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THE ROLE OF THE SKIN MICROBIOME IN THE DEVELOPMENT OF ALLERGIC INFLAMMATION IN ATOPIC DERMATITIS.

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Abstract

The article is devoted to atopic dermatitis, which is a chronic skin disease that significantly affects the quality of life of children and their relatives. The incidence of atopic dermatitis is constantly increasing. The development of the disease is accompanied by significant changes in the composition of skin microbiome. The adequate commensal colonization prevents invasion of pathogens. Furthermore, epithelial cells produce antimicrobial proteins (human β-defensin-1, -2 and -3, cathelicidin LL-37, ribonuclease 7) that directly kill or inhibit the growth of the pathogens. Patients with atopic dermatitis have impaired skin immunity. It manifests in a decrease of T-cells cytokines (IL-4 and IL-13), high sensitivity to alpha-toxin-induced cell death, decreased level of lamellar bodies and acid sphingomyelinase, suppressed filaggrin expression, contributing to a high level of Staphylococcus aureus skin colonization.

S. aureus secretes a variety of pathogenicity factors that facilitate its persistence on the infected skin. Staphylococcal enterotoxins A, B, C and toxic shock syndrome toxin also play the role of superantigens, which increase inflammation by a massive release of proinflammatory cytokines, including TNF-α and IL-1β. Affected by S. aureus superantigens regulatory T-cells lose their immunosuppressive activity. Moreover, enterotoxins act like a new group of allergens provoking IgE inflammation. S.aureus pathogenicity is enhanced by the ability to form biofilms.

Thus, impaired skin immunity function, decrease of commensals and increase growth of S. aureus play an essential role in the development of skin inflammation in atopic dermatitis and should be considered as the main reference points in the study of the disease in the future.

Keywords: *Atopic dermatitis, allergic inflammation, skin microbiome, skin immunity, staphylococcus aureus, superantigens.*

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease. The prevalence of AD is higher in industrialized countries and has continued to increase steadily over the past several decades. The disease often begins in the first year of life and has an undulating course with periods of remission and exacerbations. Over time, symptoms may disappear completely or persist and relapse throughout life. In many patients, early onset of AD is the first clinical manifestation of allergy and a predictor of the development of respiratory allergic pathology in the future. AD has social significance, influencing not only the physical, but also the mental and psychological state of the patient and his family.

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Healthy human skin

Human skin is an organ which protects the internal environment from foreign antigens, and also appears to be the habitat for many microorganisms (bacteria, viruses, archaea, and fungi) that form the microbiome. Each square centimeter of skin contains more than a million bacteria [*Grice EA et al., 2008*]. Populations of such microorganisms can be divided into a transient group (random, non-reproducible), a temporary group (the colonization of the skin occurs at a particular time under certain conditions), and a constant group (microorganisms reproduce and grow permanently). It is the "permanent" populations that make up the normal microbiome and are in mutualistic symbiosis with the host. Possessing the ability to synthesize protective molecules and natural antimicrobial peptides, commensal bacteria prevent the colonization of pathogenic microorganisms and the development of diseases [*Kong H, 2011*].

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Due to anatomical and physiological characteristics, human skin can be divided into predominantly dry, moist, and sebaceous areas [*Grice EA et al., 2009*]. Each region has its specific microbiome composition. Moreover, it was shown that the ecological niche affects the microbiome composition in a greater degree than individual genetic characteristics [*Gao Z et al., 2007, Costello EK et al., 2009*]. The skin microorganisms growth also depends on many exogenous factors such as ambient humidity and temperature, lifestyle, clothing, antibiotic treatments, cosmetics, etc., and endogenous factors which include the age, sex, genetic, and immunological characteristics of a person [*Fierer N et al., 2010*]

The microbiome of a newborn's skin depends on the type of delivery. In natural childbirth a baby's skin is mainly colonized by lactobacilli of the reproductive tract, and during operative delivery it is colonized by the microbiome of the mother's skin. Newborn skin differs from adult skin within the first day of life, and but by the age of 1 month their microbiome composition is no longer different [*Dominguez-Bello MG et al., 2010*]. In newborns, the microbiome composition remains the same on the entire body surface. Staphylococci spp. are prevalent in the skin due to better hydration of the stratum corneum. The microbial diversity increases gradually, and by the first year it becomes similar to the adult microbiome and specific to each anatomical region [*Capone KA et al., 2011*].

