and increase in Bacteroides.	Distinct gut microbiome composition and decreased diversity.	[106]
2. Atopic Dermatitis	Higher levels of *Faecalibacterium prausnitzii*, *Clostridium*, and *Escherichia* (in infants). Lower levels of *Akkermansia*, *Bacteroidetes*, and *Bifidobacterium*.	Probiotics consumption can prevent AD *.	[107,108,109,110,111,112,113,114]

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3. Psoriasis	Changes in β-diversity. Gut microbiome changes in reaction to biologicals.	Increased risk of intestinal immune disorders. Diet and gut microbiome can have an impact on inflammation.	[115,116,117,118,119,120]
4. Hidradenitis suppurativa	Unknown	Increased risk in developing CD * and UC *.	[121,122]
5. Rosacea	Can be associated with SIBO *. *Acidaminococcus* and *Megasphaera* increase and *Peptococcaceae* and *Methanobrevibacter* decrease.	Can be associated with *H. pylori* infection.	[123,124,125]

Molecules with potential a modulatory effect on skin and gut either directly or indirectly.

Molecule	Documented/Possible effect in gut	Documented/Possible effect on skin	Reference
Bacterial metabolites			
SCFAs *	Anti-inflammatory effects	Anti-inflammatory effects	[132]
Vitamin D	Suppress inflammation in IBD*	Not reported	[133]
Urocanic Acid	Suppress inflammation in IBD*	Not reported	[134]
GABA *	Neurotransmitter modulation	Itch restriction	[135,136]
Dopamine	Neurotransmitter modulation	Inhibition of hair growth	[135,137]
Serotonin	Neurotransmitter modulation	Melatonin modulation	[135,138]
Acetylcholine	Neurotransmitter modulation	Barrier function	[135,139]
Phenol and **p-cresol**	Biomarker of gut dysbiosis	Impaired epidermal barrier function	[140]

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Dietary components			
Catechins	Anti-inflammatory effects	Anti-inflammatory effects	[141]
Polyphenols	Anti-inflammatory effects	Anti-inflammatory effects	[142]
Lycopene	Selectively utilized by host microbiota	Protection against photodamage	[143,144]
Prolamin	Not reported	Protection against AD *	[145]
Phytomolecules	Not reported	Anti-ageing	[146]
Gluten	Coeliac disease	Skin Rashes	[58,59]

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Gut–Skin Axis: Current Knowledge of the Interrelationship between

5.3. Gut Microbiome and Diet Implications in AD

Studies have shown a gut dysbiosis association in patients with atopic dermatitis. The gut microbiome of AD patients was enriched in *Faecalibacterium prausnitzii*, had more genes encoding for release of molecules that can damage the gut epithelium, and had lower levels of butyrate and propionate, which possess anti-inflammatory properties [107]. Higher levels of *Clostridium* and *Escherichia* were found in the gut of atopic infants compared to healthy controls [108,109,110,111]. *Clostridium* and *Escherichia coli* in the intestine can contribute to an inflammatory state [110]. On the other hand, lower levels of *Akkermansia*, *Bacteroidetes*, and *Bifidobacterium* were found in AD patients, compared to healthy controls [112,113]. Butyrate-producing bacteria (f.i. *Coprococcus*) were more abundant in healthy infants or infants with mild AD, compared to infants with severe AD [192]. A likely effective therapeutic option for AD involves the consumption of probiotics, for which a considerable number of studies have been published [193]. In most of the studies *Lactobacillus* and *Bifidobacterium* have been tested [194]. Studies have been conducted in children and adults and during pregnancy, for which often contrasting efficacy results have been obtained [195].

