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REVIEW

Change in gut microbiota for eczema: Implications for novel therapeutic strategies

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Abstract Eczema is one of the most common inflammatory diseases, often constituting a lifelong burden for afflicted individuals. The complex interaction of host genetic and multiple environmental factors contribute to its pathogenesis. A relationship between maladjustment of gut microbiota and eczema has been brought into the light of day in most previous studies. In eczema preclinical models, specific intestinal microbial species have been demonstrated to prohibit or dwindle immune responsiveness, indicating that these strains among commensal gut bacteria may exert either a morbific or phylactic function in eczema progression. As such, oral probiotics can serve as a medicinal approach for eczema therapy. Given that relative scientific work is still at the early stage, only limited data are available in the field. New sequencing techniques have been fortunately performed to gain access to an extended research on the relationship between gut bacterial flora and human diseases. In the current review, we identified the role of intestinal microbiota in the development of eczema and how specific bacterial strains adjust the immune responsiveness in the midst of disease progression. Probiotics as an applicable treatment for eczema were evaluated in other threads as well.

Introduction

Eczema, also known as atopic dermatitis, is a common childhood condition characterised by the inflammation of skin with intense itching.[1] The prevalence of eczema has been increasing worldwide during the past decades, particularly in industrialised nations and amongst children.[2-4] Even though research studies on genetic predisposition to eczema have implicated genes (e.g. *IL4*, *IL4R*, *IL13*, *CMA1*, *SPINK5*, *FLG*, *IL-6*),[5-12] the aetiology of systemic inflammation still requires further investigation. The gut is a crucial immune organ besides its function in metabolism and in the body it includes the biggest lymphoid tissue mass.[13] The gut is a habitat to vast and various species of microbes.[13,14] Crucial signals derived from the gut microbiota contribute to the development of host immunity. Hence, Gut microbes

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are very important to maintain human health and disease. Recent studies in experimental subjects have demonstrated that maladjustment of the intestinal microbiota is related to the development of eczema.[15,16] Changes in terms of the abundance of certain intestinal microbial species have been revealed to prohibit or dwindle immune responsiveness in eczema experimental subjects, they may be biomarkers in eczema prevention and therapy. In spite of being a relatively novel area of research, evidence hitherto indicates that the intestinal microbiota may serve as fecund targets for prevention or control of eczema which is primarily characterised by innate and adaptive immune dysbiosis. In the current study, we reviewed recent series to further investigate changes in microbiota composition which trigger eczema disease, and the efficacy of probiotics/prebiotic in the therapy for eczema is also assessed based on the previous studies.

Eczema pathogenesis and the role of gut microbiota within it

Eczema pathogenesis

Eczema is a chronic form of childhood disorder that is characterised by remitting and relapsing cutaneous symptoms. These symptoms include itching and dryness, flaking, blistering, oozing, and bleeding.[17] Eczema is often the first manifestation of atopy in infants who will develop asthma or allergic rhinitis later in childhood.[18,19] Different dendritic cells subtypes, such as Langerhans cells (LC), inflammatory dendritic epidermal cells (IDEC) and plasmacytoid dendritic cells (PDC), play a key role in eczema and impact on the mechanisms underlying eczema, such as the recruitment of inflammatory cells, T-cell priming, and cytokine and chemokine release. Lesional skin of eczema patients harbours significant numbers of LC; IDEC and PDC expressing the high-affinity receptor for immunoglobulin E (IgE).[20–22] An enhanced T helper 2 (Th2) immune response, reflected by an increased frequency of allergen-specific T cells producing interleukin (IL)-4, -5 and-13, and a decrease in interferon (IFN)-γ-producing T-cells.[23,24] IL-4 can be involved in IgE isotype switching, while IL-5 can attract eosinophils and prolong their survival, which may result in the peripheral blood eosinophilia and increased IgE serum levels in eczema patients.[25] Moreover, there is a preferential apoptosis of circulating Th1 cells in eczema, which may also contribute to Th2 predominance in eczema patients.[26] Interestingly, eczema patients have significantly increased numbers of circulating regulatory T cells that exhibit normal immunosuppressive activities in vitro.[27] Studies on genetic predisposition to eczema have implicated eczema-related genes such as (e.g. *IL4*, *IL4R*, *IL13*, *CMA1*, *SPINK5*, *FLG*, *IL-6*),[5–12] environmental factors have also been shown to contribute to the disease pathogenesis. There are also other possible mechanisms that aberrant barrier functions in gut mucosa lead to greater antigen transfer across the mucosal barrier and the routes of transport are altered, thereby evoking aberrant immune responses and release of pro-inflammatory cytokines with further impairment of the barrier functions.[28] Such increased inflammation would lead to further increases in intestinal permeability and in a vicious circle of increasing allergenic responses, and a more permanent dysregulation of the immune responses to ubiquitous antigens in genetically susceptible individuals.[29] The alteration of gut microbiota has an important impact on the peripheral and central immune system. Many unclear mechanisms still exist.

The role of gut microbiota in eczema

Recently, it has been indicated that microbial triggers have been implicated in eczema.[30] The vast majority of these studies suggested that subjects with eczema exhibit alterations in the relative abundance of ''beneficial'' and potentially ''harmful'' bacteria compared to healthy subjects (Table 1). There is convincing evidence from experimental subjects suggesting that kind of factors (e.g., diet, level of physical activity, during pregnancy, and with the use of broad-spectrum antibiotics) are related to eczema disease via affecting gut microbiota. The existence of a link between eczema and the gut microbiota was indicated based on studies in patients with eczema. Infants with eczema harboured significantly lower gut microbial diversity when compared to healthy controls, suggesting that alteration of the entire intestinal microbiota and the lack of exposure to certain bacterial targets may be contributing factors that amounted to their diseased state.[31,32] In keeping with the observation, by comparing with healthy subjects, gut microbial diversity significantly decreased in infants with IgE-associated eczema, the diversity of the bacterial phylum *Bacteroidetes* and phylum *Proteobacteria* also significantly reduced, the level of the phylum *Proteobacteria* significantly decreased.[33] *Proteobacteria* comprises gram-negative bacteria, typically with endotoxin lipopolysaccharides (LPS) incorporated into the cell wall. Endotoxin can induce a TH1 response through the innate immune system by enhancing IL-12 production from monocytes and dendritic cells,[34] and low exposure to endotoxin has been associated with an increased risk of atopic eczema.[35] In addition, a strong endotoxin exposure might down regulate atopy-promoting Th2 responses.[33] Similarly, Nylund et al.,[36] also found that infants with eczema appeared to have a significant decrease in the abundance of *Bacteroidetes* compared to healthy infants. Therefore, these increasing studies suggest that changes in the composition of gut microbiota play a significant role in induction and furthering the progression of eczema. The abundance of *Ruminococcaceae* was significantly lower at one week of age in infants with IgE-associated eczema than controls.[37] Meanwhile, the abundance of *Ruminococcus* was significantly negatively associated with TLR2-induced IL-6 and TNF-α. The abundance of the phylum *Proteobacteria* and the family *Enterobacteriaceae* significantly decreased in infants with IgE-associated eczema compared to controls. The abundance of *Proteobacteria* was significantly inversely related with TLR4-induced TNF-α. The abundance of *Enterobacteriaceae* was significantly negatively associated with TLR4-induced TNF-α and IL-6. At one year, α-diversity of *Actinobacteria* was significantly lower in infants with IgE-associated eczema compared with controls. *Ruminococcaceae* belonging to *Firmicute* have been associated with the maintenance of gut health. There is emerging interest in the role of

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