The role of immunological and microbiological factors in healthy skin.

Human skin is constantly affected by a huge number of microorganisms and other environmental factors. A low pH value, skin temperature and adequate commensal colonization prevent invasion of pathogens. Furthermore, epithelial cells produce antimicrobial proteins that directly kill or inhibit growth of the pathogens. The most important antimicrobial substances are: human β-defensin (HBD)-1, -2 and -3, cathelicidin LL-37, and ribonuclease 7. The water-lipid layer, along with antimicrobial peptides, maintains barrier and protective function of the skin [*Gallo RL et al., 2012*]. Macrophages and Langerhans cells provide additional synthesis of antimicrobial peptides in the lesional skin and in early stages of skin infection.

Special pathogen recognition receptor of the human innate immune system such as Toll-like receptors (TLR) 2, which also form heterodimers with TLR6 or TLR1, recognize diacylated and triacylated lipoproteins and lipopeptides, respectively. This induces synthesis of thymic stromal lympho-

poietin (TSLP) and, consequently, activates the ability of dendritic cells to trigger T helper cell (Th) -2 response, sensitization to environmental allergens or a specific pathogen, and AD aggravation. TSLP along with dendritic cells also activates the secretion of IL-4, IL-13, and INF-γ by T-killers. Thus, TSLP is one of the major factors connecting the body and environment via Th-2 response. Pathogens induce TLR-mediated nuclear factor kappa B activation which triggers transcription of cytokines, chemokines, and other effector molecules transcription. Lactobacillus spp., Escherichia coli and attenuated strains of pathogenic Salmonella species effectively inhibit signaling pathways and the immune response in general. Commensals in turn suppress the inhibiting factor kappa B degradation via ubiquitination mechanism [Neish AS et al., 2000; Collier-Hyams LS et al., 2005; Tien MT, 2006].

The long-term effect of Pathogen-Associated Molecular Patterns commensals on epithelial cells causes selective down-regulation of apical TLR2 and TLR4 expression which move to intracellular compartments (Golgi apparatus, etc.) or to the basolateral membrane, where they retain their full signal ability to detect internalized antigens. TLR5 is expressed exclusively on the basolateral surface [*Abreu MT et al., 2001; Gewirtz AT et al., 2001*]. Such receptor allocation in the intestinal mucosa allows the detection of pathogenic microorganisms only if they pass through the barrier of epithelial cells. This prevents an excessive immune response to commensals. Full activation of innate immunity requires not only TLR signaling pathways, but also so-called "danger signals" from destroyed cells [*Matzinger P et al., 2007*]. Thus, the body maintains a balance between tolerance and immunogenicity. It is also necessary for adequate functions of symbionts.

SKIN IMMUNITY IN AD

AD patients have decreased secretion of antibacterial agents such as IL-4 and IL-13 in T cells [*Howell MD et al., 2006*]. Additionally, these interleukins increase keratinocytes' sensitivity to alpha-toxin-induced cell death [*Brauweiler AM et al., 2014*]. Furthermore, it leads to a decreased level of lamellar bodies, specialized organelles containing lipids that form external waterproof layer of the epithelium. The decreased lamellar bodies result in decreased acid sphingomyelinase. Staphylococcus aureus colonizes the skin of the majority of AD patients. *S. aureus* alpha-toxin binds to sphingomyelin, which splitting becomes slower. IL-4 and IL-13 are able to suppress filaggrin expression. As a result, Th-2 cytokines contribute to growth of S.aureus, as well as intensify negative effects of pathogenic bacterial agents.

Recognition of *S. aureus* via TLR2-TLR6 complexes results in the synthesis of both TSLP and IL-6. IL-6 allows the activation of myeloid-derived suppressor cells which reduce immune response to pathogenic agents. Thus, the skin infected with S.aureus has suppressed immunity that facilitates colonization and persistence of pathogens [*Skabytska Y et al., 2014*].

