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Interactions of the microbiota with the mucosal immune system

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Summary

The field of mucosal immunology has, for the last 10 years, been largely dominated by advances in our understanding of the commensal microbiota. Developments of novel experimental methodologies and analysis techniques have provided unparalleled insight into the profound impact the microbiota has on the development and function of the immune system. In this cross-journal review series published in *Immunology* and *Clinical and Experimental Immunology*, we aim to summarize the current state of research concerning the interplay between the microbiota and mucosal immunity. In addition, the series examines how the increased understanding of the microbiota is changing the nature of immunological research, both in the laboratory and in the clinic.

As we began our careers in immunology, some 15 years ago, there was relatively little understanding of the effects of the commensal microbiota on the state and development of the immune system. In most immunological forums, if the microbiota was discussed at all, it was peripherally mentioned, with few concrete data or mechanistic characterization. While differences in microbiota were occasionally invoked in an almost jocular manner, as a possible source of variability in animal experimental models in different laboratories, little attempt was made to try to address this problem. However, very quickly, a series of technical and scientific advances brought the complexity and importance of microbial communities to the forefront of immunological research. The state of the microbiota was linked to profound differences in a range of diseases and pathologies, both in the intestine and other mucosal tissues, but also systemically.[1] Perhaps most notably, the discovery that segmented filamentous bacteria (SFB) had a major impact on the abundance of the then-newly discovered T helper type 17 (Th17) cell subset in the intestinal mucosa[2] proved to be a decisive turning point. Immunologists in general, but especially those of us studying the mucosal immune system, came to recognize the impact that differences in microbiota could have in experimental systems. Importantly, this paralleled a growing appreciation by the medical community that microbial composition could have profound consequences, both positive and negative, for human health.

This new interest was reflected in immunological literature, with a notable increase in immunological research into the commensal microbiota. In many ways, immunologists were (and still are) at an extremely exciting stage of research, engaging with real cross-disciplinary efforts to understand the interplay between the microbiota and the immune system. This review series, published across the BSI journals *Immunology* and *Clinical and Experimental Immunology* (CEI), aims to provide an introduction to the immunological readership on the recent advances in microbial research, with particular emphasis on the interplay between the microbiota and the immune system.

Directly addressing this need, in this issue of *Immunology* Ahern and Maloy[3] give an overview of the current state of microbiota research, with particular emphasis on the necessity of incorporating the microbiota in immunological experiment design. They summarize the current

experimental approaches that can be used to analyse microbial communities, modulate the microbiota and identify key effector species. Crucially, they highlight the need for standardization of the technical approaches used to investigate microbiota–immunity interactions, which should facilitate the comparison of studies performed in different laboratories. Finally, they discuss the advantages and limitations of using mice as an experimental model and extrapolating results from animal models to human health and disease.

The impact of a healthy microbiome on intestinal homeostasis is particularly vital in the neonatal period, when the microbial community is initially established. In particular, the 'neonatal window of opportunity' appears to be crucial in imprinting the immune system. Perturbation or dysbiosis of infant microbiota can have far-reaching consequences for health, influencing the development of allergy, obesity and various inflammatory disorders in later life.[4,5] Hornef and Torow[6] discuss how the colonization of the intestinal microbiota during the neonatal period has a major effect on the development of the mucosal immune system. Moreover, they highlight that various factors, such as mode of delivery and factors in breast milk, can impact neonatal microbial colonization, but also affect the layered development of innate and adaptive mucosal immunity in infancy and may have far-reaching implications for the development of immune-mediated diseases throughout life.

It is worth emphasizing that our immune system co-evolved in the presence of commensal microbiota and, especially at mucosal surfaces, the two are continuously engaged in a series of reciprocal interactions. Therefore, the normal functioning of the mucosal immune system, which has to maintain a delicate balance between maintenance of homeostasis and defence against pathogens, is closely linked to microbiota throughout life. Scott and Mann[7] discuss the recent advances in understanding the mechanistic interactions of the microbiota and the mucosal mononuclear phagocyte system. Mononuclear phagocytes, comprising dendritic cells and macrophages, are present in nearly all tissues of the body and have key roles in regulating tissue homeostasis and controlling the extent and nature of innate and adaptive immune responses. The authors discuss the recent studies that describe how microbiota-derived stimuli and metabolites shape the phenotype and function of mononuclear phagocytes and highlight the common and distinct pathways at different mucosal sites.

Innate lymphoid cells (ILCs) are a relatively newly discovered immune population which, similarly to the mononuclear phagocytes, reside in peripheral tissues and have important dual roles in homeostasis and immunity. Notably, ILCs are particularly prevalent in mucosal tissues, where they interact with and are conditioned by the commensal microbiota, as discussed in the review by Ganal-Vonarburg and Dürr[8]. These authors highlight how ILC cytokine production can be modified by microbial stimuli, which has a major effect on the various ILC functions, such as maintenance of epithelial barriers or polarization of immune responses. Importantly, the authors also emphasize the growing evidence firmly establishing the ILC–microbiota axis as a key component of the immune response to mucosal pathogens.

As these and other reviews demonstrate, the immune system is modulated by the commensal microbiota. However, the reverse is also true – the host immune system plays a vital role in shaping the microbiota. This is particularly evident in the case of secretory immunoglobulin (Ig)A (sIgA), an antibody isotype abundantly produced in the intestinal mucosa. Notably, while IgA has a well-documented role in protection from mucosal pathogens, under homeostatic conditions a large proportion of sIgA binds the microbiota.[9] Hoces *et al.*[10] discuss the varied effects that sIgA can have on the members of the gut microbiome, ranging from immune exclusion and growth inhibition to enhanced growth and colonization. Furthermore, exemplifying the need for a cross-disciplinary approach, they emphasize that sIgA–microbial interaction should be analysed in its proper context – the unique environment on the intestinal lumen.

Building on the concepts introduced by Hornef and Torow, Nibbering and Ubags[11] examine the role for the microbiota in the development of atopic disease. They discuss the theory that reduced exposure to infectious agents in infancy may predispose to the development of atopic disease, such as atopic dermatitis and allergic asthma, in adulthood: the so-called 'hygiene hypothesis'.[12] Changes to the microbiota may also maintain or perpetuate atopic disease, as the local microbiome changes markedly in atopic dermatitis and allergic asthma patients, although whether this is the cause or effect of disease remains unclear. The authors also describe how dysbiosis in the gut can influence the occurrence of distal, atopic pathologies and discuss the role the 'western' diet may have in the increasing prevalence of atopic disease.

As our understanding of the importance of the microbiota increases, promising new treatments have emerged. Perhaps most impactful has been the transfer of 'healthy' donor microbiota into patients, referred to as fecal microbiota transplantation (FMT). The effectiveness of this treatment, most notably in recurrent *Clostridium difficile* infection, has been extraordinary and has provided a real impetus to the development of microbiota-based therapies in IBD and other inflammatory disorders. Quraishi *et al.*[13] stress a pressing need to understand the mechanisms by which FMT confers its beneficial effects. Indeed, characterizing the molecular and cellular interactions by which FMT modulates the host immune system may lead to safer and more effective microbiota-based therapies.

The last decade has seen major advances in our understanding of the microbiota and how it shapes various aspects of host immunity. The advent of next-generation sequencing (NGS) and new omics-based analysis tools have provided a relatively straightforward way for the wider scientific community to characterize and study the commensal microbiota, although dealing with the sheer volume and complexity of NGS data may pose a challenge in the future. Nevertheless, exciting times lie ahead, as insights from fundamental science are translated to the clinic and the power of manipulating the microbiota in inflammatory disease is realized.

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