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Skin microbiota

Skin microbiota–host interactions [3]

The skin is a dynamic ecosystem inhabited by skin microbes (bacteria, archea, fungi and viruses) thee microbes are fundamental to skin physiology and immunity.

The skin, on the other hand, is replete in diverse and unusual lipids not found elsewhere in the body [4, 5] (Fig2 in [3]). Some of these lipids, such as sapienic acid, can have antimicrobial activities, while others, such as triglycerides, can be metabolized by microbes into free fatty acids and di- and monoglycerides that can be bioactive against other microbes or stimulatory to host cells [6, 7]. Sanford and colleagues showed that short-chain fatty acids (SCFAs) produced by microbes colonizing the skin surface lead to the inhibition of the histone deacetylase (HDAC) activity. It is known from microbes that populate the intestinal tract produce high levels of SCFAs that inhibit HDAC activity [8-10].

These findings support beneficial clinical associations between the microbial metabolome of the gut and normal immune function and provide one mechanistic explanation for how bacteria can regulate inflammation [1, 2].

Microbiome in healthy skin, update for dermatologists [11]

The skin is a complex barrier organ made of a symbiotic relationship between microbial communities and host tissue via complex signals provided by the innate and the adaptive immune systems. The skin microbiota are established during birth, the fetal skin will be colonized by microorganisms from the mother [12] . This very initial flora is low in diversity and resembles that of the delivery site, i.e. a vaginal birth will colonize a new-born with vaginal flora and a caesarean section birth with flora typical of tummy skin [13-15].

This process of skin colonization during early neonatal life is required to establish immune tolerance to commensal microorganisms [16]. During this very short time span, an abrupt inflow of highly activated regulatory T cells into neonatal skin is observed. The core skin microbiota is considered to be commensal, meaning that these microorganisms are usually harmless and most probably provide some benefit to the host. Under normal conditions these microorganism are non-pathogenic [17, 18].

From a bacteriological point of view, our skin can be considered a culture medium. Its composition is mainly the consequence of our genetics, diet, life style and the area we are living in. As a result each human skin is unique and at a genus level each microbiota present in the different areas of our skin is

unique. There are four main types of environments on the human skin moist, sebaceous, dry and others. [19]. Moist areas include the axilla, inner elbow or inguinal fold. Sebaceous areas include the forehead, the alar crease (side of the nostril), the retro auricular crease (behind the ear) and the back [20] whereas the drier sites include the upper buttock area [21]. Further microenvironments include the sweat glands, the hair follicles and the dermal layers. Multiple independent detection techniques showed that bacteria are not only present on the skin surface, but are also found in deeper layers of the epidermis and even in the dermis and dermal adipose tissue [22].

These layers have specific microbiome profiles and also contain many specialized cell types such as dendritic cells, melanocytes and Langerhans cells that each express unique repertoire of functional pattern recognition receptors (PRRs) which respond actively when exposed to components of microorganisms [22-25].

Why is the skin microbiome so important?

The skin barrier and the microbiota act like a shield that protects the body against external aggressions. The composition of skin microorganism communities determines the barrier function of the skin. Altering the equilibrium in the microbiome populations might disturb the skin barrier function and activates chronic skin diseases like atopic dermatitis [26-30], psoriasis[21, 22] or acne [21, 22, 31-33].

The factors influencing the equilibrium of the microbes on the skin are summarized in the following figure.

