

Human Preprotachykinin-I Gene Promoter

Background

Through the neurokinin receptors a family of neuropeptides known as tachykinins interacts with a complex network of factors such as cytokines and hormones to exert a multitude of biological activities such as neurotransmission, hematopoietic homeostasis, angiogenesis, cell transformation and immune modulation.

The Preprotachykinin-I (PPT-I) gene encodes the tachykinin family of neurotransmitters 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. The two predominant neuropeptides, substance P and neurokinin-A, exert opposing effects on hematopoiesis. Neurokinin-A interacts with NK-2 receptor to inhibit hematopoiesis and SP stimulates hematopoiesis via NK-1 receptor. The N-terminal region of SP can inhibit hematopoiesis and could therefore act as a negative feedback on SP. The negative hematopoietic effects imply a protective role on the lymphohematopoietic stem cells. This latter role could be important in allowing higher doses of therapeutic agents including chemotherapeutic agents. Recent studies show that the NK receptors are expressed differently in bone marrow mesenchymal stem cells, mammary epithelial cells and in neural tissue. Thus, the PPT-I biology could be exploited to develop therapies for diseases associated with hematologic deficiencies, leukemia, cancer, and inflammatory processes.

Further, PPT-I gene has been shown to be overexpressed in breast and other endocrine cancers that metastasize to the bone marrow. Since tachykinins are involved in the maintenance of homeostasis and neoangiogenesis, imbalance in SP and NK-A can lead to tumor metastasis. Overexpression of PPT-I in non-transformed mammary epithelial cells suggest that this gene could be oncogenic.

The present invention relates to the use of PPT-I as a novel target in the development of therapies and diagnostics for a multitude of diseases

Description of the Technology

Promoter regions containing the consensus cAMP response elements (CRE) and CRE-like elements involved in transcription for the PPT-I, NK-2 and SP-R genes have been identified and cloned. Using these vectors and expression systems a role for PPT-I encoded gene products and corresponding receptors, NK-1 and NK-2, in breast cancer has been established. Also, certain mutations in the promoter region that could be associated with breast cancer and breast cancer metastasis have been identified.

Studies using breast cancer cell lines and tissue biopsies revealed an increased expression of PPTI gene encoded peptides as well as the NK-1 and NK-2 receptors. Further, breast cancer cell proliferation could be inhibited by specific antagonists to NK-1 and NK-2 receptors. Additional evidence that implicate PPT-I peptides and receptors in breast cancer progression come from the discovery that breast cancer cytosolic extracts obtained from breast cancer cells promote translation of PPT-I compared to extracts from normal controls or benign breast cancer biopsies. Since PPT-I peptides have been implicated in hematopoietic homeostasis, a role for these peptides in metastasis can be envisaged.

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Breast and other cancers that show a preference for homing to the bone marrow overexpress PPT I. Knockout and knockin studies with breast cancer cells revealed that PPT-I is important in cell transformation and also in having a central role in the integration of cancer cells as part of the bone marrow microenvironment.

Deliverables

- . • Vectors containing the promoter regions for PPT-I and receptor genes NK-1 and NK-2
- . • Deletion mutants (CRE mutants, mutants of CRE-like elements)
- . • Expression Systems
- . • Vectors containing RNA interference for PPT-I, NK-1 or NK-2
- . • Knockin and knockout breast cancer cell lines

Applications

- . • To identify variants of the genes 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 agents for screening and diagnosing individuals predisposed to diseases associated with abnormal expression of PPT-I and its receptors.
- For the development of antibodies for research use.

Patent Status

- . • United States patent application filed.
- . • Application published on 10/10/2002 (Publication No.: US 2002-0146810 A1)

Licensing Opportunity

- This technology is available for exclusive license.

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