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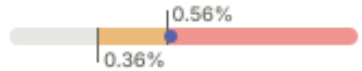
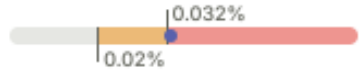
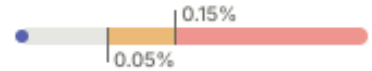
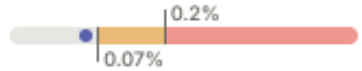
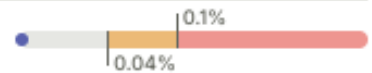
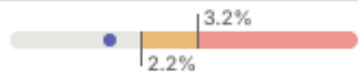
Evidence from a meta-analysis supports the use of probiotics for the treatment of AD in infants; however, the benefit likely results from primary prevention of atopic dermatitis, as also concluded by the World Allergy Organization [114,196,197]. The prophylactic effect of probiotics is likely due to its mediating role on the host immune system. Probiotics can interact with dendritic cells, can balance Th1/Th2 immunity, and can enhance Treg activity, as described in in vitro and in animal models [198,199]. These studies show the impact of the gut microbiome (dysbiosis) on Th2-type immune response to allergens in the skin [200]. Diet has been implicated in atopic dermatitis and Th2-driven inflammations. A reduced consumption of fruit, vegetables, and ω-3 fatty acids and increased consumption of ω-6 fatty acids have been linked to atopic dermatitis [201,202]. Epidemiologic studies have demonstrated associations of atopic dermatitis (and asthma) with margarine, fish, ω-6 polyunsaturated fatty acid (PUFA), and ω-3 PUFA [202]. Further research is nonetheless

⚠ Escherichia flexneri (sp)	0.682%	
⚠ Escherichia dysenteriae (sp)	0.107%	
Citrobacter (g)	0.000%	
Enterobacter (g)	0.051%	
Enterobacter hormaechei_A (sp)	0.050%	
⚠ Morganella (g)	0.055%	
Morganella morganii (sp)	0.055%	
Raoultella (g)	0.000%	
Streptococcus (g)	0.750%	
Streptococcus lutetiensis (sp)	0.383%	
Streptococcus salivarius (sp)	0.141%	
Streptococcus sp001556435 (sp)	0.105%	

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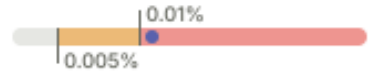
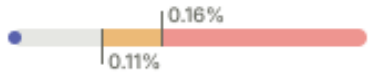
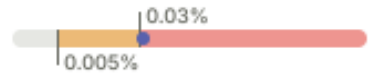
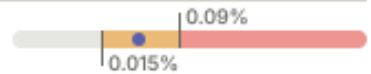
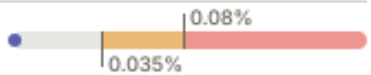
⚠ Staphylococcus (g)	0.050%	
Pseudomonas aeruginosa (sp)	0.000%	
Haemophilus influenzae (sp)	0.000%	
Haemophilus parainfluenzae (sp)	0.000%	
⚠ Enterococcus faecium (sp)	0.058%	
! Enterococcus faecalis (sp)	0.047%	
Clostridioides difficile (sp)	0.000%	
Clostridium perfringens (sp)	0.000%	
Acinetobacter baumannii (sp)	0.000%	
Campylobacter (g)	0.000%	

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Common Dietary TH2 Drivers and Triggers:

•**Dairy Products:** Casein and whey in cow's milk, cheese, and yogurt are top triggers, particularly in children.

•**Eggs:** Egg protein, especially in egg whites, can trigger immediate and delayed eczematous reactions.

•**Gluten & Wheat:** Linked to increased risk of atopic dermatitis and increased keratinocyte-derived TSLP, which drives the Th2 immune response in the skin.

•**Soy Products:** Documented as a leading trigger, particularly in infancy.

•**Peanuts & Tree Nuts:** Major triggers, often causing systemic reactions.

•**Sugar & High-Glycemic Foods:** Refined sugars increase systemic inflammation, contributing to flare-ups.

•**Processed Foods & Meat:** High intake of processed foods, including processed meats, is associated with a higher risk of atopic dermatitis in a dose-dependent manner.

•**Certain Seafood:** Shellfish and prawns are often cited, while some fish may be tolerated.

•**Certain Fruits/Acidic Foods:** Citrus fruits, tomatoes, and strawberries are reported as triggers by some sufferers.

