KIT Gene

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1. Introduction

The *KIT* gene provides instructions for making a member of a protein family called receptor tyrosine kinases. Receptor tyrosine kinases transmit signals from the cell surface into the cell through a process called signal transduction. The KIT protein is found in the cell membrane of certain cell types where a specific protein, called stem cell factor, attaches (binds) to it. This binding turns on (activates) the KIT protein, which then activates other proteins inside the cell by adding a cluster of oxygen and phosphorus atoms (a phosphate group) at specific positions. This process, called phosphorylation, leads to the activation of a series of proteins in multiple signaling pathways.

The signaling pathways stimulated by the KIT protein control many important cellular processes such as cell growth and division (proliferation), survival, and movement (migration). KIT protein signaling is important for the development and function of certain cell types, including reproductive cells (germ cells), early blood cells (hematopoietic stem cells), white blood cells called mast cells, cells in the gastrointestinal tract called interstitial cells of Cajal (ICCs), and cells called melanocytes. Melanocytes produce the pigment melanin, which contributes to hair, eye, and skin color.

2. Health Conditions Related to Genetic Changes

2.1. Piebaldism

At least 69 *KIT* gene mutations have been identified in people with piebaldism. This condition is characterized by white patches of skin and hair caused by a lack of melanocytes in those areas. The mutations responsible for piebaldism lead to a nonfunctional KIT protein. The loss of KIT signaling is thought to disrupt melanocyte migration and proliferation during development, resulting in patches of skin that lack pigmentation.

2.2. Gastrointestinal Stromal Tumor

Mutations in the *KIT* gene are the most common genetic changes associated with gastrointestinal stromal tumors (GISTs). GISTs are a type of tumor that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine. In most cases, these *KIT* gene mutations are acquired during a person's lifetime and are called somatic mutations. Somatic mutations, which lead to sporadic GISTs, are present only in the tumor cells and are not inherited. Less commonly, *KIT* gene mutations that increase the risk of developing GISTs are inherited from a parent, which can lead to familial GISTs.

KIT gene mutations associated with GISTs create a protein that no longer requires binding of the stem cell factor protein to be activated. As a result, the KIT protein and the signaling pathways are constantly turned on (constitutively activated), which increases the proliferation and survival of ICCs, leading to GIST formation.

2.3. Systemic Mastocytosis

Somatic mutations in the *KIT* gene have been found to play a role in systemic mastocytosis. This condition is a blood disorder that typically appears after adolescence, varies in severity, and can affect many different body systems. Systemic mastocytosis occurs when mast cells abnormally accumulate in tissues. Mast cells normally trigger inflammation during an allergic reaction and signal an immune response when they are activated by an environmental trigger.

In most cases of systemic mastocytosis, the accumulated mast cells have a *KIT* gene mutation. More than 80 percent of individuals with systemic mastocytosis have a mutation in the *KIT* gene that replaces the protein building block (amino acid) aspartic acid with the amino acid valine at position 816 in the protein (Asp816Val or D816V). This and other *KIT*

gene mutations result in production of altered proteins that are constitutively activated. As a result, signaling pathways that promote the proliferation of cells are overactive, which leads to increased production of mast cells and accumulation of the cells in various tissues. Cells with altered KIT proteins are more active than normal, leading to increased immune responses and signs and symptoms of systemic mastocytosis. In systemic mastocytosis, the excess mast cells lead to an increased immune response and signs and symptoms similar to an allergic reaction, such as skin redness and warmth (flushing), nausea, abdominal pain, nasal congestion, low blood pressure (hypotension), and headache.

2.4. Other Cancers

Somatic mutations in the *KIT* gene have been identified in several cancers. *KIT* gene mutations are involved in some cases of acute myeloid leukemia, which is a cancer of a type of blood cell known as myeloid cells, and sinonasal natural killer/T-cell lymphoma (NKTCL), another blood cell cancer that occurs in the nasal passages. In addition, some people with seminoma, a type of testicular cancer, have a somatic *KIT* gene mutation. The genetic changes involved in acute myeloid leukemia and seminomas lead to a KIT protein that is constitutively activated. The constant signaling causes overproliferation of the cells that make up these tumors. It is unclear how the *KIT* mutations in NKTCL are involved in the condition.

3. Other Names for This Gene

- C-Kit
- CD117
- KIT_HUMAN
- mast/stem cell growth factor receptor Kit
- p145 c-kit
- PBT
- piebald trait protein
- proto-oncogene c-Kit
- proto-oncogene tyrosine-protein kinase Kit
- SCFR
- tyrosine-protein kinase Kit
- v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
- v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene-like protein

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