MICROORGANISMS IN AD

In the stratum corneum superficial and deep compartments are distinguished. Moreover, the bacteria are stable even in deeper layers of the skin (in the dermis and subcutaneous adipose tissue). The balanced microbiome of the skin is a protective mechanism against antigens. Among all gram-positive *Staphylococci, S. epidermidis* is the dominant strain in healthy skin and it inhibits the growth of *S. aureus*. In children, colonization of skin by *S. epidermidis* and *S. cohnii* during the first year of life has a protective effect on the development of AD. Disorders in the skin microbiome are an independent risk factor for AD progression. In most cases, the skin of AD patients is colonized by *S. aureus*, half of which are toxigenic. However, the number of both *S. aureus* and S. epidermidis increases in the lesional skin. During AD flares these species start producing antibacterial substances, which are antimicrobial peptides and bacteriocins. At this time there is a decrease in the number of other types of microorganisms, including Propionibacterium, Corynebacterium, and Streptococcus. After a successful local treatment the diversity of the skin microbiome restores [*Wollina U et al., 2017; Yamazaki Y et al., 2017*]

The role of S. aureus in AD

Staphylococcus aureus is a Gram-, catalase-, and coagulase-positive facultative aerobe which causes numerous diseases worldwide. *S. aureus* usually localizes in the nasal vestibule. Approximately a quarter of people are permanent carriers of *S. aureus*, a third of people are periodic bacterial carriers, and in the rest group *S. aureus* is not detected. In children with AD (30-90%), there is a high incidence of infection of lesional skin, an increase of *S. aureus* colonization in severe types of pathology [*Kudryavtseva AV et al., 2014; Kudryavtseva AV et al., 2015; Seiti Yamada Yoshikawa F et al., 2019*].

S. aureus secretes a number of pathogenicity factors that facilitate the colonization of the skin and contribute to its persistence. Some factors, especially enterotoxins, pore-forming cytotoxins, and extracellular enzymes (proteases, lipases) could be secreted into the environment. Other factors are located on the surface of the pathogen, which included capsule and fibronectin-binding proteins (polysaccharides; staphyloxanthin; fibrinogen-binding proteins A and B, that recognize adhesive molecules of the extracellular matrix; iron-regulated surface determinant protein; lipoteichoic acid). These groups of proteins contribute to the adhesion and persistence of *S. aureus* on the surface of the skin, while mucous membranes prevent its recognition by the host`s immune system and disable neutrophilic phagocytosis [*Tuffs SW et al ., 2018*]

Superantigens are significant pathogenicity factors.

It is well known that *S. aureus* produces about twenty immunologically different types of enterotoxins, indicated by the letters of the alphabet from A to V in order of their discovery. *S. aureus* toxins, the main of which are toxic shock syndrome toxin 1 (TSST-1) and enterotoxins A, B, C (SEA, SEB, SEC), have superantigen properties [*Williams MR et al., 2015; Fluer FS et al., 2017*]. A distinctive feature of superantigens is the ability to cause a strong primary response without processing by antigen-presenting cells. Superantigens bind directly to the variable part of the T-cell receptor β-chain and to the major histocompatibility complex II (MHC II) of antigen-presenting cells (macrophages, dendritic cells, keratinocytes). This leads to the activation of nonspecific mass native T cells, a massive release of proinflammatory cytokines, including TNF-α and IL-1β, and increased inflammation. Superantigens stimulate the production of IL-12, which is necessary for homing receptors expression on the surface of T-lymphocytes. Affected by *S. aureus* superantigens regulatory T-cells lose their immunosuppressive activity [*Ou LS* et al., 2004].

