Immunology

Roving lymphocytes

from Ian McConnell

THE immune system is a roving bag of cells without a fixed anatomy. Unlike the nervous system it does not require a complex wiring programme for recognizing stimuli *in vivo* because lymphocytes are mobile cells which constantly traffic between and through lymphoid organs. The different traffic and localization patterns of lymphocytes *in vivo* raise questions on cell–cell recognition within a constantly mobile pool of cells. What is the nature of the interaction between lymphocytes and vascular endothelia? Are vascular endothelia specialized at different sites to permit different patterns of lymphocyte recirculation? What changes occur in endothelia at sites of chronic inflammation where lymphocytes leave the circulation in greater numbers? And is the failure of lymphocytes to penetrate certain tissues such as the central nervous system due to the absence of specialized endothelia? It is also unknown what factors control the partition and movement of lymphocyte populations and their subsets to domains within lymphoid tissue. In this issue of *Nature*, Gallatin, Weissman and Butcher[1] describe work in this field which represents new beginnings in the understanding of the molecular basis of lymphocyte recirculation.

During differentiation, lymphocytes acquire the characteristics which permit them to traverse specialized endothelia and enter lymphoid tisue[2,3]. This selective interaction between mature lymphocytes and the specialized parts of the post-capillary venule known as the high endothelial venule (HEV) is seen in secondary lymphoid organs such as peripheral and central lymph nodes, gut-associated lymphoid tissue (for example Peyer's patches) and in extra-lymphoid sites of granuloma formation where the normal flattened endothelial cells change to resemble those of the HEV[4]. Lymphocyte recirculation through the spleen, which is also a secondary lymphoid organ, is organized differently and is not regulated by HEV.

The overall patterns of lymphocyte recirculation and by implication the nature of lymphocyte–endothelial cell interactions have been largely established by the lymphatic cannulation experiments of Gowans, Ford and their colleagues in the rat and Morris and his colleagues in sheep[5]. Whilst both systems have established some of the ground rules for lymphocyte recirculation, recent experiments using the cannulated sheep lymph-node model challenge the accepted view that lymphocyte traffic through lymphoid tissue is entirely random.

Lymphocytes isolated either from the efferent lymph leaving peripheral lymph or gut-associated mesenteric lymph nodes[6], or from the afferent lymph draining a granuloma[7,8] and returned intravenously after radiolabelling to the same animal will preferentially recirculate through those regions from which they were first isolated. In these experiments lymphocytes are randomly mixed within the blood and selection at different tissue sites must be mediated at the level of the lymphocyte–endothelium interaction within different vascular beds of peripheral nodes, gut-associated lymphoid tissue and skin. In addition the antigen-specific selective mechanism operating on the traffic of antigen-reactive cells from blood into lymph nodes may also be explained by the presence of antigen on the luminal surface of endothelial cells[9,10]. In this situation endothelial cells might be acting as antigen-presenting cells. Recent studies showing that lymphokines from activated T cells induce endothelial cells to express class II molecules of the major histocompatibility system, required for antigen presentation, further implicate endothelial cells in non-random lymphocyte traffic[11].

Evidence that the endothelial cells of the HEV contain a glycosylated macromolecule that may induce lymphocytes to cross the HEV from the blood further strengthens the idea that HEV-associated macromolecules play a part in lymphocyte traffic[12,13].

The first indication that lymphocyte–HEV interactions could be studied *in vitro* came from Woodruff and her colleagues[14,15] who devised a novel quantitative assay which permitted the measurement of lymphocyte–HEV interactions through the adherence of lymphocytes *in vitro* to endothelial cells within sections of lymphoid tissue. Using this system they have shown that lymphocyte–endothelial cell adherence is both energy- and calcium-dependent, and mediated by surface determinants on lymphocytes that are sensitive to trypsin and appear to interact with the HEV. They have also described the purification from lymph of two soluble factors that regulate lymphocyte–endothelial cell adherence. One of these, a 160,000-molecular-weight glycoprotein, inhibits lymphocyte adhesion to HEV and is thought to be shed from the lymphocyte surface. Antisera to this molecule bind to recirculating lymphocytes and specifically block lymphocyte entry into lymph nodes *in vivo*[16].

Further analysis of the molecular basis of lymphocyte traffic is described in this edition of *Nature* by Gallatin, Weissman and Butcher. Earlier work from this group has shown that murine lymphoma cells preferentially bind to either peripheral lymph-node HEV or Peyer's patch HEV but not both[17]. This correlates with findings *in vivo*[6] that there may be sub-populations of lymphocytes recirculating either through peripheral lymphoid tissue or through gut-associated lymphoid tissue.

To search for cell-surface molecules on those lymphoma cells which bind to separate HEVs Gallatin *et al.* have raised monoclonal antibodies to lymphoma cells that bind to peripheral lymph nodes. By screening on both types of lymphoma they have identified one monoclonal antibody (MEL 14) that specifically blocks the adherence of normal and lymphoma lymphocytes to peripheral-node HEV but not to Peyer's patch HEV and, moreover, specifically blocks lymphocyte traffic into peripheral lymph nodes but not to Peyer's patches *in vivo*. Immunoprecipitation studies with surface-labelled lymphocytes revealed a single 80,000-molecular-weight band in reducing conditions.

Surprisingly, normal lymphocytes which bind to Peyer's patch HEV also react with the antibody, though this does not inhibit adherence or traffic of these cells through Peyer's patch HEV. Their explanation for this is that lymphocytes express a family of 'receptors' for different 'acceptors' that vary in their distribution on endothelial cells. This interpretation does not fit with other data suggesting that there may be sub-populations of recirculating cells[6-8].

The experiments of Gallatin *et al.* are notable for two reasons. First, they suggest that lymphocytes may possess recirculating phenotypes that can be defined by monoclonal antibodies. Such monoclonal antibodies may already be in existence and will be revealed by their anomalous reaction patterns on lymphocytes isolated from different parts of the lymphoid system. Second, they stress the value of considering leukaemias and lymphomas as malignant transformations of lymphocytes with particular recirculating phenotypes where the pathology can be understood in terms of the normal recirculation patterns of lymphocytes at different stages of differentiation. □

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