•**Caffeine & Specific Drinks:** Caffeine (in coffee, chocolate, tea) can suppress Th1 immune function and overstimulate the Th2 immune system. [1, 2, 3, 4, 5, 6]

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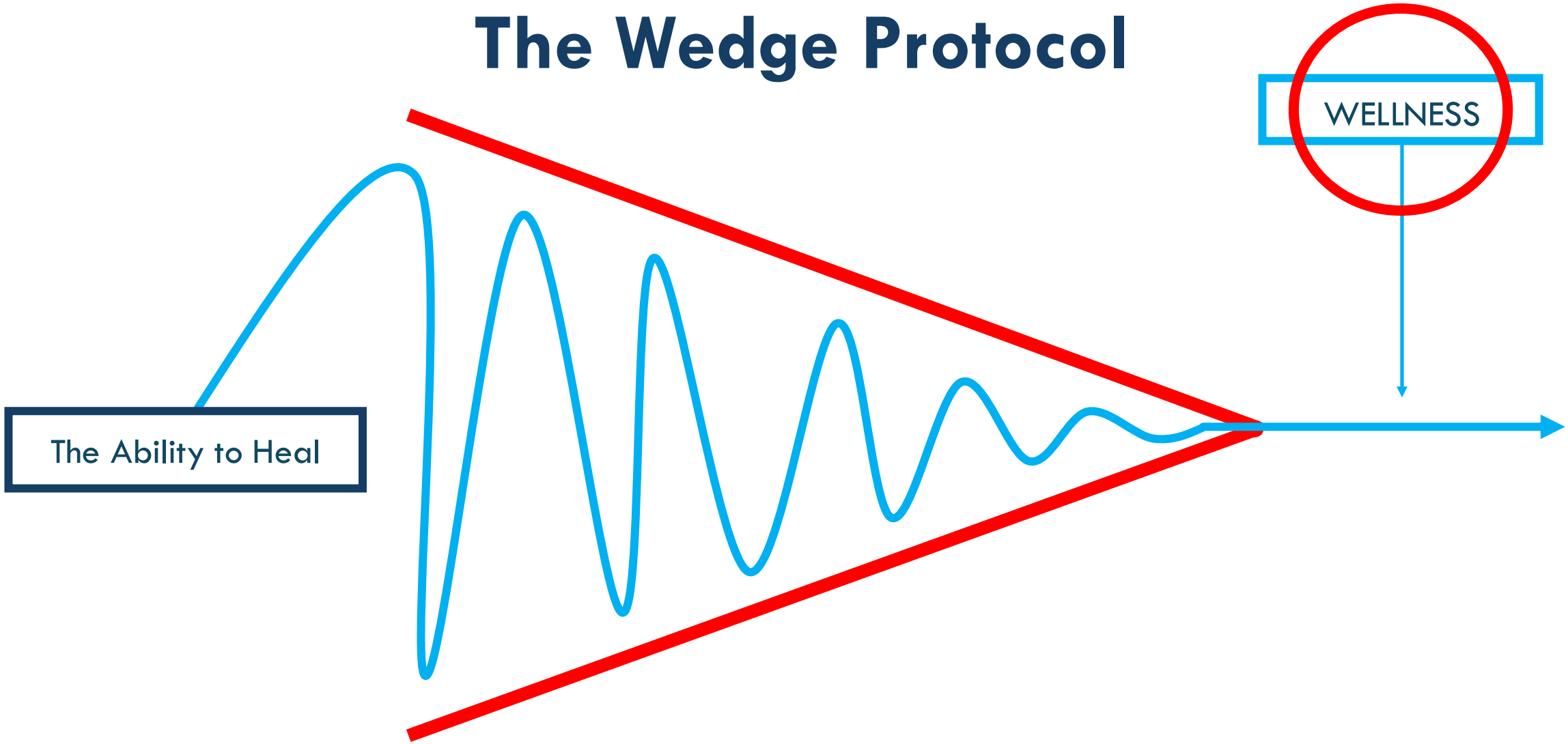
The Wedge Protocol



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