S. aureus also secretes releases pore-forming toxins, including cytolysins (α-, β-, γ - and δ-toxins), leukocidins, and phenol-soluble modulins. Despite the fact that all toxins have different structures and affect different cells (leukocytes, epithelial cells), their mechanisms are similar. Pore formation in the membranes of target cells leads to inflammation and cell death. Staphylococcal α-toxin (α-hemolysin) is one of the most significant destructive cytolytic toxins. The concentration of α-toxin on the skin surface correlates with the AD severity, but to activate it, the presence of sphingomyelin on the cell surface is required [*Hong SW et al., 2014*]. The toxin specifically recognizes the end-group phosphocholine sphingomyelin. Then α-toxin monomers form heterodimer complexes on the surface of keratinocytes irreversibly wedged into the cell membrane. Such formed pores lead to cell lysis. Recent studies have demonstrated that *S. aureus* is able to release soluble α-toxins into the extracellular space as well as vesicles containing up to 90 proteins, DNA, RNA and toxins [*Lee EY et al., 2009*]. Vesicles are spherical complexes from 20 to 200 nm in size. They are immunogenic and involved in the AD pathogenesis [*Hong SW et al., 2011*]. α-hemolysin from the vesicle penetrates into the cytoplasm of keratinocytes inducing cell necrosis, while free α-hemolysin causes apoptosis of these cells. Hemolysin vesicle activates the production of keratinocytes proinflammatory cytokines - IL-1β and IL-6, infiltration of the dermis by inflammatory cells (mast cells and eosinophils). As a result, thickening of the epidermis and eosinophilic inflammation of the dermis occur [*Hong SW et al., 2011*]. Such influence of fibroblasts and mast cells in vitro stimulates the secretion of Th2-

type cytokines: TSLP, macrophage inflammatory protein-1α, IL-6 and eotaxin. TSLP, in turn, activates myeloid dendritic cells, stimulating them to create a favorable microenvironment for Th2-response [*Liu YJ et al., 2007*]. Thus, α-toxin interaction contributes to the skin barrier damage and facilitates the penetration of allergens, which lead to sensitization via Th2-response activation.

Sphingomyelinase C (or β-toxin) is the only cytolysin with the enzyme properties. The cell surface sphingomyelin is the target for it. Cell sensitivity to this toxin depends on the amount of sphingomyelin. The most exposed cells are monocytes, red blood cells, neutrophils and lymphocytes (especially proliferating T-lymphocytes) [*Huseby MJ et al., 2007*]. In addition, β-toxin accelerates the formation of staphylococcal biofilm [*Huseby MJ et al., 2010*].

Leukocidins and γ-toxin are two-component cytolysins. They consist of two separately secreted subunits that are active only while connected to each other. Recently much attention has been given to Panton-Valentine leukocidin (PVL) that targets neutrophils mainly. Strains of community-associated multiresistant *S. aureus* (MRSA) cause severe infections of the skin and soft tissues while synthesizing this toxin. PVL-positive *S. aureus* penetrates into host epithelial cells, then into its endosomes and releases leukocidin. The toxin contributes to endosome membrane destruction and the pathogen freely enters the cell cytoplasm, where it continues to multiply. This process activates the release of inflammatory cytokines, leukocyte migration, damage and death of epithelial cells [*Chi C et al., 2014*].

The *S. aureus* pathogenic factors also include δ-toxin. Being a strong inducer of mast cells degranulation, it promotes strengthening of local inflammation [*Nakamura Y et al., 2013*].

S. aureus releases many extracellular enzymes, including lipase, nuclease, hyaluronidase, staphylokinase, and several proteases, such as serine proteases (V8, exfoliative toxins A and B), cysteine proteases, metalloproteinases. Enzymes destruct tissues and inactivate the host's antimicrobial protective mechanisms (lipids, defensins, antibodies), which helps microorganisms to spread.

S. aureus is often regarded as an extracellular organism, but there is evidence about its possible penetration of host cells by fibronectin-binding proteins [*Sinha B, Fraunholz M, 2010*]. However, the possibility of penetration into keratinocytes is not inherent in all *S. aureus* strains. Residing inside epithelial cells, microorganisms can avoid endosome exposure. NOD-like receptors recognize *S. aureus* and trigger Th1- or Th17-mediated inflammation via inflammasomes activation, all of which play a critical role in severe types of AD development [*Roth SA, 2014*].

