

Regulation of human B cell chemotaxis by HIV-1 gp120

with

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Importance of B cell chemotaxis ?

Gwenoline Borhis: Antigen-presenting cells, mature T and B cells, are the major contributors to the immune response. However, they remain segregated in particular areas of lymphoid tissue until they are required to cooperate in a humoral response. According to the route of entry -skin, mucosa or blood- antigens (Ag) are ferried to lymph nodes, Peyer's patches, and tonsils or spleen, respectively, where the immune response is initiated (1). Ag-inexperienced (or naïve) B cells strongly express CXCR4, CXCR5 and CCR6 at their membrane whereas CCR7 is mostly cytoplasmic (2,3). Consequently, they recirculate from blood to primary B cell follicles in response to their respective ligands: CXCL12, CXCL13 and CCL20 (1). B cell receptor (BCR)-activated B cells express less CXCR4 and CXCR5, lose CCR6 but acquire surface CCR7 allowing them to relocate to the border between B and T cell areas, a site of strong CCL19 and CCL21 production (4). At this site, Ag-activated B

and T cells interact leading to B cell proliferation and the generation of a germinal center (GC). GC B cells no longer respond to chemotaxis but CXCR4 and CXCR5 expression determines the organization of GC into dark and light zones (5). The dark zone is required for somatic mutations whereas isotype switching and affinity maturation of antibodies take place in the light zone. Two types of progeny leave GC: long-term plasmablasts and memory B cells. Long-term plasmablasts do not express CXCR5, CCR7 or CCR6 but express CXCR4 and migrate into bone marrow where they differentiate into plasma cells producing high affinity antibodies (6). Most IgA-expressing plasma cells bear CCR9- the receptor of CCL25- or CCR10 - the receptor of CCL27 and CCL28- which tune their spatial relocation into gut (7). Memory B cells strongly express CXCR4, CXCR5, CCR6 and CCR7 and circulate between blood and parts of secondary lymphoid organs (2).

How important are chemokine receptors and ligands ?

Gwenoline Borhis: Chemokine interactions with their receptors orchestrate B cell trafficking during the humoral response. These interactions must be preceded by B cell rolling/adhesion involving various selectin/addressin pairs (8). To enter peripheral

lymph nodes, resting naive and memory B cells engage L-selectin (CD62L) that interacts with Peripheral Node Addressin (PNAd) expressed by high endothelial venules (HEV). Migration into Peyer's Patches and other gut-associated tissue requires

interactions between $\alpha 4\beta 7$ and the mucosal addressin cell adhesion molecule-1 (MadCaM-1) on intestinal endothelial cells. The homing of B cells to mesenteric lymph nodes -a composite mucosal and peripheral lymphoid tissue- requires both CD62L and $\alpha 4\beta 7$ (9). Thereafter, chemokine-mediated triggering causes integrin activation and allows transmigration. The ICAM1/LFA-1 pair controls transmigration through peripheral lymph

nodes and Peyer's patches, and migration of B lymphocytes from the splenic marginal zone into white pulp also requires the $\alpha 4\beta 1$ /VCAM-1 pair (10). This multistep process is highly tissue-specific and LPS and inflammatory cytokines can interfere with B cell trafficking by impairing local production of chemokines and the production or function of receptors. Viral chemokines can also perturb immune responses.

Role of gp 120: its effects on the B cell chemotaxis and CD62L decrease?

Gwenoline Borhis: The glycoprotein (gp)120, non-covalently associated with gp41, forms the envelope of the Human Immunodeficiency Virus 1 (HIV-1). When gp120 interacts with CD4, it opens a new cryptic binding site for CCR5 (R5 strains) or CXCR4 (X4 strains) and unmasks the fusiogen peptide of gp41. Gp120 can also bind some VH3-expressing BCR leading to apoptosis of peripheral memory B cells (11). Although B cells are not infected *in vivo*, B cell phenotypes and functions are severely impaired in HIV-infected patients. We showed that X4 and R5 gp120 inhibit B-cell chemotaxis towards CXCL12, CCL20 and CCL21 (12).

This gp120-induced inhibition was strictly dependent on CXCR4 or CCR5 and lipid rafts but not on CD4 or VH3-expressing BCR. Gp120/CXCR4 and gp120/CCR5 interactions may lead to the cross-desensitization of CCR6 and CCR7 and block PLC β 3 and PI3K activation, two pathways essential for B cell chemotaxis (13). X4 and X4/R5gp120 also induce cleavage of CD62L by a mechanism dependent on MMP1/3, CD4, CXCR4, G α i and p38MAPK, whereas R5 gp120 did not. As CD62L is required for the entry of B cells into lymph nodes, its decrease might cause abnormal B cell accumulation in the splenic marginal zone and in the gut.

Therapeutic outlook ?

Gwenoline Borhis: B cells exposed to soluble or virion-attached gp120 are probably unable to mount an effective humoral response because of their incorrect localization. Recombinant gp120 or gp120-

expressing constructs being tested in vaccines might thus have detrimental effects on the B cell repertoire. Trials in animal models would elucidate the effects of gp120 on humoral responses.

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