Gene Section

Review

TGFBR3 (transforming growth factor, beta receptor III)

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Published in Atlas Database: April 2008
Online updated version: http://AtlasGeneticsOncology.org/Genes/TGFBR3ID42541ch1p33.html
DOI: 10.4267/2042/44433

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Identity

Other names: BGCAN; Betaglycan; TbetaRIII; TGFR-3
HGNC (Hugo): TGFBR3
Location: 1p22.1

DNA/RNA

Description
The TGFBR3 gene encodes 16 exons.

Transcription
The human TGFBR3 gene has two promoters, a proximal promoter and a distal promoter and produces a 4.2 kb mRNA. TGF-beta1 has been demonstrated to down regulate TbetaRIII expression through direct inhibition of the proximal TbetaRIII promoter.

Protein

Description
TbetaRIII is an 853 amino acid transmembrane proteoglycan, which contains a short 41 amino acid cytoplasmic domain. TbetaRIII is a proteoglycan which contains glycosaminoglycan (GAG) side chain modifications (S535 and S546) composed of heparin and chondroitin sulfate. The TbetaRIII core has predicted molecular weight of 100 kDa, however fully processed TbetaRIII migrates at an apparent molecular weight of 180 to 300 kDa due to these glycosaminoglycan post-translational modifications. TbetaRIII contains a class I PDZ binding motif and a beta-arrestin2 interacting motif in the cytoplasmic domain, as well as a ZP-1 (zona pellucida) domain in the extracellular domain. The cytoplasmic domain of TbetaRIII is phosphorylated by TbetaRII. TbetaRIII also undergoes ectodomain shedding to produce soluble TbetaRIII (sTbeta-RIII).

Expression
TbetaRIII is ubiquitously expressed on nearly all cell types. Some cell types, including endothelial and hematopoietic cells, appear to have low to no TbetaRIII expression. The level of TbetaRIII expression is cell type specific.

Localisation
TbetaRIII exists as a transmembrane protein in the cell membrane and as a secreted protein, known as soluble TbetaRIII (sTbetaRIII), which can be detected in the extracellular matrix and serum.

Function
TbetaRIII is a member of the TGF-beta superfamly signaling pathways, which have essential roles in mediating cell proliferation, apoptosis, differentiation, and migration in most human tissues. TbetaRIII is the most abundantly expressed TGF-beta superfamily receptor and functions as a TGF-beta superfamily co-receptor, by binding the TGF-beta superfamily members, TGF-beta1, TGF-beta2, or TGF-beta3, inhibin, BMP-2, BMP-4, BMP-7, and GDF-5 and presents these ligand to their respective signaling receptors to activate or repress (in the case of inhibin) TGF-beta1, BMP, or activin signaling to the Smad transcription factors. For example, in the case of TGF-beta1, 2, or 3, Tbeta-RIII presents ligand to the TGF-beta type II receptor (TbetaRII). Once bound to ligand, TbetaRII then recruits and transphosphorylates the TGF-beta type I receptor (TbetaRI), activating its kinase function and leading to the phosphorylation of Smad2/3. Phosphorylation of Smad2 and Smad3 leads
to formation of a complex with Smad4, and accumulation of this complex in the nucleus, where along with co-activators and co-repressors they regulate the transcription of genes involved in proliferation, angiogenesis, apoptosis, and differen-tiation. In addition to regulating receptor mediated Smad signaling, TbetaRIII also mediates ligand dependent and independent p38 pathway signaling. TbetaRIII can also undergo ectodomain shedding to generate soluble TbetaRIII (sTbetaRIII), which binds and sequesters TGF-beta superfamily members to inhibit their signaling. Although sTbetaRIII expression has been demonstrated to correlate with the cell surface expression of TbetaRIII, little is known about the regulation of sTbetaRIII production. The regulation TbetaRIII expression is sufficient to alter TGF-beta signaling. The cytoplasmic domain of TbetaRIII interacts with GIPC, a PDZ-domain containing protein, which stabilizes TbetaRIII cell surface expression and increases TGF-beta signaling. The cytoplasmic domain of TbetaRIII is also phosphorylated by TbetaRII, which results in TbetaRII binding to the scaffolding protein beta-arrestin2. The TbetaRIII/beta-arrestin2 interaction results in the co-internalization of beta-arrestin2/TbetaRIII/Tbeta RII and the down-regulation of TGF-beta signaling. During development TbetaRIII has an important role in the formation of the atrioventricular cushion in the heart. Consistent with an important role for TbetaRIII during development, TGFbetaR3 null mice are embryonic lethal due to heart and liver defects. TGFbetaR3 has been recently identified as a tumor suppressor in multiple types of human cancers, including breast, lung, ovarian, pancreatic and prostate cancer. The loss of TGFbetaR3 in these cancer types correlates with disease progression, and results in increased motility and invasion in vitro and increased invasion and metastasis in vivo.

**Homology**

TbetaRIII shares several regions of homology with the superfamily co-receptor, endoglin, with 2 regions of homology in the extracellular domain, a large domain near the amino terminus with 21% homology, and a shorter domain near the sites of GAG modification with 50% homology. In addition, their cytoplasmic domains share 70% homology.