An important feature that facilitates the *S. aureus* colonization on mucous membranes and the skin is its affinity for surface components of the epithelium (fibrinogen, fibronectin, cytokeratins) to which *S. aureus* is attached by surface components of the microbial membrane (fibrinogen-binding proteins A and B, surface iron-regulated protein, lipoteichoic acid of the cell wall) [*Burian M et al., 2010*]. Moreover, the expression of fibronectin is regulated by the main Th2-type cytokine - IL-4, which presented in high concentrations in patients with AD [*Mempel M et al., 1998*].

S. aureus not only colonizes the affected skin but also acts upon the immune system for creation and support of a favorable microenvironment [*Miller LS* et al., 2011]. *S. aureus* strains suppress the production of antimicrobial substances by keratinocytes and thus create a micro eco-system which is free of other bacteria (*S. epidermidis* particularly), that can interfere with *S. aureus* strains growth [*Baviera G et al., 2014*]. The ability to form biofilms preserves *S. aureus* eradication. However, it is necessary to interrupt the vicious cycle composed of infection, inflammation, creation of Th-2 environment, and sensitization to allergens [*Allen HB et al., 2014*]. Due to the reinforcement of antibacterial resistance and the MRSA occurring, it is necessary to develop alternative treatments. There are some evidences that regular use of sodium hypochlorite baths leads to the reversible suppression of human keratinocytes Nuclear factor kappa B (NF-κB) NF-kV-dependent

gene (CCL2 and superoxide dismutase-2) expression [*Leung TH et al., 2013*]. However, even in cases of successful eradication, lesional skin is extremely quickly recolonized by *S.aureus* strains.

New approaches to *S. aureus* eradication include the development of creams that contain normal flora, in particular selected strains of Staphylococcus epidermidis, creams with antimicrobial peptides and creams with bacteriophage endolysin enzymes. [*Kashani HH et al., 2017; Nakatsuji T et al., 2017; Wang B et al., 2017*] [The main advantage and difference of the latter method from antibiotics is its selective effect on *S. aureus*, including resistant strains and MRSA. It does not disrupt the homeostasis of normal microflora and does not harm other microorganisms, even with prolonged use.

Conclusion

Skin microbiome plays an essential role in the development of allergic inflammation in patients with AD. Decrease levels of commensals, including *S. epidermidis*, together with the impaired skin immunity function lead to increase growth of *S. aureus*. *S. aureus* virulent factors aggravate and prolong inflammation of the lesional skin. *S. aureus* eradication and re-establishment of normal skin microbiome should be included into therapeutic regimens of the disease. Future researches should focus on the detailed study of the individual role of microorganisms, both pathogens and commensals, in the pathogenesis of AD. This will clarify and prepare theoretical basis for the development of new approaches for the treatment of the disease.

REFERENCES

1. *Abreu MT, Vora P, Faure E, Thomas LS, Arnold ET, Arditi M.* Decreased expression of Toll-like receptor-4 and MD-2 correlates with intestinal epithelial cell protection against dysregulated proinflammatory gene expression in response to bacterial lipopolysaccharide. J Immunol. 2001 Aug 1;167(3):1609-1616. doi: 10.4049/jimmunol.167.3.1609.
2. *Allen HB, Vaze ND, Choi C, Hailu T, Tulbert BH, Cusack CA, Joshi SG.* The presence and impact of biofilm-producing staphylococci in atopic dermatitis. JAMA Dermatol. 2014 Mar;150(3):260-265. doi: 10.1001/jamadermatol.2013.8627.
3. *Baviera G, Leoni MC, Capra L, Cipriani F, Longo G, Maiello N, Ricci G, Galli E.* Microbiota in healthy skin and in atopic eczema. Biomed Res Int. 2014;2014:436921. doi: 10.1155/2014/436921.
4. *Brauweiler AM, Goleva E,* Leung DYM. Th2 cytokines increase Staphylococcus aureus alpha toxin-induced keratinocyte death through the signal transducer and activator of transcription 6 (STAT6). J Invest Dermatol. 2014 Aug;134(8):2114-2121. doi: 10.1038/jid.2014.43.
5. *Burian M, Rautenberg M, Kohler T, Fritz M, Krismer B, Unger C, Hoffmann WH, Peschel A, Wolz C, Goerke C.* Temporal expression of adhesion factors and activity of global regulators during establishment of Staphylococcus aureus nasal colonization. J Infect Dis. 2010 May 1;201(9):1414-1421. doi: 10.1086/651619.
6. *Capone KA, Dowd SE, Stamatas GN, Nikolovski J.* Diversity of the human skin microbiome early in life. J Invest Dermatol. 2011 Oct;131(10):2026-2032. doi: 10.1038/jid.2011.168.
7. *Chi CY, Lin CC, Liao IC, Yao YC, Shen FC, Liu CC, Lin CF.* Panton-Valentine leukocidin facilitates the escape of Staphylococcus aureus from human keratinocyte endosomes and induces apoptosis. J Infect Dis. 2014 Jan 15;209(2):224-235. doi: 10.1093/infdis/jit445.
8. *Collier-Hyams LS, Neish AS.* Innate immune relationship between commensal flora and the mammalian intestinal epithelium. Cell Mol Life Sci. 2005 Jun;62(12):1339-1348. doi: 10.1007/s00018-005-5038-y.

