EDITORIAL

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# The right place at the right time

Immune cells are in constant communication with their environment. The immune system has evolved to respond to cues that direct cellular development, movement and effector function. These signals can be soluble mediators, such as chemokines or cytokines, or can involve intimate cell-to-cell contact that conveys reciprocal receptor signaling to elicit responses appropriate for a given immune challenge. The immune system is extremely flexible, in that it can tolerate rapid cell proliferation when faced with specific pathogenic threats, yet it is capable of returning to a homeostatic basal state once the threat subsides. Adaptive immunity, which entails attributes of antigenic specificity and memory, requires additional cellular interactions. These involve stromal antigen-presenting cell contacts with developing lymphocytes to select repertoires of cells capable of self versus nonself recognition as well as the generation of regulatory cell populations that can control potential adverse self-reactivity. Likewise, the establishment and maintenance of immunologic memory is thought to require specific environmental cues that include antigenic dose and temporal duration.

The total number of cells that make up the immune system represent only 1–2% of the cells present in a person, yet immune cells must have access to and survey nearly every surface and tissue to combat potential infections or repair tissue damage. The immune system therefore faces an enormous challenge in receiving the essential information required for proper function. This daunting challenge might be insurmountable were it not for specialized tissue environments that facilitate such information transfer.

In this issue of *Nature Immunology*, we present a Focus devoted to Specialized Immunological Niches. We have commissioned four review articles that discuss the latest findings on how immune cells communicate in selected microenvironments, including the bone marrow, thymus, lymph nodes and immune-privileged sites. Cahalan and Gutman discuss in their overview the signals that influence immune cell movement within niches and from one niche to another as well as the technologies that allow visualization of these cells *in situ*. Our focus website (http://www.nature.com/ni/focus/niches/index.html) features additional online content, including an annotated list of seminal papers that have propelled the field forward and a selection of recent papers published by the Nature Publishing Group, as well as highlights of newly published work describing immune cells interacting with their environment. A new feature added to this focus issue is the online video library, which adds the dimension of time to show dynamic interactions occurring between immune cells in these specific microenvironments. Registered users will have free access to this entire collection of online content during the month of April.

The idea of a specialized microenvironment is introduced by Adams and Scadden in their review of the bone marrow niche. This niche shelters stem cells of the hematopoietic system, which are responsible for producing all blood cells. In this niche, relatively quiescent hematopoietic stem cells interact with osteoblasts that line the bone marrow cavity as well as with many soluble factors. Together these components regulate stem cell self-renewal and the total number of stem cells. However, the bone marrow is also responsive to external cues and is subject to feedback mechanisms that can rapidly increase blood cell production, as required, for example, during traumatic blood loss. Adams and Scadden discuss the many intrinsic factors expressed by stem cells and extrinsic factors produced in their proximity that have been shown to influence stem cell function.

Early thymic progenitors that have exited the bone marrow circulate to the thymus, where they receive signals that reinforce T lineage differentiation. Robey and colleagues describe the intrathymic journey of developing thymocytes. The thymus actually consists of many smaller microenvironments, each specialized to support the selection process that produces and exports a functional repertoire of mature single-positive $CD4^+$ and $CD8^+$ T cells. Thus, the thymus is a dynamic environment, in contrast to the static interactions that occur between cells in the bone marrow. Indeed, the thymus can be compared to a bustling city in which the developing thymocyte is continually tested for fitness. In their review, Robey and colleagues discuss the many chemokine gradients that direct movement in thymus and the cellular interactions that underlie thymocyte positive and negative selection.

The periphery poses a problem for antigen-specific cells that are responsible for adaptive immunity. How can they be at the right place at the right time? Relatively low frequencies of naive lymphocytes that circulate throughout the body must somehow find and respond appropriately to cognate antigen. Ruddle and colleagues review the present knowledge of the structure and function of secondary lymphoid tissues, which provide an environment that facilitates lymphocyte interactions with antigen-presenting cells. This review describes how these specialized structures arise during ontogeny and in chronic inflammatory conditions during which ectopic lymphoid tissues develop and can contribute to disease.

Not all tissues, however, benefit from immune cell–mediated attack, even if endangered by a pathogen. Niederkorn reviews how immune recognition and responses are regulated at sites of immune privilege, which include the brain and the eye. Many active suppressive mechanisms, in addition to physical barriers that limit immunological recognition, contribute to this process that ensures nonreactivity by immune cells. These privileged anatomical sites often contain specialized regulatory immune cells to retard attack even by primed lymphocytes.

Developments in real-time imaging techniques have allowed researchers the opportunity to observe immune cells *in situ*. In this Focus issue, we provide only a sampling of the insights gained from such studies of selected immunological niches. With these tools, answers to increasingly sophisticated experimental questions probing how microenvironmental cues influence immune cell activity are now within reach.