CXCR4 Gene

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1. Normal Function

The *CXCR4* gene provides instructions for making a receptor protein that spans the outer membrane of cells, specifically white blood cells and cells in the brain and spinal cord (central nervous system). Receptor proteins have specific sites into which certain other proteins, called ligands, fit like keys into locks. After attachment of its ligand, called SDF-1, the CXCR4 protein turns on (activates) signaling pathways inside the cell. These pathways help regulate cell growth and division (proliferation), the process by which cells mature to carry out specific functions (differentiation), and cell survival. Once signaling is stimulated, the CXCR4 protein is removed from the cell membrane (internalized) and broken down so it can no longer activate the signaling pathways.

The CXCR4 receptor is also involved in the movement (migration) of cells. Cells that have the CXCR4 protein in their membrane are attracted to SDF-1. High levels of this ligand are found in the bone marrow, which helps certain blood cells migrate to and stay in the bone marrow until they are needed elsewhere in the body. Retention of early blood cells known as hematopoietic stem cells in the bone marrow is important to ensure that stem cells are available when needed. White blood cells also remain in the bone marrow until they are needed in the body to fight infection.

2. Health Conditions Related to Genetic Changes

2.1 Waldenström Macroglobulinemia

Mutations in the *CXCR4* gene are found in approximately 30 percent of people with Waldenström macroglobulinemia. This rare form of blood cancer is characterized by an excess of abnormal white blood cells called lymphoplasmacytic cells in the bone marrow and overproduction of a protein called IgM. These mutations are acquired during a person's lifetime and are present only in the abnormal white blood cells. This type of genetic change, called a somatic mutation, is not inherited. Waldenström macroglobulinemia is thought to result from multiple genetic changes, one of which can be a *CXCR4* gene mutation.

CXCR4 gene mutations involved in Waldenström macroglobulinemia lead to production of an abnormally short CXCR4 protein that cannot be internalized, prolonging signaling activated by the protein. This signaling leads to enhanced survival and proliferation of cells containing the abnormal protein, which may contribute to the abundance of lymphoplasmacytic cells characteristic of Waldenström macroglobulinemia.

2.2. Other Disorders

At least nine mutations in the *CXCR4* gene have been found to cause WHIM syndrome, a condition characterized by impaired immune function and recurrent bacterial and viral infections. Several of the mutations that cause WHIM syndrome are also found in individuals with Waldenström macroglobulinemia (described above). However, in WHIM syndrome, the mutations are typically inherited and are found in every cell of the body (known as germline mutations).

As in Waldenström macroglobulinemia, the *CXCR4* gene mutations that cause WHIM syndrome impair internalization of the CXCR4 protein. Researchers suggest that white blood cells that have the CXCR4 protein in their membrane longer than usual are abnormally retained in the bone marrow (a condition known as myelokathexis). A lack of these immune cells circulating through the body likely impairs the body's immune reaction to bacteria and viruses, leading to the recurrent infections common in WHIM syndrome.

3. Other Names for This Gene

- C-X-C chemokine receptor type 4
- CD184
- CD184 antigen
- chemokine (C-X-C motif) receptor 4
- CXCR4_HUMAN
- D2S201E
- FB22
- fusin
- HM89
- HSY3RR
- LAP-3
- LAP3
- LCR1
- LESTR
- leukocyte-derived seven transmembrane domain receptor
- lipopolysaccharide-associated protein 3
- LPS-associated protein 3
- neuropeptide Y receptor Y3
- NPY3R
- NPYR
- NPYRL
- NPYY3R
- SDF-1 receptor
- seven transmembrane helix receptor
- seven-transmembrane-segment receptor, spleen
- stromal cell-derived factor 1 receptor

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