

Hematopoietic Growth Factor Inducible Neurokinin-1 Gene

Background

Hematopoietic homeostasis in the bone marrow is maintained by a network of soluble factors. Principal among them is a family of neurotransmitters known as tachykinins that interacts with cytokines and hormones to maintain hematopoietic homeostasis. Tachykinins are encoded by the Preprotachykinin-I (PPT-I) gene in both neural (brain) and non-neural tissues such as lymphoid organs and bone marrow. Some examples of tachykinin peptides encoded by PPT-I include substance P (SP) and neurokinin-A. These peptides bind to their corresponding receptors, NK-1, NK-2 and NK-3, with different affinities and mediate a range of physiological functions. Further, these receptors are expressed differentially in bone marrow, mammary epithelial cells and neural tissues. While the expression of NK-1 is constitutive in neural tissues, in bone marrow cells its expression is inducible by hematopoietic regulators. NK-1 receptors and its ligands have been implicated in the pathology of several abnormalities such as lymphoproliferative disorders such as Hodgkin's and non-Hodgkin's lymphoma, cancer, leukemia and inflammatory diseases. **Thus, the presence of variants or analogs of NK-1 in bone marrow cells and other tissues was investigated as a way to identify additional pathways or targets for the modulation of abnormalities where this receptor might be involved.**

Description of the Technology

A single clone was isolated from the screening of unstimulated bone marrow stromal cell cDNA library with NK-1 probe. The gene was termed *Hematopoietic Growth Factor Inducible Neurokinin-1* type (HGFIN) because of its expression in differentiated hematopoietic cells and peripheral immune cells and its absence in progenitor bone marrow mononuclear cells. However, HGFIN could be induced by growth factors in bone marrow stromal cells indicating that HGFIN is relevant at all levels of the hematopoietic hierarchy. Furthermore, the concomitant down regulation in differentiated bone marrow cells of the transcription factor Id2, an inhibitor of cell differentiation, indicated that HGFIN is involved in cell differentiation. Evidence that HGFIN might have additional roles came from studies with a mitogen, LPS. HGFIN expression was decreased in differentiated cells treated with this mitogen indicating that HGFIN is a cell cycle inhibitor. These discoveries reveal a role for HGFIN in hematopoietic proliferation and regulation and therefore, suggest that the exploitation of its biology would be beneficial in the treatment of lymphoproliferative disorders

Additionally, HGFIN expression was detected in lung, liver, kidney, pancreas and skeletal muscle tissues, and in breast cancer, but not in brain. Taken together, these data suggest that HGFIN could be used as a differentiation marker to follow bone marrow cells as they exit the bone marrow into peripheral tissues.

Human melanoma and breast cancer cell lines also showed expression of HGFIN. Endocrine and other cancers overexpress PPT-I and NK receptors. Since HGFIN can bind to substance P, the major PPT-I peptide, targeting of NK receptors in malignant cells (hematopoietic and other cancer cells) will still make the HGFIN membrane protein available to interact with substance P. Thus NK-1 and other NK receptors have to be targeted in combination with HGFIN in the treatment of cancers. Since PPT-I and NK receptors are involved in the early integration of cancer cells to the bone marrow, the ability of HGFIN to bind substance P indicate that in the bone marrow, HGFIN is a potential target.

Advantages

- Chemotherapy and radiotherapy have side effects
- The use of bone marrow transplantation therapy is limited by their high cost, high risk, and higher failure rates.
- The current invention is a non-invasive approach

Applications

- For the treatment of abnormalities associated with bone marrow cell differentiation such as acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma
- For the development of gene therapy strategies for the treatment of abnormalities associated with bone marrow cell differentiation.
- To identify variants of the gene associated with cancer, or hemotopoietic diseases for purposes of developing screening assays to identify individuals predisposed to cancer and hemotopoietic diseases
- The reporter constructs may be used to develop assays for screening drugs for therapeutic and diagnostic applications in cancer and hemotopoietic diseases
- For the development of small molecules, antisense molecules, antibodies, peptide or proteins for therapeutic interventions in the treatment of cancers, inflammatory diseases, neurological disorders, and hemotopoietic diseases.
- For the development of antibodies for research use.
- Can be used as a transdifferentiation marker to follow the path of cells from bone marrow.

Deliverables

- Vectors and expression systems (pro and eukaryotic)
- Purified protein
- Sequence of HGFIN

Patent Status

- United States patent application filed.
- Application was published on 11/14/2002 (publication No.: US-2002-0168653-A1)

Licensing Opportunity

- This technology is available for non-exclusive or exclusive license.

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