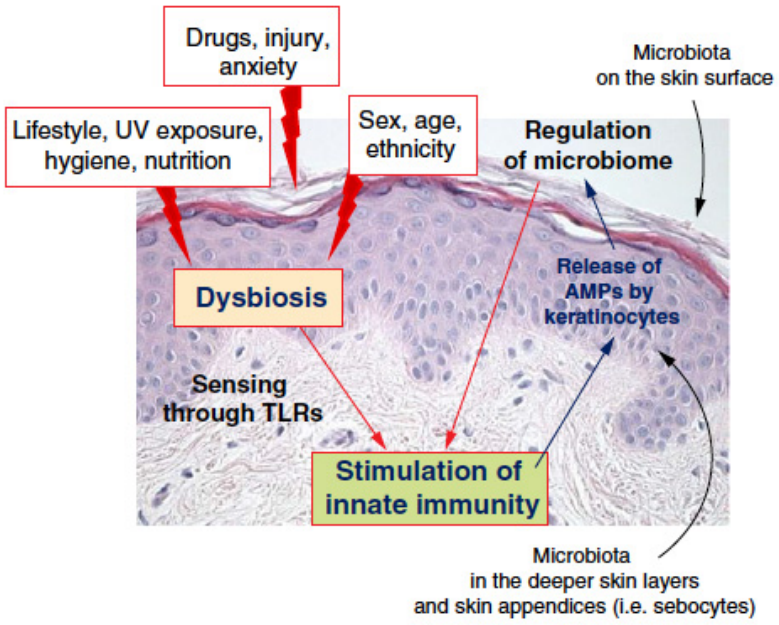

Figure 1: Factors leading to symbiosis and innate immunity response of the skin [11].

The skin microbiota modulate the expression of various innate factors, including interleukin 1a (IL-1a) [34]; components of complement [35]; and antimicrobial peptides

(AMPs), which are produced by keratinocytes and sebocytes. In the following figure the crosstalk between microbes and released metabolic substances and their impact on diverse metabolic functions and the immune system are depicted [3].