9. *Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R.* Bacterial community variation in human body habitats across space and time. Science. 2009 Dec 18;326(5960):1694-1697. doi: 10.1126/science.1177486.

10. *Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R.* 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 Jun 29;107(26):11971-5. doi: 10.1073/pnas.1002601107.

11. *Fierer N, Lauber CL, Zhou N, McDonald D, Costello EK, Knight R.* Forensic identification using skin bacterial communities. Proc Natl Acad Sci U S A. 2010 Apr 6;107(14):6477-6481. doi: 10.1073/pnas.1000162107.

12. *Fluer FS, Kudryavtseva AV, Neskorodova KA,* Titarev SI [Production of enterotoxins A, B, C and toxin of toxic shock syndrome by various types of staphylococci extracted from the skin of children with atopic dermatitis] [Published in Russian] Pediatria. 2017; 96 (6): 87-91.

13. *Gallo RL, Hooper LV.* Epithelial antimicrobial defence of the skin and intestine. Nat Rev Immunol. 2012 Jun 25;12(7):503-516. doi: 10.1038/nri3228.

14. *Gao Z, Tseng CH, Pei Z, Blaser MJ.* Molecular analysis of human forearm superficial skin bacterial biota. Proc Natl Acad Sci U S A. 2007 Feb 20;104(8):2927-2932. doi: 10.1073/pnas.0607077104.

15. *Gewirtz AT, Navas TA, Lyons S, Godowski PJ, Madara JL.* Cutting edge: bacterial flagellin activates basolaterally expressed TLR5 to induce epithelial proinflammatory gene expression. J Immunol. 2001 Aug 15;167(4):1882-1885. doi: 10.4049/jimmunol.167.4.1882.

16. *Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC;* NISC Comparative Sequencing Program, Bouffard GG, Blakesley RW, Murray PR, Green ED, Turner ML, Segre JA. Topographical and temporal diversity of the human skin microbiome. Science. 2009 May 29;324(5931):1190-1192. doi: 10.1126/science.1171700.

17. *Grice EA, Kong HH, Renaud G, Young AC;* NISC Comparative Sequencing Program, Bouffard GG, Blakesley RW, Wolfsberg TG, Turner ML, Segre JA. A diversity profile of the human skin microbiota. Genome Res. 2008 Jul;18(7):1043-1050. doi: 10.1101/gr.075549.107.

18. *Hong SW, Choi EB, Min TK, Kim JH, Kim MH, Jeon SG, Lee BJ, Gho YS, Jee YK, Pyun BY, Kim YK.* An important role of α-hemolysin in extracellular vesicles on the development of atopic dermatitis induced by Staphylococcus aureus. PLoS One. 2014 Jul 3;9(7):e100499. doi: 10.1371/journal.pone.0100499.

19. *Hong SW, Kim MR, Lee EY, Kim JH, Kim YS, Jeon SG, Yang JM, Lee BJ, Pyun BY, Gho YS, Kim YK.* Extracellular vesicles derived from Staphylococcus aureus induce atopic dermatitis-like skin inflammation. Allergy. 2011 Mar;66(3):351-359. doi: 10.1111/j.1398-9995.2010.02483.x.

