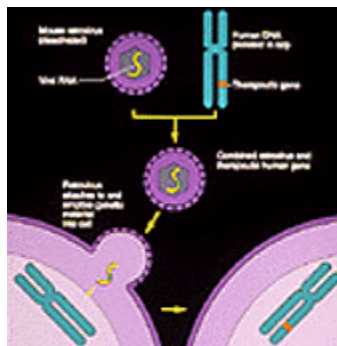




Severe combined immunodeficiency



Gene therapy has been attempted to treat severe combined immunodeficiency caused by a missing enzyme, adenosine deaminase. [Image credit: National Cancer Institute.]

Severe combined immunodeficiency (SCID) represents a group of rare, sometimes fatal, congenital disorders characterized by little or no immune response. The defining feature of SCID, commonly known as "bubble boy" disease, is a defect in the specialized white blood cells (B- and T-lymphocytes) that defend us from infection by viruses, bacteria and fungi. Without a functional immune system, SCID patients are susceptible to recurrent infections such as pneumonia, meningitis and chicken pox, and can die before the first year of life. Though invasive, new treatments such as bone marrow and stem-cell transplantation save as many as 80% of SCID patients.

All forms of SCID are inherited, with as many as half of SCID cases linked to the X chromosome, passed on by the mother. X-linked SCID results from a mutation in the interleukin 2 receptor gamma (IL2RG) gene which produces the common gamma chain subunit, a component of several IL receptors. IL2RG activates an important signalling molecule, JAK3. A mutation in JAK3, located on chromosome 19, can also result in SCID. Defective IL receptors and IL receptor pathways prevent the proper development of T-lymphocytes that play a key role in identifying invading agents as well as activating and regulating other cells of the immune system.

In another form of SCID, there is a lack of the enzyme adenosine deaminase (ADA), coded for by a gene on chromosome 20. This means that the substrates for this enzyme accumulate in cells. Immature lymphoid cells of the immune system are particularly sensitive to the toxic effects of these unused substrates, so fail to reach maturity. As a result, the immune system of the afflicted individual is severely compromised or completely lacking.

Some of the most promising developments in the search for new therapies for SCID center on 'SCID mice', which can be bred deficient in various genes including ADA, JAK3, and IL2RG. It is now possible to reconstitute

the impaired mouse immune system by using human components, so these animals provide a very useful model for studying both normal and pathological immune systems in biomedical research.

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