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Preface:

Immunity at the Barriers

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Maintenance of barrier defense is an essential component of mammalian host health and survival. Most antigens encountered by the immune system enter the body through the skin or mucosal surfaces of the respiratory, gastrointestinal, and urogenital tract. The vast majority of infectious microorganisms use these tissues as portals of entry. An additional feature of barrier tissues is their constitutive and ever evolving relationship with highly diverse and site-specific beneficial microbial communities referred to as the microbiota. Therefore, these tissues are charged with the formidable task of protecting the host from pathogenic challenges, while maintaining a peaceful coexistence with resident microbiota and preserving vital physiologic tissue functions.

At these sites, failure to control responses can lead to severe inflammatory disorders including asthma, inflammatory bowel disease, psoriasis, or food allergies. The incidence of these chronic inflammatory diseases, as with most pathologies at barrier tissues, has risen significantly in the past several decades [1]. Understanding how immunity is controlled at barrier tissues as well as the key stressors of these environments is not only of major public health interest but is also the object of intensive investigation. The review series on Immunity at the Barriers published in this issue of the *European Journal of Immunology*

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highlights some of the key questions and recent findings associated with our growing understanding of how barrier immunity is regulated.

In recent years, immunological research has evolved from a lymphoid tissue-centric view of the immune system to the integration of tissue microenvironments as a fundamental determinant of immune responses. This developing area of research has led to the growing understanding that one of the cardinal features of barrier tissues is their capacity to respond to defined challenges in a highly site-specific manner [2]. Maintenance of tolerance and restoration of tissue homeostasis following insults or exposure to pathogens rely on a complex and coordinated set of innate and adaptive responses. Such tissue-specific immune specialization relies on the capacity of defined and site-specific populations of immune cells to integrate local cues such as microbial products, metabolites, cytokines, or hormones. These tailored networks are essential to the induction of responses that preserve the physiological and functional requirements of a defined tissue. How epithelial cells, mast cells, innate lymphoid cells, dendritic cells, or lymphocytes control homeostatic barrier immunity and how deregulation of these responses leads to severe inflammatory diseases is the main focus of this review series.

To maintain a homeostatic relationship with the microbiota and limit antigenic and pathogen exposure, protection is primarily mediated by an epithelial layer that forms a physical barrier and is supported by both adaptive and innate arms of the immune system. Over the past few years, it has become clear that epithelial cells via their capacity to produce mucus, antimicrobial peptides, metabolites, and cytokines are a central determinant of immunity in tissue microenvironments [3]. Expanding on this concept, the reviews by Lambrecht and Hammad [4], and Kurashima et al. [5] discuss how aberrant responses of gut or lung epithelial cells downstream from effector responses lead to the breakdown of tissue homeostasis and severe pathologies such as asthma or inflammatory bowel disease, respectively.

Despite the specialization of each tissue and microenvironment, the expression of defined cytokines such as those coupled with Th17 responses is relatively conserved between barrier sites such as the lung, gastrointestinal tract, or skin. Indeed, via their capacity to act both on epithelial cells and to control inflammatory cells, IL-22 and cytokines of the IL-17 family contribute to both barrier homeostasis and immunity [6, 7]. In this review series, Way et al. [8] discuss the factors controlling the induction and function of Th17 cells in the lung and the link between uncontrolled Th17-cell responses and immunopathology. As discussed by Kurashima et al. [5], innate sources of IL-17 or IL-22, particularly from innate lymphoid cells, are required for barrier maintenance, tissue repair, and host defense.

An important focus of the present issue is the role of defined populations of dendritic cells in the control of barrier immunity. In tissue microenvironments, particularly during inflammation, surface markers do not always faithfully distinguish subsets of cells. As discussed by Persson et al. [9], this polemic has recently been partially resolved by the development of a more ontogenetic definition of dendritic cell lineages [10]. The discovery that unique subsets of dendritic cells residing in tissues such as the gut are endowed with the capacity to sustain tolerogenic responses has helped shape our understanding of how barrier

immune homeostasis is maintained [11]. However it has recently become apparent that this function can be contextual and that the same population of antigen-presenting cells can swiftly adopt a proinflammatory potential. Several lines of research also describe how, in tissues, the optimal induction of both regulatory and effector responses is more complex than initially postulated and relies on the coordinated action of several antigen-presenting cells. These concepts discussed by Persson et al. [9] highlight the specialization and functional plasticity of tissue resident dendritic cells.

An important and growing line of research is the translation of these studies to the identification and characterization of the human dendritic cell network in tissues such as the gut or the skin, as highlighted in the review by Eynav Klechevsky [12]. Furthermore, as pointed out by Flutter and Nestle [13], our capacity to further understand the specificity of tissue responses not only relies on our ability to experimentally integrate the complexity of each tissue but also to devise models that closely mimic tissue-specific human pathologies.

Collectively, this group of reviews serves to highlight the rapidly growing knowledge of the pathways and cell types that regulate immune cell homeostasis at barrier surfaces and spotlight some of the future challenges to be addressed in understanding barrier immunity in the context of infection, inflammation, and tissue repair.

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