CXCR4 Is Important for Lymphopoiesis Not Only in Mice, but Also in Man

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We read the Immunity paper titled “Hematopoietic Stem Cell Niches Produce Lineage Instructive Signals to Control Multipotent Progenitor Differentiation” (1). This study used a combination of in vivo and in vitro experiments and suggested that CXCR4 indirectly controls lymphopoiesis by moving Common Lymphoid Progenitors (CLP) to near IL-7 producing cells in bone marrow (BM). This leads to IL-7Ra (CD127) signaling and STAT5 alpha phosphorylation. In other words, the paper recommends control of cell positioning in BM niches as a double edge sword, is an essential checkpoint in lymphopoiesis, which enables hematopoietic precursor cells to access lymphoid differentiating cytokines.

In this letter, we spot an editorial error with the Immunity paper, Figure 1 panel I. It is more reasonable that CXCL12 enriched results to be the "White bars" and control as the "Black bars" on the Figure 11 in order to fit with the story of the paper. We expect if we culture hematopoietic stem cells (HSCs), multipotent progenitors (MPPs) and CLPs in the presence of CXCL12 and vehicle, CLPs become more chemotactic than other cells based on the CXCL12 gradient in comparison with the vehicle group. This is due to higher expression and better functionality of CXCR4 on CLPs compared to other hematopoietic cells in BM as shown in the previous panels of figure 1. This then goes well with the storyline of the paper.

CXCR4 expression and functionality have been shown to be very important in lymphopoiesis (1,2). However, what has been noticed with a congenital immunodeficiency disorder called WHIM syndrome (Warts, Hypogammaglobulinemia, Infection, and Myelokathexis syndrome), each of four autosomal dominant gain of function mutations in human cxcr4 gene leads to hyperactivity of the protein (3-5). This results in an inability of the CXCR4 receptor to be downregulated after ligand recognition into the inactive state (lack of ligand-induced receptor internalization which is caused by truncation of 10-19 amino acid in the C-terminal of protein) (6). WHIM syndrome is characterized by myelokathexis of neutrophils in BM, disability in lymphopoiesis (especially low level of B lymphocytes) and hypogammaglobulinemia especially for IgG which consequently leads to Human Papilloma Virus (HPV) susceptibility and wart formation in affected individuals. Even though normal neutrophil production and development occurs in these patients, neutrophils are trapped within BM (hypercellularity) without being released into the bloodstream (neutropenia) (7,8).

We believe this study can also be translated onto this syndrome. It has signs where there are links between the two.

References

