nature immunology

On the move

Leukocytes express an array of chemoattractant and adhesion receptors that govern their migration, behavior and survival.

Motility is key to the function of immune cells, which circulate throughout the body seeking out signs of infection or tissue damage. After detecting such 'danger signals', immune cells can quickly cross vascular barriers and efficiently localize near and neutralize the offending pathogen. Leukocyte entry into afferent lymphatic vessels provides a ready 'emergency' route that leads directly to draining lymph nodes, where such cells can quickly 'alert' additional immune cells to signs of danger. Priming of lymphocytes for adaptive immune responses requires their migration from the bloodstream to allow their interaction with antigen-laden dendritic cells within these activated lymph nodes. Likewise, homeostatic maintenance of immune cell production and survival requires their ability to migrate to and from specific splenic or lymphoid tissue locations. Exit of both naive and primed lymphocytes through the efferent lymphatics returns these cells to the bloodstream, whereupon they continue their surveillance. Throughout these processes cells must integrate multiple signals directing their migration, as well as their response upon arrival at their destination.

In this issue of *Nature Immunology*, we present a Focus on Leukocyte trafficking. We have commissioned five review articles and an overview that discuss current research findings on the molecular, cellular and tissue-specific cues required for proper immune cell localization and function. Much progress, especially in visualizing cells as they transit through living tissues, has been made in the immune cell trafficking field since our first Focus issue on Chemokines was published in 2001. The very real need to tightly regulate leukocyte trafficking to avoid or lessen immune cell–mediated collateral tissue damage makes this focus topic of great interest to both clinicians and research immunologists.

In their overview, Sallusto and Baggiolini highlight how far the field has 'traveled' since the initial discovery of chemokines and their receptors over 20 years ago. They also lay out challenges for the future in our attempts to better understand the specificity, redundancy and interplay between various chemoattractants and their cognate receptors. Such understanding will be necessary to allow development of safer and more effective therapies for pathophysiologic conditions of chronic inflammation or autoimmunity.

Thelen and Stein in their review article introduce chemokines—the chemical signals directing cellular traffic—and their G protein–coupled receptors, which link external chemotactic cues to the cytoskeleton. In particular, they discuss how chemotactic gradients are formed and critically review evidence for higher order receptor assemblies. Integration of multiple chemoattractant intracellular signaling pathways is required for directional movement. How this occurs within cells is only beginning to be understood in molecular terms, but it involves interactions of multiple Rho-family GTPases that coordinate cell polarity and movement. Friedl and Weigelin follow up with a detailed molecular analysis of how leukocytes migrate in interstitial tissues upon exiting the bloodstream. They contrast 'amoeboid' movements of leukocytes—which are relatively fast—with the slower mesenchymal movement of fibroblasts and other cell types and provide a rationale for why this mode of migration befits leukocyte function.

Luster and colleagues focus on T lymphocyte migration within lymphoid tissues and during episodes of tissue inflammation. One surprising facet that has been uncovered by the study of chemokines is that distinct lymphocyte subsets use different combinations of chemokine receptors to orchestrate effector functions. Such differences exist not only between B versus T cells, but also between naive versus memory lymphocytes and, of special interest lately, among various $CD4^+$ T_H cell subsets, such as T_{reg} and T_H-17 cells. Different tissues also pose different requirements for immune cell surveillance and function. Sigmundsdottir and Butcher describe how environmental cues, such as sunlight and vitamin A, contribute to imprinting tissue-specific trafficking programs on immune cells of the skin and gut. Unraveling the relationships and regulation that govern lymphocyte homing patterns will no doubt provide further insight into 'normal' function in specific tissues and into disease that arises when these cells mount immune responses elsewhere.

Mackay discusses recent advances in pharmaceutical industry efforts to target chemokines, chemoattractant receptors and their signaling pathways as potential therapies for autoimmune diseases and chronic inflammation. Many promising compounds and monoclonal reagents in the pipeline target molecules central to cellular migration. Natalizumab—which targets integrin α_4 molecules—has been approved for use in the clinic. More are sure to come.

With this Leukocyte trafficking focus, we introduce a new online-only feature in which we have invited experts to voice a brief opinion on current areas of research that we refer to as 'Outstanding questions'. This forum will be updated regularly and moderated by the *Nature Immunology* editors. For the inaugural 'question' topic, we have asked Bill Muller, Francisco Sanchez-Madrid and Britta Engelhardt to comment on the topic of physiologic routes for cellular diapedesis. Interested readers are directed to our focus website (http://www.nature.com/ni/focus/trafficking/) to view these opinions and other questions planned for the future. We invite readers to send us comments on this area of ongoing research. We may post your response at a later date.

While it is clear that we have learned much about the migration properties and requirements of leukocytes since the 1980s, we have likely only begun to scratch the surface of understanding the complexity of this transit system. Identifying the 'rules of the road' that apply to various vascular networks, how cells can shift gears in diverse tissue environments and how leukocytes navigate efficiently despite competing traffic signals will all be important topics for the future. And, in particular, how do these traffic signals change in the face of disease?