FROM DISSEMINATION PATTERN TO CLINICAL AND THERAPEUTIC ASPECTS OF NON-HODGKIN LYMPHOMAS

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Non-Hodgkin lymphoma (NHL) is a heterogenous and highly disseminated disease, but the mechanisms of its **growth and dissemination** are not well understood. Normal lymphocyte trafficking is essential for the regulation of systemic immune processes, as wel as lymphocyte differentiation and development. Most mature lymphocytes recirculate continuously fom blood to tissue and back to the blood again. This recirculation is regulated by lymphocyte-endothelial interactions and mediated by **adhesion molecules and selected chemokines**. Such interactions may be maintened in lymphoma trafficking paterns. Normal ***lymphocyte homing*** (that is a multistep process) and recirculation molecules are implicated in lymphoma dissemination and invasion. NHL represent the malignant counterparts of lymphocytes arrested at a specific stage of maturation, and lymphoma dissemination is a reflection of conserved physiological behavior. Understanding the molecular mechanisms underlying this behavior may provide novel targets for treatment of lymphoma patients.

The homing signature of a lymphocyte is dependent on differention stage and antigen experience. The conserved homing programs mediate the dissemination of NHL. NHL related to small recirculating lymphocytes (small-lymphocytic lymphoma/chronic lymphocytic leukemia and mantle-cell lymphoma) usually show systemic dissemination at presentation, whereas NHL related to lymphocytes undergoing active proliferation and differentiation (diffuse large B-cell lymphoma, Burkitt lymphoma) often are initially localized. **The dissemination patterns reflect basic rules of lymphocyte homing, explaining the strikingly tissue-specific dissemination** (e.g., mucosal lymphomas, cutaneous lymphomas, and multiple myeloma). The best characterized pathways of lymphocyte homing are those mediating homing to the gut-associated lymphoid tissue and skin, as both intestine and skin represent barrier tissues exposed to high antigen load.

Cell migration is essential during differentiation. In the tissue microenvironment, different cell types exhibit distinct migration strategies. 1.Mesenchymal migration: Mesenchymal cells display an adhesive phenotype and develop a spindle shape. The elongated morphology is dependent on integrin-mediated adhesion and the presence of traction forces on both cell poles. Simultaneous with integrin and actin concentration at focal contacts, the cells recruit surface proteases to these substrate contact sites to digest and remodel the extracellular matrix, thus generating matrix defects that allow cell migration. Other cells may follow along the generated matrix defect creating a moving cell chain. 2. Cluster/cohort migration: Migrating cancer cell collectives use an integrin- and protease-dependent migration mode similar to mesenchymal migration, but the migrating cells within the cohorts are interconnected by cadherins and gap-junctional communication. 3. Ameboid migration: Lymphoid cells display a characteristic "ameboid" type of migration, in which integrin-mediated adhesion is dispensable and cell movement is driven by short-lived relatively weak interactions with the substrate. The lack of focal contacts and high deformability of lymphocytes allow movement at high velocity, while the fast deformability of lymphocytes allows them to overcome matrix barriers by physical mechanisms, independent of proteolytic matrix degradation.

Lymphocyte interaction with endothelium. In the postcapillary venules, selectin-sialomucin interactions (or interactions mediated by integrin α4β1 or α4β7) mediate "rolling" of lymphocytes on the endothelium. Chemokines, presented by heparan sulfate proteoglycans expressed on the endothelium, bind to chemokine receptors, which are G protein–coupled receptors, leading to increased affinity/avidity integrins on the surface of lymphocytes. Interaction of these integrins with their ligands results in stable adhesion of lymphocytes to endothelium and in diapedesis, involving engagement with junction adhesion molecules (JAMs) and PECAM-1 (CD31).

There is a specific recruitment of tumor cells by locally produced chemokines and activated endothelium, with tumor dissemination to sites of trauma and inflamation in lymphoma patients. Extranodal lymphoma arising in the gut-associated lymphoid tissues or the skin show a strong preference to disseminate to mucosal sites and skin, respectively, and they may eventually disseminate to lymph nodes.

