EDITORIAL

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Immunity in the tissues

Tissue-resident leukocytes contribute to tissue function and homeostasis as well as immune surveillance.

Numerous innate and adaptive immune cells reside in nonlymphoid tissue environments where they contribute to immune defenses. These cells are important players in regulating tissue homeostasis and function. In this issue of *Nature Immunology*, we present five specially commissioned Reviews that explore the roles of tissue-resident leukocytes and their interactions within the parenchymal tissues and hematopoietic cousins. Access to all of the Focus content can be found online at http://www.nature.com/ni/focus/tr_leukocytes/.

Skin is a frontline barrier organ that confronts constant microbial challenge and mechanical injury. Heath and Carbone discuss diverse components of skin barrier protection and the interactions of resident leukocytes with the surrounding stromal cells. Epidermal keratinocytes are the surveillance sensors of the skin through their expression of multiple pattern-recognition receptors. Upon challenge, keratinocytes elaborate antimicrobial peptides, cytokines and chemokines that activate and recruit patrolling leukocytes. The dermis and epidermis are home to innate lymphoid cells and γδ T cells that seed the tissue early in development and can replicate *in situ* to maintain their numbers. Skin contains multiple antigen-presenting cells, which are necessary to maintain tissue tolerance and homeostasis as well as respond to infection. Activated lymphocytes, including αβ T cells, arrive as the skin is colonized by microbes and are maintained as memory populations, sustained by growth factors supplied by keratinocytes and other tissue-resident cells.

Taylor and colleagues focus on tissue-resident macrophages, a diverse population of immune cells that engulf dying cells and cellular debris, in addition to capturing immune complexes and other opsonized material. Controversies exist regarding the ontogeny and self-renewal properties of tissue macrophages, which likely reflect the heterogeneity of these populations and the lack of discrete phenotypic markers able to identify unique subsets. A major question facing the field is whether unique roles can be ascribed to distinct macrophage populations. Although this possibility may be true for steady-state scenarios, functional redundancy of tissue-resident and bone marrow–derived macrophages is likely necessary during infection to contain rapidly replicating microbes. This prompts the question of whether the tissue rather than the ontogenetic origin of the macrophage dictates functionality of these cells.

Jenne and Kubes discuss the liver as a frontline immune organ to blood-borne pathogens and commensals that escape the gut into the circulation and arrive via the portal vein. The liver is poised for immune surveillance by its very architecture of blood sinusoids, which are lined by specialized liver sinusoidal endothelial cells that are capable of capturing and cross-presenting antigen. Kupffer cells also are unique macrophages that reside in the liver and serve as immune sentinels. Unlike other macrophage populations, Kupffer cells are located on the intraluminal side of the vasculature and can capture live bacteria under flow conditions. The liver harbors abundant $CD8^+$ T cells, natural killer cells and natural killer T cells. This confluence of immune cells with continual exposure to microbes and foreign food epitopes in the liver environment requires dominant tolerance mechanisms to be engaged. Indeed, the liver avoids a continual state of inflammation by dendritic cell production of interleukin 10 (IL-10) and by adaptation leading to higher thresholds for activation in response to pathogen-associated microbial products. However, these tolerizing pathways can promote chronic infections when faced with hepatic pathogens such as hepatitis viruses.

Regulatory T cells (T_{reg}) can suppress immune-cell priming in lymphoid tissues, but they also have immunosuppressive roles against myeloid populations and effector cells in tissues. Mathis and colleagues describe roles for T_{reg} cells in nonlymphoid tissues beyond modification of immune responses. Tissue T_{reg} populations also exhibit heterogeneity, and their function is adapted to the tissue itself. A prominent example occurs with visceral adipose tissue T_{reg} cells, which express the transcription factor PPAR-γ and can influence systemic glucose metabolism. Muscle-specific T_{reg} cells also can enhance repair of injured skeletal muscle, likely by dampening local inflammatory responses. These tissue-specific T_{reg} populations exhibit distinct repertoires of T cell antigen receptors and chemokine receptors, suggesting that these populations are selected by the tissue. If this is true, then the following questions arise; 'how many distinct T_{reg} populations exist?' and 'what factors regulate their generation and maintenance?'.

Gajewski and colleagues examine the specialized setting of tumor environments and the leukocyte infiltrates that are recruited to these abnormal tissues. Successful tumors, by definition, can evade immune system–mediated destruction. Tumors can be classified by the presence or not of tumor-specific $CD8^+$ T cells. A number of tumors do contain activated $CD8^+$ T cell infiltrates, thus responding to tumor-specific antigen, but dominant suppressive effects, including upregulation of the inhibitory costimulatory molecule PD-L1 and production of indoleamine-2,3-dioxygenase, hamper the T cells' ability to kill tumor cells. Recruitment of tumor-specific T_{reg} cells or suppressive myeloid cells that express IL-10, tumor growth factor-β and arginase likewise limits effective antitumor T cell responses. However, a number of tumors lack an inflamed phenotype with T cell infiltration, suggesting that the adaptive immune system may be ignorant to the presence of such tumors. Identifying the immunophenotype of tumors can therefore guide clinicians toward means of effective therapeutic interventions for specific patients.

Effector memory lymphocyte populations that remain in tissues after primary challenge are obviously important components to tissue immunity and have been highlighted in a previous Focus dedicated to immunologic memory. However, growing awareness shows that immunity involves a community of innate and adaptive immune cells interacting with parenchymal cells. Understanding these relationships and their modes of communication may improve therapeutic strategies to boost immunologic well-being.