

Human Lymphoid Development in the Absence of Common gamma-Chain Receptor Signaling.

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Public Summary:

The entire immune system develops in the bone marrow from hematopoietic stem cells (HSC) through a set of carefully regulated stages. The earliest stages of differentiation from HSC generate rare cells called lymphoid progenitors, which then in turn produce more mature functional cells of the immune system, the T cells, B cells and NK cells. We have recently discovered methods to identify the earliest lymphoid progenitor stages in normal human bone marrow. In this paper we used this knowledge to explore if lymphoid progenitors are formed normally in the bone marrow of children with certain severe types of genetic immune deficiency (aka severe combined immune deficiency or "bubble baby syndrome"). We found that even though these children cannot produce T cells, they have normal lymphoid progenitors in the bone marrow, demonstrating that their specific genetic mutations block immune cell production after the progenitor stage of development.

Scientific Abstract:

Despite the power of model systems to reveal basic immunologic mechanisms, critical differences exist between species that necessitate the direct study of human cells. Illustrating this point is the difference in phenotype between patients with SCID caused by mutations affecting the common gamma-chain (γ mac) cytokine signaling pathway and mice with similar mutations. Although in both species, null mutations in either IL-2RG (which encodes γ mac), or its direct downstream signaling partner JAK3, result in T and NK cell deficiency, an associated B cell deficiency is seen in mice but not in humans with these genetic defects. In this study, we applied recent data that have revised our understanding of the earliest stages of lymphoid commitment in human bone marrow (BM) to determine the requirement for signaling through IL-2RG and JAK3 in normal development of human lymphoid progenitors. BM samples from SCID patients with IL-2RG (n = 3) or JAK3 deficiency (n = 2), which produce similar "T-NK-B+" clinical phenotypes, were compared with normal BM and umbilical cord blood as well as BM from children on enzyme treatment for adenosine deaminase-deficient SCID (n = 2). In both IL-2RG- and JAK3-SCID patients, the early stages of lymphoid commitment from hematopoietic stem cells were present with development of lymphoid-primed multipotent progenitors, common lymphoid progenitors and B cell progenitors, normal expression patterns of IL-7RA and TLSPR, and the DNA recombination genes DNTT and RAG1. Thus, in humans, signaling through the γ mac pathway is not required for prethymic lymphoid commitment or for DNA rearrangement.

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