20. *Howell MD, Gallo RL, Boguniewicz M, Jones JF, Wong C, Streib JE, Leung DY.* Cytokine milieu of atopic dermatitis skin subverts the innate immune response to vaccinia virus. Immunity. 2006 Mar;24(3):341-348. doi: 10.1016/j.immuni.2006.02.006.

21. *Huseby M, Shi K, Brown CK, Digre J, Mengistu F, Seo KS, Bohach GA, Schlievert PM, Ohlendorf DH, Earhart CA.* Structure and biological activities of beta toxin from Staphylococcus aureus. J Bacteriol. 2007 Dec;189(23):8719-8726. doi: 10.1128/JB.00741-07.

22. *Huseby MJ, Kruse AC, Digre J, Kohler PL, Vocke JA, Mann EE, Bayles KW, Bohach GA, Schlievert PM, Ohlendorf DH, Earhart CA.* Beta toxin catalyzes formation of nucleoprotein matrix in staphylococcal biofilms. Proc Natl Acad Sci U S A. 2010 Aug 10;107(32):14407-14412. doi: 10.1073/pnas.0911032107.

23. *Kashani HH, Schmelcher M, Sabzalipoor H, Seyed Hosseini E, Moniri R.* Recombinant Endolysins as Potential Therapeutics against Antibiotic-Resistant Staphylococcus aureus: Current Status of Research and Novel Delivery Strategies. Clin Microbiol Rev. 2017 Nov 29;31(1):e00071-17. doi: 10.1128/CMR.00071-17.

24. Kong HH. Skin microbiome: genomics-based insights into the diversity and role of skin microbes. Trends Mol Med. 2011 Jun;17(6):320-328. doi: 10.1016/j.molmed.2011.01.013.

25. Kudravtseva AV, Savvina YA, Morozova OA [The species differences of staphylococci isolated from skin lesions in children and adolescents with atopic dermatitis] [Published in Russian] Ross allergol zhurn.2015; (3): 41—46.

26. Kudravtseva AV, Morozova OA, Savvina YA. [The influence of antiseptic solutions on the Staphylococcus colonization of the affected skin in children with atopic dermatitis] [Published in Russian] Pediatria. 2014; 93 (1): 83-88

27. *Lee EY, Choi DY, Kim DK, Kim JW, Park JO, Kim S, Kim SH, Desiderio DM, Kim YK, Kim KP, Gho YS.* Gram-positive bacteria produce membrane vesicles: proteomics-based characterization of Staphylococcus aureus-derived membrane vesicles. Proteomics. 2009 Dec;9(24):5425-5436. doi: 10.1002/pmic.200900338.

28. Leung TH, Zhang LF, Wang J, Ning S, Knox SJ, Kim SK. Topical hypochlorite ameliorates NF-κB-mediated skin diseases in mice. J Clin Invest. 2013 Dec;123(12):5361-5370. doi: 10.1172/JCI70895.

29. Liu YJ. Thymic stromal lymphopoietin and OX40 ligand pathway in the initiation of dendritic cell-mediated allergic inflammation. J Allergy Clin Immunol. 2007 Aug;120(2):238-244; quiz 245-6. doi: 10.1016/j.jaci.2007.06.004.

30. Matzinger P. Friendly and dangerous signals: is the tissue in control? Nat Immunol. 2007 Jan;8(1):11-13. doi: 10.1038/ni0107-11.

31. *Mempel M, Schmidt T, Weidinger S, Schnopp C, Foster T, Ring J, Abeck D.* Role of Staphylococcus aureus surface-associated proteins in the attachment to cultured HaCaT keratinocytes in a new adhesion assay. J Invest Dermatol. 1998 Sep;111(3):452-456. doi: 10.1046/j.1523-1747.1998.00293.x.

32. *Miller LS, Cho JS.* Immunity against Staphylococcus aureus cutaneous infections. Nat Rev Immunol. 2011 Jul 1;11(8):505-518. doi: 10.1038/nri3010.

