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Role of Gut Microbiota and Infectious Burden in the Development of Autoimmune and Allergic Diseases

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The human gut is the natural niche to an enormous and complex community of commensal bacteria of more than 1000 different species. Because of intimate relation between gut microbiota and host immune system, gut microbiota effectively modulate the development of both the innate and adaptive immune system. Several scientists have worked in this field and linked some members of the gut microbiota to autoimmune diseases. So far, significant attention has been given on the role of gut microbiota in gastrointestinal tract related autoimmune diseases such as inflammatory bowel disease (IBD). Several studies have identified the dysbiosis of specific microbiota in IBD patients. A reduction in *Firmicutes* and *Bacteroides* species and an overgrowth of proteobacteria have been observed in IBD patients.[1,2] Many studies have demonstrated the role of gut microbiota in modulating the systemic immune components besides the local gut immune system. Hence, gut microbiota have been linked to the development of extra-intestinal autoimmune disorders such as rheumatoid arthritis and Type 1 diabetes. [3,4]

Multiple factors such as genetics, age, and environment might contribute to the development of autoimmune diseases. Microorganisms such as viruses and bacteria are the major environmental factors initiating the autoimmunity. There are several mechanisms through which pathogens can induce autoimmunity. Antigen-specific mechanisms including molecular mimicry, expression of modified cryptic, or new antigenic determinants, and superantigens. Nonspecific mechanisms include enhanced processing and presentation of self-antigens, immune cell activation, cytokine release, and cell apoptosis/ necrosis. Depending on the interaction with the host, microorganisms not only induce autoimmune diseases, but also they may protect from autoimmunity or even abrogate an ongoing autoimmune process. Therefore, it is important to recognize microorganisms as potential modulators of the immune system.

In line with the hygiene hypothesis, the decreasing incidence of infections in western countries is coincided with the increasing incidence of both autoimmune and allergic diseases. Several studies reported the inverse correlation between the incidence of allergic, autoimmune diseases and various infectious diseases including hepatitis A, gastrointestinal and parasitic infections.[5] Exposure to farming and cowsheds early in life prevents atopic diseases, especially if the mother is exposed during pregnancy.

Allergic diseases such as atopic eczema, food allergy, asthma and allergic rhinoconjunctivitis are the most common chronic conditions in children from developed countries. Many studies suggested that reduced gut microbiota diversity during infancy has been associated with allergic diseases later in childhood.[6,7]

This phenomenon could be explained by the fact that the gut immune system reacts with new bacterial antigens, and repeated exposures enhance the

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development of immune regulation. There may be several interacting immunologic mechanisms accounting for the increased incidence of asthma and allergies in children from developed countries. The most commonly quoted mechanism is the lack of skewing of the Th2/Th1 balance away from allergy-promoting Th2 cells toward Th1 cells, which usually takes place with increasing age and exposure to microbes. This lack of skewing of the Th2/Th1 balance may be the result of the reduced production of IL-12 and IFNs by innate immune pathways that are stimulated by bacterial products through their toll-like receptors. An alternative view is that the lower microbial burden does not act by inducing a lower production of Th1-polarizing cytokines but by decreasing the activity of T-regulatory cells. Some studies have linked the prevalence or relative abundance of specific organism to atopic outcomes. For example, early-life colonization by *Clostridium difficile* reportedly increases risk for childhood wheeze, eczema and asthma[8], whereas certain *Bifidobacteria* and *Lactobacilli* are considered protective.[9] Hence, it remains unclear, whether gut microbiota composition/diversity is important for immune system development and avoidance of atopic disease or not.

How these gut microbiota or infectious agents modulate the immune response? They might regulate the immune response by multiple mechanisms such as reducing the inflammatory signaling cascade, stimulation of regulatory T cell subsets (Tregs) and toll-like receptors. Inflammatory signaling cascade could be inhibited by down regulating NFk-β pathway and decreased production of IL-8. More recently, it has been reported that NFk-β subunit c-Rel regulates Bach2 expression in B-cell lymphoma.[10] Bach2 is a 92-kDa transcription factor of the basic leucine zipper family. In B cells, Bach2 is critical for somatic hypermutation and class-switch recombination. In $CD4^+$ T cells, Bach2 promotes the development of $Foxp3^+$ Tregs by suppressing effect or cell transcriptional programs. Genetic polymorphisms within the Bach2 locus in humans are associated with susceptibility to numerous autoimmune and allergic diseases. To conclude, future studies should concentrate on the interaction of gut microbes or infectious agents and host immune system to better understand the pathogenesis of autoimmune and allergic diseases.

REFERENCES

1. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci 2007; 104(34):13780-5.
2. Sokol H, Seksik P, Rigottier-Gois L, Lay C, Lepage P, Podglajen I, et al. Specificities of the fecal microbiota in inflammatory bowel disease. Inflamm Bowel Dis 2006; 12(2):106-11.
3. Vaahtovuo J, Munukka E, Korkeamäki M, Luukkainen R, Toivanen P. Fecal microbiota in early rheumatoid arthritis. J Rheumatol 2008; 35(8):1500-5.
4. Badami E, Sorini C, Coccia M, Usuelli V, Molteni L, Bolla AM, et al. Defective differentiation of regulatory FoxP3+ T cells by small-intestinal dendritic cells in patients with type 1 diabetes. Diabetes 2011; 60(8):2120-4.
5. Flohr C, Tuyen LN, Lewis S, Quinnell R, Minh TT, Liem HT, *et al.* Poor sanitation and helminth infection protect against skin sensitization in Vietnamese children: a cross-sectional study. J Allergy Clin Immunol 2006; 118(6):1305–11.
6. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol 2012; 129(2):434–40.
7. Bisgaard H, Li N, Bonnelykke K, Chawes BL, Skov T, Paludan-Muller G, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol 2011; 128(3):646–52.
8. Van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, Koppelman GH, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. J Allergy Clin Immunol 2011; 128(5):948–55.
9. Murray CS, Tannock GW, Simon MA, Harmsen HJ, Welling GW, Custovic A, et al. Fecal microbiota in sensitized wheezy and non-sensitized non-wheezy children: a nested case–control study. Clin Exp Allergy 2005; 35(6):741–5.
10. Hunter JE, Butterworth JA, Zhao B, Sellier H, Campbell KJ, Thomas HD, et al. The NF-kB subunit c-Rel regulates Bach2 tumour suppressor expression in B-cell lymphoma. Oncogene 2015; 1–9.