Published in final edited form as:
Semin Immunol. 2008 February ; 20(1): 1–3.

B Cell Subpopulations and Secondary Lymphoid Organ Architecture

John F. Kearney

The Extra cellular Matrix of the Spleen as a Potential Organizer of Immune Cell Compartments

In the first contribution Zerina Locmic and Lydia Sorokin at the University of Munster discuss the structure and compartmentalization of the non-hematopoietic components of the mouse spleen with references to the other lymphoid tissues where possible. The extracellular matrix (ECM) and its specialized forms, which make up the basement membrane, constitute scaffolds and barriers involved in facilitating cell movement and promoting the compartmentalization of cells in the spleen. These non-hematopoietic structures are important for controlling how and when cells move, their differentiation pathways, and their ultimate phenotype and physiology. They can also guide cell movement or promote proliferation indirectly by binding cytokines, chemokines, and growth factors. Sorokin's group has applied their extensive expertise in extra cellular matrix and basement membrane structure to analyse the spleen and has shown that there is an association of distinct matrices with distinct immune cell compartments. Apart from the well-known differences in cellular composition of the follicular, marginal zone, and red pulp of spleen, they describe striking difference in the organization and composition of matrices and basement membranes in these areas. She describes the striking diversity of the heterotrimeric laminins formed by the 5α, 4β, and 3γ chains described to date. The multiplicity of isoforms resulting from the combinatorial associations of these chains and the significance of their unique distribution in the spleen is not known. However laminins are major receptors for the β1 and β3 integrins as well as a host of other receptors and molecules associated with growth factor and cytokine storage. It is likely that these structural differences have functional implications. In conclusion this review points out that examination of genetically manipulated mice now available and those constructed in the future would increase our knowledge of ECM/basement membrane interaction with cells of the immune system.

Follicular dendritic cell networks of primary follicles and germinal centers: phenotype and function

In associated with the lymphoid matrix and network of structural components described in the previous review are a variety of stromal cells known as reticular stromal cells. These cells have heterogeneous morphology and phenotypic markers that appear dependant on compartment site. In this review Chris Allen and Jason Cyster review the phenotypes and function of follicular dendritic (FDC) cell networks of primary follicles and germinal centers. The complex origin and precursor-progeny of these cells are discussed. The multiple factors that appear to be involved in the further specialization of FDCs within the light and dark zones of the germinal centers which makes them different again from the bulk of FDCs in the primary follicle, are

discussed in detail. The function of FDCs is thought to be involved in the presentation of antigens in the form of complexes to B cells in both areas. The conflicting data on the role of FDCs on the initiation of B cell responses, germinal center formation and the establishment of memory B cells versus antibody–forming plasma cells are discussed in this context. The review concludes with a wide ranging discussion with respect to uniquely expressed FDC-molecules and other promising leads which may further our understanding of FDC function in health and disease.

Ectopic lymphoid tissues and local immunity

Data collected over the last 20yrs has implicated a variety of cytokines, inducer cells and other cell-cell interactions in the pre-programmed development of encapsulated lymphoid tissues such as lymph nodes as well as a variety of nonencapsulated lymphoid tissues typically found associated with the gut. It is now apparent that similar tertiary lymphoid structures bearing many resemblances to the normal structures of the lymphoid system arise in ectopic sites. These sites may involve chronic infection or inflammation, but may also contribute to local protective immune responses. Damian Carragher, Javier Rangel-Moreno and Troy Randall present a comprehensive review of the development of tertiary lymphoid tissues by comparing and contrasting the various mechanisms involved in normal and ectopic lymphoid development. Depending on the compartment site stromal cells similar to those discussed in the previous review appear to play a major role in the organization of tertiary lymphoid tissues. However very little is known of the factors controlling the specialized development of these mesenchymal derived cells. The more fascinating sites of ectopic lymphoid tissue production occur in a wide variety of autoimmune diseases and at sites of infection. In many autoimmune cases, the appearance of ectopic lymphoid tissue is associated with increasing severity of disease. Similar to infections exemplified by *Helicobacter pylori*, *Borrelia burgdorferi* and others, these centers of highly active lymphoid development often appear to be antigen-driven (whether self or environmental) and may be sites of malignant transformation. However it is also possible that the development of tertiary lymphoid tissue associated with tumors may be beneficial, as may be the case with infection of lung associated tissues. For these reasons, the authors emphasize the importance of understanding the molecular and cellular mechanisms driving the production of these ectopic sites of lymphoid tissues.