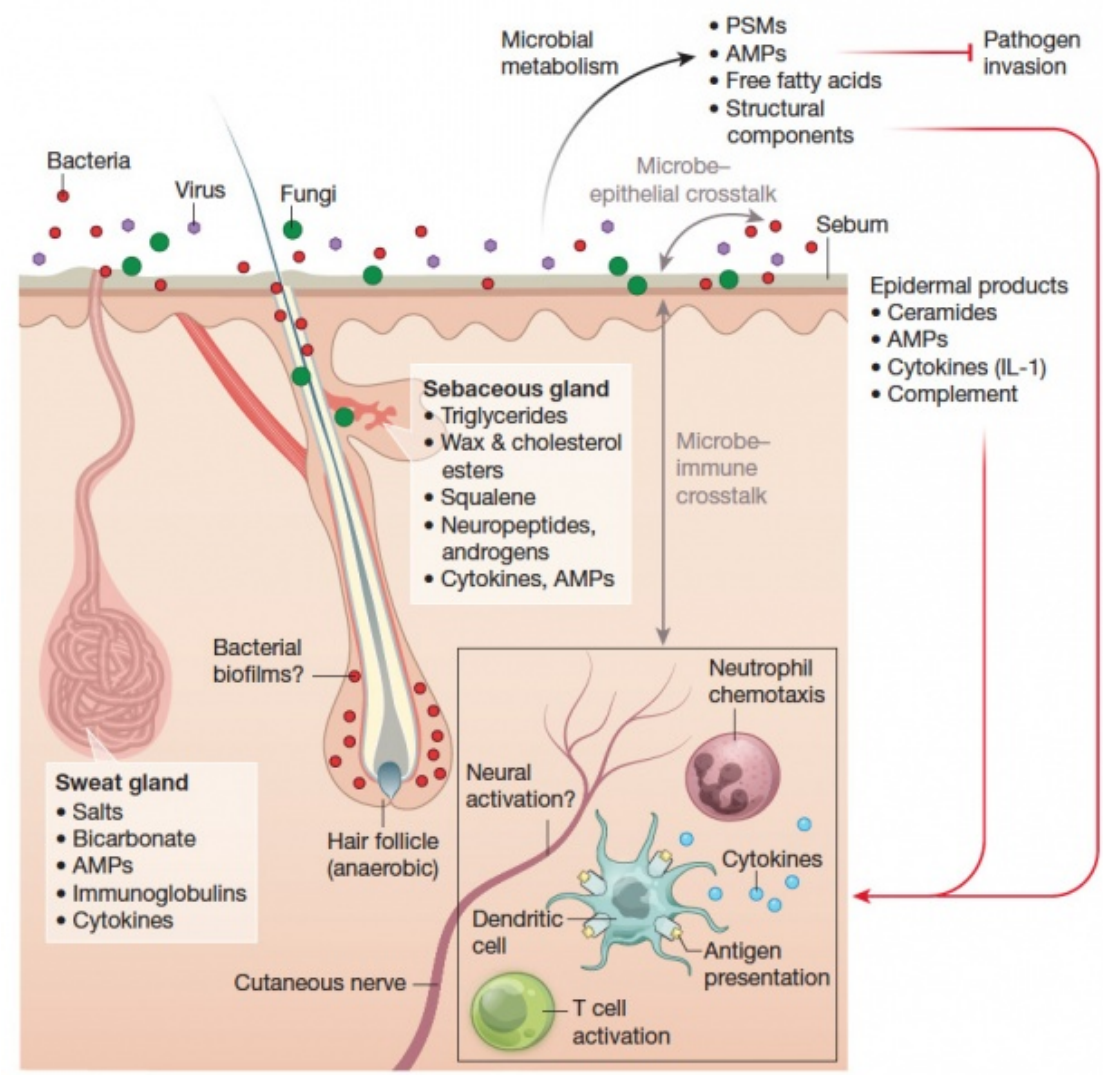

Figure 2: **Crosstalk between skin microbiota and the host.** Diverse microbes (viruses, fungi and bacteria) cover the skin surface and associated structures (hair follicles, sebaceous glands and sweat glands),
possibly forming biofilms at some sites. These microbes metabolize host proteins and lipids and produce bioactive molecules, such as free fatty acids, AMPs, phenol-soluble modulins (PSMs), cell wall components, and antibiotics158,159. These products act on other microbes to inhibit pathogen invasion, on the host epithelium to stimulate keratinocyte-derived immune mediators such as complement and IL-1, and on immune cells in the epidermis and dermis. In turn, host products and immune cell activity influence microbial composition on the skin [3].

Data from this figure show, that the non-classical MHC class I molecules, an evolutionarily ancient arm of the immune system may play an important role in promoting
homeostatic immunity to the microbiota and the skin resident bacteria can have myriad effects on the host; In addition to promoting immune barrier responses, commensal–immune interactions can also affect

epithelial biology. The effects of commensal–immune interactions on many other cutaneous processes, including adnexal development, tumorigenesis, ageing, and sensory nerve function, remain to be determined.

Involvement of the peripheral nervous system may be more general and integral to skin immunity than has been previously recognized. More recently, a direct mechanistic link between neurons and immune cells has been discovered. For instance, in the gut, mucosal neurons were found to produce a neuropeptide, neuromedin U (NMU), that binds an NMU receptor on group 2 innate lymphoid cells (ILC2s) and triggers a protective immune
response [36].

Library

1. Frank, D.N., et al., *Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases.* Proc Natl Acad Sci U S A, 2007. **104**(34): p. 13780-5.
2. Wang, T., et al., *Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers.* ISME J, 2012. **6**(2): p. 320-9.
3. Chen, Y.E., M.A. Fischbach, and Y. Belkaid, *Skin microbiota-host interactions.* Nature, 2018. **553**(7689): p. 427-436.
4. Nicolaides, N., *Skin lipids: their biochemical uniqueness.* Science, 1974. **186**(4158): p. 19-26.
5. Strauss, J.S., P.E. Pochi, and D.T. Downing, *The sebaceous glands: twenty-five years of progress.* J Invest Dermatol, 1976. **67**(1): p. 90-7.
6. Drake, D.R., et al., *Thematic review series: skin lipids. Antimicrobial lipids at the skin surface.* J Lipid Res, 2008. **49**(1): p. 4-11.
7. Puhvel, S.M., R.M. Reisner, and M. Sakamoto, *Analysis of lipid composition of isolated human sebaceous gland homogenates after incubation with cutaneous bacteria. Thin-layer chromatography.* J Invest Dermatol, 1975. **64**(6): p. 406-11.
8. Chang, P.V., et al., *The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition.* Proc Natl Acad Sci U S A, 2014. **111**(6): p. 2247-52.
9. Maslowski, K.M., et al., *Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43.* Nature, 2009. **461**(7268): p. 1282-6.
10. Waldecker, M., et al., *Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon.* J Nutr Biochem, 2008. **19**(9): p. 587-93.
11. Dreno, B., et al., *Microbiome in healthy skin, update for dermatologists.* J Eur Acad Dermatol Venereol, 2016. **30**(12): p. 2038-2047.
12. Capone, K.A., et al., *Diversity of the human skin microbiome early in life.* J Invest Dermatol, 2011. **131**(10): p. 2026-32.
13. Baviera, G., et al., *Microbiota in healthy skin and in atopic eczema.* Biomed Res Int, 2014. **2014**: p. 436921.
14. Dominguez-Bello, M.G., et al., *Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns.* Proc Natl Acad Sci U S A, 2010. **107**(26): p. 11971-5.
15. Ladizinski, B., et al., *The human skin microbiome.* Int J Dermatol, 2014. **53**(9): p. 1177-9.
16. Scharschmidt, T.C., et al., *A Wave of Regulatory T Cells into Neonatal Skin Mediates Tolerance to Commensal Microbes.* Immunity, 2015. **43**(5): p. 1011-21.
17. Cogen, A.L., V. Nizet, and R.L. Gallo, *Skin microbiota: a source of disease or defence?* Br J

