Investigating the role of host-microbiota interaction in the pathogenesis of immune-mediated disorders.

Deregulated immune responses are involved in a large number of diseases with a huge societal impact including autoimmunity, auto-inflammatory diseases, sepsis and cancer. The microbiome plays critical roles in the development and education of major components of the host’s immune system, while the immune system orchestrates the maintenance of host-microbe symbiosis. It’s now clear that aberrant interactions between the microbiome and the host’s immune system, in genetically susceptible individuals, has a strong impact in shaping both local and systemic inflammatory responses. We have recently demonstrated that intestinal microbes play a critical role in the distinctive immune dysregulation of Omenn syndrome (OS), caused by hypomorphic Rag mutations and characterized by a profound immunodeficiency associated with autoimmune-like manifestations. The symptoms are very similar to graft-versus-host disease, as inflammatory reactions particularly involve the environmental interfaces such as the skin and gut, leading to distinctive early onset erythroderma and protracted diarrhea. Infiltration in other organs such as the kidney and liver is also reported, and other features include eosinophilia, extremely elevated serum IgE levels and hypogammaglobulinaemia, susceptibility to infections, and failure to thrive. Both in humans and mice, OS is mediated by oligoclonal activated T and B cells. We found that hypomorphic Rag2R229Q mutation is associated with altered intestinal microbiota composition and defects in the gut–blood barrier, leading to enhanced systemic translocation of microbial products. Intestinal inflammation and gut barrier leakage synergistically supported also the activation of skin epithelial cells, favouring the recruitment of T cells to the skin. Decreasing bacterial load in Rag2R229Q mice with long-term dosing of antibiotics (ABXs) reduced local and circulating proinflammatory Th1 and Th17 T cell populations, visibly ameliorated both intestinal and systemic autoimmunity, and normalized serum hyper-IgE.

References: Selected publication:


**Keywords:** immunity, immunodeficiency, immune-mediated disease, microbiota, infection

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