Making humanized mice

Mice deficient in the recombinase activating genes 1 and 2 (Rag1 and Rag2, respectively) do not exhibit leaky production of T and B lymphocytes. The immune phenotypes in Rag1$^{-/-}$ and Rag2$^{-/-}$ strains are similar. However, Rag-deficient animals produce normal levels of NK cells, and thus additional mutations are required in order to produce animals better suited for xenoengraftment studies.

The non-obese diabetic (NOD) mouse is commonly used because the NOD mutation results in a reduction of NK cell activity. NOD/SCID mice are NODs with a knockout of the pkrdc gene, an enzyme involved in linking DNA after V(D)J recombination

The common gamma chain receptor (γc, also referred to as the IL-2 receptor gamma chain) is a component of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors and is the gene involved in X-linked SCID. The addition of the γc mutation to the Rag1, Rag2, and NOD/SCID backgrounds further blocks T and B cell development due to a lack of IL-2 signaling and also prevents maturation and expansion of NK cells via a lack of IL-15 signaling.

Methods to prepare humanized NOD/SCIDγc$^{-/-}$ mice and humanized Rag1$^{-/-}$γc$^{-/-}$ mice are very similar. (There are two γc$^{-/-}$ mutations available; so there are NSG mice (a γc knockout) and NOG mice (with a truncated γc). It should be noted that the methods used to prepare human HSCs and to inject animals with grafts are relatively straightforward and in many cases require a simple, intrahepatic or intravenous injection. The BLT model (bone marrow, thymus, liver) engrafts NOD/SCID or NOD/SCIDγc$^{-/-}$ mice with a combination of human fetal liver and thymic tissue (the SCID-hu thy/liv model) followed by a CD34^{+} hematopoietic stem cell graft. As a result of the relatively simple techniques needed to generate humanized mice, many new laboratories are adopting these models, for transplantation, tumor biology, monoclonal antibody, and HIV studies.

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