33. *Nakamura Y, Oscherwitz J, Cease KB, Chan SM, Muñoz-Planillo R, Hasegawa M, Villaruz AE, Cheung GY, McGavin MJ,* Travers *JB, Otto M, Inohara N, Núñez G.* Staphylococcus δ-toxin induces allergic skin disease by activating mast cells. Nature. 2013 Nov 21;503(7476):397-401. doi: 10.1038/nature12655.

34. Nakatsuji T, Chen TH, Narala S, Chun KA, Two AM, Yun T, Shafiq F, et al., Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. Sci Transl Med. 2017 Feb 22;9(378):eaah4680. doi: 10.1126/scitranslmed.aah4680.

35. Neish AS, Gewirtz AT, Zeng H, Young AN, Hobert ME, Karmali V, Rao AS, Madara JL. Prokaryotic regulation of epithelial responses by inhibition of IkappaB-alpha ubiquitination. Science. 2000 Sep 1;289(5484):1560-1563. doi: 10.1126/science.289.5484.1560.

36. Ou LS, Goleva E, Hall C, Leung DY. T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. J Allergy Clin Immunol. 2004 Apr;113(4):756-763. doi: 10.1016/j.jaci.2004.01.772.

37. *Roth SA, Simanski M, Rademacher F, Schröder L, Harder J.* The pattern recognition receptor NOD2 mediates Staphylococcus aureus-induced IL-17C expression in keratinocytes. J Invest Dermatol. 2014 Feb;134(2):374-380. doi: 10.1038/jid.2013.313.

38. Seiti Yamada Yoshikawa F, Feitosa de Lima J, Notomi Sato M, Álefe Leuzzi Ramos Y, Aoki V, Leao Orfali R. Exploring the Role of *Staphylococcus Aureus* Toxins in Atopic Dermatitis. Toxins (Basel). 2019 Jun 5;11(6):321. doi: 10.3390/toxins11060321.

39. Sinha B, Fraunholz M. Staphylococcus aureus host cell invasion and post-invasion events. Int J Med Microbiol. 2010 Feb;300(2-3):170-175. doi: 10.1016/j.ijmm.2009.08.019.

*40. Skabytska Y, Wölbing F, Günther C, Köberle M, Kaesler S, Chen KM et al.,*Cutaneous innate immune sensing of Toll-like receptor 2-6 ligands suppresses T cell immunity by inducing myeloid-derived suppressor cells.

Immunity. 2014 Nov 20;41(5):762-775. doi: 10.1016/j.immuni.2014.10.009.

41. *Tien MT, Girardin SE, Regnault B, Le Bourhis L, Dillies MA, Coppée JY, Bourdet-Sicard R, Sansonetti PJ, Pédron T.* Anti-inflammatory effect of Lactobacillus casei on Shigella-infected human intestinal epithelial cells. J Immunol. 2006 Jan 15;176(2):1228-1237. doi: 10.4049/jimmunol.176.2.1228.

42. *Tuffs SW, Haeryfar SMM, McCormick JK.* Manipulation of Innate and Adaptive Immunity by Staphylococcal Superantigens. Pathogens. 2018 May 29;7(2):53. doi: 10.3390/pathogens7020053.

43. *Wang B, McHugh BJ, Qureshi A, Campopiano DJ, Clarke DJ, Fitzgerald JR, Dorin JR, Weller R, Davidson DJ.* IL-1β-Induced Protection of Keratinocytes against Staphylococcus aureus-Secreted Proteases Is Mediated by Human β-Defensin 2. J Invest Dermatol. 2017 Jan;137(1):95-105. doi: 10.1016/j.jid.2016.08.025.

44. *Williams MR, Gallo RL.* The Role of the Skin Microbiome in Atopic Dermatitis. Curr Allergy Asthma Rep (2015) 15: 65 DOI 10.1007/s11882-015-0567-4.

45. *Wollina U.* Microbiome in atopic dermatitis. Clin Cosmet Investig Dermatol. 2017 Feb 22;10:51-56. doi: 10.2147/CCID.S130013.

46. *Yamazaki Y, Nakamura Y, Núñez G.* Role of the microbiota in skin immunity and atopic dermatitis. Allergol Int. 2017 Oct;66(4):539-544. doi: 10.1016/j.alit.2017.08.004.

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