

As a result of this IL-15 has been identified as a growth factor for the development of NK cells. It has also been shown to be important in T cell maturation and trafficking. Mice with an IL-15 mutation have no NK cells but relatively normal T cell development. However, maintenance of CD8 T cells is defective.

Humans with a deficiency of IL-7 receptor α chain have no T cells but normal levels of NK cells which highlights that IL-7 signalling is essential for T cell development but not for NK cell development.

SCID due to defects in antigen receptor gene arrangement: RAG

Another set of defects leading to SCID are those which cause failure of DNA rearrangement in developing lymphocytes. Defects in either RAG1 or RAG2 results in arresting the lymphocyte development because of a failure to rearrange the antigen receptor genes. This leads to a complete lack of T and B cells, NK cell development is not impaired.

Some children lack either RAG1 or RAG2. This means that they are able to make a small amount of RAG protein and so a small amount of V(D)J recombination is able to take place. This disease is known specifically as Omenn's syndrome. In addition to increased susceptibility to opportunistic infections, the patient will also have symptoms similar to that seen in a graft vs host disease. The T cells which are produced in this disease have abnormal and highly restricted repertoire. The clinical feature suggest that these T cells are autoreactive and ergo cause the graft vs host disease symptoms.

SCID due to defect in antigen receptor gene arrangement: radiation sensitive SCID.

Radiation sensitive: These patients have very few B and T cells due to failure of antigen receptor gene rearrangement. This is due to a defect in the enzyme DNA-dependent protein kinase catalytic subunit (DNA-PKcs) which is usually involved in antigen receptor gene rearrangement.

A different mutation found in some people with autosomal SCID is in the protein Artemis. This acts in the same pathway as DNA-PKcs. These two form a complex which acts to open the hairpin structures to allow the formation of the VDJ joints to complete the VDJ recombination.

DNA-PKcs is also known to have a ubiquitous role in DNA repair of double stranded breaks which occur during antigen receptor gene rearrangement and ionising radiation.

SCID due to defects in TCR signalling –

There are several gene defects which interfere with T cell receptor signalling.

Patients who lack CD3 γ or epsilon chains defective pre-TCR signalling – T cells do not progress through to normal thymic development.

Others who have defects in cytosolic protein tyrosine kinase ZAP-70 which usually works to transmit signals from the T cell receptor have a loss of CD8 $^{+}$ T cells emerging from the thymus and CD4 cells do not respond to stimuli.

Finally, CD45 mutations result in a deficiency of peripheral T cell numbers and abnormal B cell maturation.

WAS – Wiskott-Aldrich syndrome –

Immunodeficiency due to defects in phagocytic cells

Deficiencies in phagocyte numbers or function can result in severe immunodeficiency. Complete absence of neutrophils does not permit survival in a normal environment. Phagocyte-associated immunodeficiencies can result from each of defects in cell production, adhesion, activation and killing of microorganisms.

There are three types of phagocyte production, phagocyte interaction and phagocyte killing of microorganisms.

Inherited deficiencies of neutrophil production (neutropenias) are classified either as **severe congenital neutropenias** or as **cyclic neutropenias**. In severe congenital neutropenias which can be inherited as a dominant or recessive trait the neutrophil count is persistently extremely low, $>0.2 \times 10^9/L$ of blood when it should normally be $3-5.5 \times 10^9/L$ of blood, and patients depend of a successful bone marrow transplant for survival.

Cyclic neutropenia is a dominantly inherited disease in which neutrophils numbers fluctuate from near normal to very low or non, with an approximate cycle of 21 days. Other bone marrow derived cells – monocytes, platelets, lymphocytes and reticulocytes – undergo smaller fluctuations in numbers with the same periodicity.

Mutation in human neutrophil elastase ELA2, a component of primary granules; altered targeting of defective gene product causes apoptosis of developing cells, cause cyclic neutropenia and also cause a significant fraction of dominant severe congenital neutropenia. The mutation leads to the production of dysfunctional elastases and this in turn leads to the production of a toxic intracellular protein that blocks neutrophil maturation.

Heterozygous mutations in the oncogene GFI1 which encodes a transcriptional repressor have been detected in three patients with neutropenias. This finding arose from the unexpected observation that mice lacking the protein GFI1 and neutropenic. Closer analysis revealed that mutation in mouse Gfi1 affects the expression of ELA2 providing a link between these two genes in a common pathway of myeloid cell-differentiation. How the mutant elastase causes a 21-day cycle in neutropenia and the effects on other bone marrow derived cell types is still unknown.

Defects in the migration of phagocytic cells to extravascular site of infection can cause serious immunodeficiency.

Leukocytes reach such sites by emigrating from the blood vessel in a tightly regulated process.

The first stage is rolling adherence of leukocytes to endothelial cells through the binding of a fucosylated tetrasaccharide ligand known as sialyl-Lewis X on the leukocyte to E-selectin and P-selectin on endothelium.

The second stage is the tight adherence of leukocytes to the endothelium through the binding of leukocyte Beta2 integrins such as CD11b:CD18 to counter receptors on endothelial cells.

The third and final stage is the transmigration of leukocytes through the endothelium along gradients of chemokines originating from the site of tissue injury.