Dermatol, 2008. **158**(3): p. 442-55.
18. Kong, H.H. and J.A. Segre, *Skin microbiome: looking back to move forward.* J Invest Dermatol, 2012. **132**(3 Pt 2): p. 933-9.
19. Grice, E.A., et al., *Topographical and temporal diversity of the human skin microbiome.* Science, 2009. **324**(5931): p. 1190-2.
20. Sanford, J.A. and R.L. Gallo, *Functions of the skin microbiota in health and disease.* Semin Immunol, 2013. **25**(5): p. 370-7.
21. Zeeuwen, P.L., et al., *Microbiome and skin diseases.* Curr Opin Allergy Clin Immunol, 2013. **13**(5): p. 514-20.
22. Nakatsuji, T., et al., *The microbiome extends to subepidermal compartments of normal skin.* Nat Commun, 2013. **4**: p. 1431.
23. Miller, L.S. and R.L. Modlin, *Toll-like receptors in the skin.* Semin Immunopathol, 2007. **29**(1): p. 15-26.
24. Yu, N., et al., *Cultured human melanocytes express functional toll-like receptors 2-4, 7 and 9.* J Dermatol Sci, 2009. **56**(2): p. 113-20.
25. Zouboulis, C.C., *Sebaceous gland receptors.* Dermatoendocrinol, 2009. **1**(2): p. 77-80.
26. Salava, A. and A. Lauerma, *Role of the skin microbiome in atopic dermatitis.* Clin Transl Allergy, 2014. **4**: p. 33.
27. Sanchez, D.A., J.D. Nosanchuk, and A.J. Friedman, *The skin microbiome: is there a role in the pathogenesis of atopic dermatitis and psoriasis?* J Drugs Dermatol, 2015. **14**(2): p. 127-30.
28. Seite, S. and T. Bieber, *Barrier function and microbiotic dysbiosis in atopic dermatitis.* Clin Cosmet Investig Dermatol, 2015. **8**: p. 479-83.
29. Tomi, N.S., B. Kranke, and E. Aberer, *Staphylococcal toxins in patients with psoriasis, atopic dermatitis, and erythroderma, and in healthy control subjects.* J Am Acad Dermatol, 2005. **53**(1): p. 67-72.
30. Williams, M.R. and R.L. Gallo, *The role of the skin microbiome in atopic dermatitis.* Curr Allergy Asthma Rep, 2015. **15**(11): p. 65.
31. Fitz-Gibbon, S., et al., *Propionibacterium acnes strain populations in the human skin microbiome associated with acne.* J Invest Dermatol, 2013. **133**(9): p. 2152-60.
32. Wanke, I., et al., *Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways.* J Invest Dermatol, 2011. **131**(2): p. 382-90.
33. Weyrich, L.S., et al., *The skin microbiome: Associations between altered microbial communities and disease.* Australas J Dermatol, 2015. **56**(4): p. 268-74.
34. Naik, S., et al., *Compartmentalized control of skin immunity by resident commensals.* Science, 2012. **337**(6098): p. 1115-9.
35. Chehoud, C., et al., *Complement modulates the cutaneous microbiome and inflammatory milieu.* Proc Natl Acad Sci U S A, 2013. **110**(37): p. 15061-6.
36. Cardoso, V., et al., *Neuronal regulation of type 2 innate lymphoid cells via neuromedin U.* Nature, 2017. **549**(7671): p. 277-281.