Lymphocyte trafficking and the tissue-specific dissemination of T-cell lymphomas. Lymphocyte migration is strictly regulated by adhesion molecules and chemokine receptors on lymphocytes and their ligands expressed by the endothelium. Naive T lymphocytes can home and recirculate via all secondary lymphoid tissues because they express both α4β7 (for mucosal homing) and L-selectin (for homing to peripheral lymph nodes). Migration of activated T lymphocytes to sites of inflammation involves several receptor-ligand pairs, including selectin-sialomucin, α4β1-VCAM-1, α4β1-CS-1, and CD44-hyaluronate interactions. Upon antigen priming by dendritic cells, T lymphocytes become memory cells and acquire a "homing signature," that is, a specific adhesion and chemokine receptor make-up, which enables them to selectively home to specific tissue environments, thereby increasing the efficacy of immunosurveillance. The T-NHLs related to lymphocyte populations with tissue-specific homing properties usually display tissue-specific dissemination patterns and express homing receptors corresponding to the tissue of origin.

The heterogenous group of peripheral T-cell lymphomas are derived from memory T cells, and comprise several well-defined entities with distinctive molecular, pathological, and clinical characteristics. The tissue of primary presentation, dissemination pattern, pathological and molecular data are important criteria for the classification of these tumors into distinctive clinicopathological entities. There is a differential expression pattern of chemokine receptors on specific lymphoma subtypes. Expression of Th1 chemokine receptors in peripheral T-cell lymphoma is related to a favorable prognosis. Nodal T-cell lymphomas express L-selectin, but lack the skin-homing receptor CLA as well as the mucosal-homing receptor α4β7. In cutaneous T-cell lymphoma the expression of CLA and CCR4 permit these cells to home effectivelly to the skin. The tumor cells of mycosis fungoides and Sezary syndrome show different homing signature, which correspond to distinctive dissemination patterns. A loss of skin-specific chemokine receptors is seen during mycosis fungoides progression. Intestinal T-cell lymphomas are most often enteropathy associated, and express the mucosal-homing receptor α4β7.

Adhesion molecule and chemokine receptor expression profiles of B-lymphocyte subsets and related lymphoid malignancies. Naive B lymphocytes coexpress L-selectin and α4β7, enabling them to migrate to the mucosa as well as to peripheral lymph nodes. Germinal center reactions in Peyer patches lead to generation of α4β7-expressing memory B lymphocytes, which subsequently can differentiate into IgA-secreting plasma cells. Most memory B cells arising in lymph nodes, on the other hand, differentiate into IgG-secreting plasma cells. These cells express CXCR4 and the integrins α4β1 and LFA-1, which can mediate homing to the bone marrow, where these cells become long-lived plasma cells. The B-cell malignancies are related to lymphocyte populations with tissue-specific homing properties.

B lymphocytes adapt their homing signature to thei specific maturational stage, and this is largely conserved in B-cell lymphomas, controlling their dissemiantion. Ectopic chemokine expression at site of chronic inflammation with lymphoid neogenesis is a key factor in the selective homing of malignant B cells to these sites. B-cell migration to the skin and other extralymphoid sites occurs exclusively in the context of chronic inflammation driven by locally persistent antigen or autoantigens. Differention of a B-cell to a plasma cell is accompanied by a coordinated change in chemokine receptor expression. Multiple factors in the bone marrow microenvironment may modulate multiple myeloma cell homing. Various chemokines and growth factors produced in the bone marrow stimulate integrin-mediated adhesion and can contribute to resistance of multiple myeloma cells to treatment.

The expression of adhesion molecules on lymphoma cells has been linked to tumor spread and poor outcome. Some adhesion molecules facilitate lymphocytes binding to the vascular endothelium with subsequent migration to the nodal areas. Serum CD44 has been correlated with disseminated disease and shortened survival in NHL. Tumor angiogenesis is critical for local growth and distant spread of NHL. Targeting adhesion and chemokine receptors, that are part of the homing signature of malignant lymhocytes, with monoclonal antibodies or small-molecules drugs, may prove a successful novel means of therapeutic intervention in lymphoma patients.

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