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INTRODUCTION

Innate lymphoid cells: key players in tissue-specific immunity

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The discovery of innate lymphoid cells (ILCs) as a separate lineage of leukocytes with specialized subsets has profoundly changed our view of the immune system in the last decade. Although NK cells, as the first known member of this family, were identified already in the late 1970s [1], it took more than 20 years until the next ILC subtype, the ROR-γt^+ lymphoid tissue inducer cell, was discovered [2, 3]. In the next years, sporadic reports indicated that the family of innate lymphocytes might actually be more heterogeneous than previously thought [4–6]. However, it was the observation (made in the late 2000s) that NK cell receptor-positive IL-22-producing innate lymphocytes were clearly distinct from conventional NK cells [7–10], together with the description of type 2 cytokine-producing ILCs in 2010 [11–14] and the identification of committed ILC progenitors [15, 16] that finally led to the definition of ILCs as a heterogeneous group of lymphocytes that represent an independent leukocyte lineage. During the last decade, extensive investigations into all aspects of ILC biology have provided us with a detailed understanding of development, activation, and effector functions of different ILC subtypes in various tissue locations. The current issue of *Seminars in Immunopathology* comprises a series of reviews that cover general principles and tissue-specific functions of ILCs in homeostasis and inflammatory diseases.

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As opposed to lymphocytes of the adaptive immune system, ILCs do not rely on rearranged antigen-recognition receptors for their activation. Instead, they can be directly activated by cytokine signals and, as emerging evidence suggests, other non-cytokine cues from the tissue microenvironment. In their article, Wilhelm and colleagues focus on how ILCs sense these environmental signals, including dietary factors, lipid metabolites, hormones and neural factors, and integrate them to promote tissue homeostasis in health and disease [17]. In addition to soluble mediators, lymphocytes are typically regulated through a large array of activating and inhibitory receptors many of which mediate direct communication with other cell types. A major question in the field is how these receptors regulate ILCs, and whether ILCs express unique receptors that may uncover non-redundant functions of ILCs. In their article, Narni-Mancinelli and colleagues provide an overview of our current understanding of surface receptors and their ligands that regulate ILC functions [18].

The clear separation of adaptive lymphocytes (e.g., B and T cells) and innate lymphocytes (ILCs, including NK cells) has recently been challenged by evidence indicating that NK cells can mount immunological memory responses. In their review, Sun and colleagues describe this interesting feature of NK cells and discuss close parallels between NK cell and T cell memory, highlighting that NK cells (and potentially other ILC subtypes) may have more adaptive properties than previously appreciated [19].

The relative abundance of ILCs especially in barrier organs, such as the gut, lung, and skin, emphasizes their importance for the cross talk of the host with the commensal microbe community that populates all mucosal and non-mucosal surfaces of the body. Hepworth and colleagues review the recent literature on how ILCs regulate immune responses in the intestine, prevent inappropriate inflammatory responses, and maintain the segregation of commensal microbes to ensure tissue health and regeneration [20]. In another article on intestinal immune regulation, Colonna and colleagues focus on the role of the aryl hydrocarbon receptor, as a major sensor for nutritional and microbial cues that

shapes the development, maintenance and function of ILCs, and other intestinal lymphocytes [21].

In addition to their important role in regulating intestinal homeostasis and tissue repair after injury, ILC subtypes are also implicated in the defense against different classes of pathogenic infections. In their review, Wirtz et al. discuss the contribution of type 2 ILCs to the immune response during infections and summarize the available evidence of how chronic dysregulation of these ILC2 responses can promote organ-specific fibrosis [22]. Since alterations in function and subtype distribution of ILCs have been observed in a variety of chronic inflammatory conditions, another article in this issue by Turner et al. addresses the emergence of ILCs as promising therapeutic targets for the modulation of immune responses in autoimmunity and chronic inflammation [23]. Although much of the initial work addressing the development, functions, and interactions of ILCs has been limited to mouse studies, there are many intriguing reports shedding light on key questions of ILC biology in the human immune system. Mjösberg and colleagues review the current knowledge about human ILCs and their interactions with other lymphocytes in health and disease [24].

In summary, the past decade has seen the emergence of ILCs as key players for tissue homeostasis and immunity that contribute to the inflammatory responses in infection, autoimmunity, and chronic diseases. Major topics in current ILC research include the mechanisms guiding the development and functions of ILCs in specific tissue environments, their interaction with other cell types, the receptors and ligands that regulate ILCs, and the question about unique and redundant functions with innate-like T cells and the adaptive immune system. In addition, it will be exciting to investigate how the fascinating progress that has been made in the understanding of ILC biology can be translated into novel ILC-directed treatment strategies for human diseases.

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