KIT

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KIT is a growth factor tyrosine kinase receptor (CD117, SCFR, c-Kit) gene SCF. At the same time, it is about Proto-oncogenes, which also has its viral counterpart v-Kit (feline sarcoma virus FeSV-4). The c-Kit receptor plays an important role in Haematopoiesis, creation melaninu, fertility and bowel motility. Signaling disorders mediated by the c-Kit receptor have been described in a number of pathological conditions, especially in some tumors and allergies, but also in e.g. Piebaldism (partial albinism). The c-Kit receptor can be pharmacologically blocked.

Molecular biology

Gene KIT

The KIT gene is located on chromosome 4 in segment 4q11. The gene is more than 34 kb DNA long, consisting of 21 exons. The first exon encodes the initiation sequence, the second to ninth exons encode the extracellular part of the receptor, the tenth exon encodes the transmembrane part of the receptor, and the remaining exons encode the intracellular part of the receptor. The promoter sequences of the KIT gene represent binding sites for regulatory proteins AP-2, bHLH, Sp1, Ets, Ets-2 and Myb.

Other regulatory factors involved in the regulation of KIT gene expression are miRNA (miR-221 a miR-222).

Struktura receptoru

The c-Kit receptor is a type III tyrosine kinase, the structure is very similar to other receptors of this group. The receptor passes through the membrane once, its N-terminal end is extracellular. The following domains can be distinguished on the receptor (in order from the N-terminal end):

- five immunoglobulin domains,
- GNNK sequence (Gly-Asn-Asn-Lys sequence),
- transmembrane domain,
- juxtamembrane domain,
- tyrosine kinase domain 1,
- sequence inserted into the kinase,
- tyrosine kinase domain 2,
- C-terminal end.

Alternative mRNA splicing leads to the existence of several receptor variants. Alternative splicing occurs in two places:

- The GNNK sequence may or may not be present,
- a serine residue may be inserted in the sequence inserted into the kinase.

Thus, there are at least four isoforms of the receptor. In postmeiotic germ cells, a significantly shortened tr-Kit transcript is also present, which consists only of the second tyrosine kinase domain and the C-terminal end.

Receptor activation

The receptor is activated by dimerization. The ligand must bind to immunoglobulin domains 1–3. This brings immunoglobulin domains 4–5 close enough to interact and bind to each other. The subsequent approach of the transmembrane domains and apparently the induction of conformational changes lead to mutual phosphorylation of the tyrosine residues of the juxtamembrane domains, the sequence inserted into the kinase and the C-terminal end of the protein.

Deactivation of the receptor

The following three mechanisms are used to deactivate the receptor:

- removal of the receptor from the cell surface and subsequent degradation,
- inactivation of the tyrosine kinase domain by phosphorylation on serine residues,

- phosphorylation of tyrosine residues.

Physiological function

The c-Kit receptor has numerous functions during embryonic development and in adulthood.

- **Hematopoiesis**. The receptor is expressed in cells of the early stages of hematopoiesis, its expression disappears during maturation. Signaling from the c-Kit receptor is an important signal promoting proliferation and survival. When White blood cell and Dendritic cells the receptor is also present in mature cells.
- **Pigmentation**. c-Kit receptor-mediated signaling conditions melanocyte survival, proliferation and migration during embryogenesis.
- **Reproduction**. Signaling mediated by the c-Kit receptor protects germ cells from apoptosis, mediates their migration and proliferation. c-Kit signaling significantly interacts with pathway signaling PI3K/Akt.
- **Gastrointestinal tract**. c-Kit signaling is crucial for the intestinal cells of Cajal, without sufficient signaling these cells disappear and intestinal motility disorders occur.
- **Nervous system**. In experiments on mice with impaired function of the c-Kit receptor, or with SCF growth factor mutation, a learning disability has been demonstrated. Physiologically, KIT is expressed in areas of neuroproliferation.
- **Cardiovascular system**. SCF signaling plays a role in a number of physiological and pathological processes including cardiac stem cell differentiation as well as cardiomyocyte terminal differentiation and vascular proliferation.
- **Lung**. In experimental mice with a defective KIT gene, emphysema develops spontaneously and the mechanical properties of the lungs change. The cause is not yet known, but it is believed to be an effect of c-Kit-mediated regulation at the level of the lung epithelium.

Molecular pathology

Cancer illnesses

KIT gene mutation has been demonstrated in numerous tumors:

- small cell lung cancer,
- malignant melanoma,
- colorectal cancer,
- gastrointestinal stromal tumor,
- testicular cancer,
- mastocytosis,
- acute myeloid leukemia.

Immune disorders

Since the expression of the KIT gene remains preserved in mast cells and in dendritic cells, signaling mediated by c-Kit represents one of the factors that may participate in the development of asthma and allergy, or that may be an interesting therapeutic target.

Use in histopathology

Since KIT is mutated and/or expressed in an altered manner in a wide range of tumors, its immunohistochemical detection is in some cases a valuable diagnostic clue. Several staining patterns can be distinguished histochemically:

- membrane staining: a number of tumors, eg seminoma;
- cytoplasmic staining: gastrointestinal stromal tumor;
- perinuclear staining (staining of the Golgi apparatus): gastrointestinal stromal tumor, seminoma;
- luminal surface: adenoid cystic carcinoma.

Links

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