Germinal Center Structure and Function: Lessons from CD19

Recently advances in intravital imaging have shed new light on the cellular interactions and the microaanatomy of germinal center formation in mouse lymph node tissues. While these studies provide a new perspective on the dynamics and cellular interactions that occur, subtle differences have been found between these respective studies and the published accounts made by conventional immunohistological studies. Additional subtle differences may exist between models with high affinity Ig transgenes that were used to study GC's and also between GC formation in lymph nodes versus spleen or other lymphoid organs. Bob Carter and Riley Myers review the effects of the quality of B cell receptorsignaling may have on the function, cell proliferation, and positioning within germinal centers during their initial development and functional lifespan in the spleen.

Plasma Cell Development: From B Cell Subsets to Long-term Survival Niches

Although plasma cells have long been recognized as the major producers of immunoglobulins and serum antibodies, the analysis of plasma cell formation and their subsequent fate in the immune system has been limited by their small numbers and the lack of discriminatory differentiation antigens to assist in their characterization. Recently a Blimp reporter mouse was developed by Stephen Nutt and has been exploited by him and the other authors of this review Kirstan Fairfax, Axel Kallies, and David Tarlinton to make considerable advances in our

understanding of plasma cells in mice. This review describes new and subtle differences between short and long lived plasma cells and discuss concepts as to the role of the long lived plasma cell and B cell memory as manifested by serum antibody. The plasma cell response of the multiple B cell subsets to T-independent and T-dependent antigens likely depends on the pathways of antigen exposure, the nature of the antigen coupled with affinity of BCRs of responding B cells. The review discusses the role of Blimp and its interactions with other transcription factors leading ultimately to its proposed function as a consolidation and amplification factor rather than an initiating factor of plasma cell terminal differentiation. One of the tantalizing concepts is that of the niche hypothesis in which it is believed that there is competition for specialized sites in spleen and bone marrow that support plasma cell persistence for long periods of time. The various factors such as up regulation of anti-apoptotic molecules, chemokine involvement, interactions with early B cell precursors and the role of cell:cell interactions are discussed in the context of both normal plasma cell function and their abnormal development in disease.

Dynamic interactions between bacteria and immune cells leading to intestinal IgA synthesis

Some elements of the mucosal immune system result from genetically programmed primary development while others appear to depend on the colonization of the gut with bacteria. Both of these types of tissues are associated with the production of the most abundant immunoglobulin isotype IgA in the gut. In this review Masayuki Tsuji, Keiichiro Suzuki, Kazuo Kinoshita and Sidonia Fagarasan review the dynamics and cellular origins of the precursor cells arising in these two mucosal associated tissues that give rise to IgA plasma cells. The authors discuss the cellular interactions involved in the formation of these sites. Some of these mechanisms involving LTalpha and TNF are similar between the organization of structures, such as Peyer's Patches, and the isolated lymphoid follicles, except the latter require the presence of bacteria. They discuss the alternative sites for IgA plasma cell generation and at what stage of B cell migration to the lamina propria or intestinal sites does class switch recombination occur and what factors influence these events. The role of IgA in the gut is, surprisingly, still controversial despite its abundance. The review touches on the role of IgA in maintaining the quality and quantity of gut flora describes flora changes in models where mutation is lessened in the IgA secreted into the intestines.

Phenotypic and functional heterogeneity of human memory B cells

Although much of what has been covered in the preceding reviews has related to mouse B Cell subpopulations and secondary lymphoid organ architecture, a similar complexity of B cell subsets is emerging in human studies. From certain aspects, although there is controversy, some of the opposing ideas of a precursor (central) versus an effector long lived antibody production have largely been supported by initial studies in humans. However, structure function analyses such as that provide by immnunohistological studies and intravital imaging available in the mouse have not been available to such an extent or at all in humans and has hampered comparative analyses of lymphoid organ structure and cell-cell interactions in these tissues. In this review Ignacio Sanz, Chungwen Wei, Eun-Hyung Lee and Jennifer Anolik discuss memory B cell heterogeneity with respect to current schemes of memory B cell classification. There is an extensive and detailed summary of how the Sanz group, by using more extensive multiparameter flow cytometry, revealed additional complexity in the composition of human memory B cell populations. Likewise, the authors present a very detailed comparative analysis of similarities and differences between memory B cell, MZ cell and other B cells, in both mouse and man suggesting that differences between the two species may not be as extensive as once thought. Of particular interest is a summary of the kinetics and

homeostasis of memory B cell subsets in disease and more topically after B cell depletion procedures used in treatment of disease.