

Unveiling the Mystery of CXCL13 Production in HIV-Infected Subjects

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Chemokines are a family of small molecules that are able to drive the movement of cells toward the site where they are requested to operate. Because of their critical role, strict surveillance of their production is required for the immune responses to function properly. In HIV-infected subjects the secretion of one of these molecules, CXCL13, is more elevated than in HIV-negatives. While CXCL13 at physiological concentrations facilitates the co-migration of B cells and follicular helper T cells into B cell follicles and germinal centers, thus ensuring a correct B cell response, an altered secretion of the chemokine leads to a deregulated B cell response. The reasons for this modified production and secretion have been explored by Dr. Kristen Cohen of the Stamatatos Lab in the Vaccine and Infectious Disease Division (VIDD) at Fred Hutch, and have been published in the *Journal of Immunology*.

The study unravels the mechanism through which HIV modifies the homeostatic production of CXCL13. The fundamental observation is that stimulation of peripheral blood mononuclear cells (PBMCs) with replication-competent HIV virions results in increased secretion of CXCL13. Moreover, monocytes constitute the main population responsible for this production, while both myeloid or plasmacytoid dendritic cells (pDCs) produce low amounts of the chemokine.

Starting from these findings, we are led deeper into the mechanism driving this phenomenon. First, activation of the two toll-like receptors (TLR) 7 and 8, localized in the endosomal compartment and able to recognize HIV RNA sequences, induces increased secretion of CXCL13 from PBMCs. Interestingly, this is not true for isolated monocytes, where TLR stimulation can induce only a minor change in the chemokine secretion. Thus, another cell type has to be involved in induction of CXCL13 secretion by monocytes. Indeed, the effect of the two TLR ligands is not present when PBMCs are depleted from pDCs, which express both receptors and, upon engagement of TLR7 and TLR8, with their ligands, produce a hormone with known antiretroviral activity, IFN-alpha. Furthermore, the blockade of IFN-alpha function with a specific antibody inhibits the production of CXCL13.

HIV causes yet another alteration of the immune system, by exploiting the body's mechanisms to fight viral infections. In fact, by binding TLR7 and TLR8, HIV RNA activates pDCs to produce IFN-

alpha, which in turn induces the transcription of CXCL13 in monocytes and causes the high protein concentration. This mechanism might be the reason of the disruption in lymphoid architecture, reduction of de novo antibody responses and hypergammaglobulinemia observed during the progression of untreated HIV infection. Thus, this study sheds new light on one of the reasons why HIV, although infecting CD4-positive T cells, also heavily affects the B cell compartment.

Dr. Cohen concludes by highlighting the importance of the same pathways in other conditions: "Type I interferon-induction of CXCL13 may help explain the increase of CXCL13 during HIV-1 infection and other inflammatory conditions. Further research is still needed to fully understand the implications of increased CXCL13 during these conditions and its contribution to immunopathogenesis."

[Cohen KW, Dugast A-S, Alter G, McElrath MJ, Stamatatos L.](#) 2015. HIV-1 Single-Stranded RNA Induces CXCL13 Secretion in Human Monocytes via TLR7 Activation and Plasmacytoid Dendritic Cell-Derived Type I IFN. *Journal of immunology*. 194(6):2769-2775.

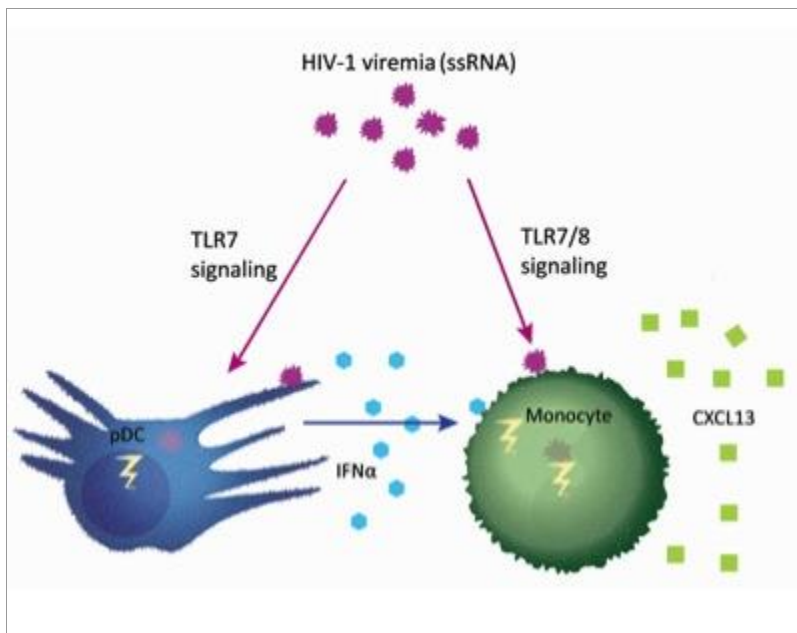


Image provided by Dr. Kristen Cohen

Figure caption: Schematic representation of IFN-alpha-mediated up-regulation of CXCL13 following HIV infection.