**Mutations**

**Somatic**

Mutations in TbetaRIII have not been found in human cancers, although inactivating mutations in other components of the TGF-beta signaling pathway are common.

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**Implicated in**

**Breast Cancer**

**Disease**

Breast cancer is the second leading cause of cancer death in women, exceeded only by lung cancer in the United States. Types of breast cancer include ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and invasive or infiltrating ductal carcinoma (IDC).

**Prognosis**

The current five year survival rate for breast cancer is 98% for localized cancer, 80% for regional cancer, and 27% for metastatic disease with distant spread.

**Oncogenesis**

TbetaRIII loss occurs relatively early in mammary carcinogenesis, with loss beginning in the pre-invasive state of DCIS. The degree of TbetaRIII loss correlates with breast cancer progression and with a decrease in patient survival. TbetaRIII loss in breast cancer is due to LOH (loss of hetero-zgyosity) at the TGFbetaR3 gene locus and potential transcriptional down regulation of TbetaRIII by increased levels of TGF-beta in the tumor microenvironment. Restoring TbetaRIII expression inhibits tumor invasion, angiogenesis, and metastasis in vivo. TbetaRIII functions, in part, through the production of sTbetaRIII by ectodo-main shedding, which antagonizes TGF-beta signaling, leading to a decrease in invasiveness and angiogenesis in vivo. In addition, TbetaRIII functions as a tumor suppressor in non-tumorigenic mammary epithelial cells through the inhibition of NFkappa-B mediation repression of E-cadherin. Loss of TbetaRIII in non-tumorigenic mammary epithelial cells leads to increased invasive capa-bilities due to up-regulated NFkappa-B activity and loss of E-cadherin expression.

**Non-small Cell Lung Cancer (NSCLC)**

**Disease**

Lung cancer is the leading cause of death of both males and females in the United States. Non-small cell lung cancer accounts for 87% of all lung cancers.

**Prognosis**

The five year survival rate for all stages of lung cancer is 15%. The survival rate is 49% for localized disease; however few cases are identified at this stage.

**Oncogenesis**

TbetaRIII has been characterized as a tumor suppressor in non-small cell lung cancer. Expression of TbetaRIII is lost in the majority of non-small cell lung cancer (NSCLC) at both the mRNA expression level and the protein level. Loss of heterozygosity (LOH) occurs in 38.5% of NSCLC human specimens and correlates with decreased TbetaRIII expression, suggesting that LOH is one mechanism of loss of TbetaRIII expression. Loss of TbetaRIII expression correlates with NSCLC.
progression and increasing tumor grade, with a trend towards decreased survival. The loss of TbetaRIII results in a functional increase in cellular migration, invasion, and anchorage independent growth of lung cancer cells. TbetaRIII regulates cellular invasion and motility in lung cancer in part through the generation of sTbetaRIII, although the mechanism of these effects remains unclear.

Prostate Cancer

Disease
Prostate cancer is the most commonly diagnosed malignancy in men and the third leading cause of cancer-related deaths among men in the United States.

Prognosis
The five year survival rate for all stages of prostate cancer is near 99%. The five year survival rate for local and regional disease approaches 100%.

Oncogenesis
TbetaRIII has been characterized as a tumor suppressor in prostate cancer. Expression of TbetaRIII is lost or decreased in the majority of human prostate cancers at both the mRNA and protein level, due to the loss of heterozygosity at the TbetaRIII locus and epigenetic regulation of the TbetaRIII promoter. Loss of TbetaRIII correlates with advancing tumor stage and an increased probability of prostate-specific antigen (PSA) recurrence. Restoring TbetaRIII expression in prostate cancer cells decreases cell motility and cell invasion in vitro and tumorigenicity in vivo. The loss of TbetaRIII is a common event in human prostate cancer cells and is important for tumor progression through effects on cell motility, invasiveness, and tumorigenicity.

Ovarian Cancer

Disease
Ovarian cancer is the fifth leading cause of cancer death among women in the United States. The majority of ovarian cancers are ovarian epithelial carcinomas or malignant germ cell tumors.

Prognosis
The overall five year survival rate is 45% for ovarian cancer. The five year survival rate is 70% for patients with regional disease. However the lack of effective treatments for metastatic disease and the aggressive nature of this disease results in a 30% survival rate for those with metastatic disease.

Oncogenesis
TbetaRIII has been characterized as a tumor suppressor in ovarian cancer. TbetaRIII expression is decreased or lost in epithelial derived ovarian cancer at both the mRNA and protein level due to epigenetic silencing which is progressive with increasing tumor grade. TbetaRIII inhibits ovarian cancer cell invasiveness and migration. TbetaRIII specifically promotes the anti-migratory action of inhibin and inhibin-mediated repression of matrix metalloproteinases, which play a role in the invasive and metastatic potential of tumor cells.

Pancreatic Cancer

Disease
Pancreatic cancer is the fourth leading cause of cancer death in the United States, with incidence levels closely matching the death rate. The majority of pancreatic cancers are adenocarcinomas, while endocrine pancreatic cancer is rare.

Prognosis
Pancreatic cancer has a low survival rate, with the median survival rate being four to six months and a five year survival rate of less than 5%. The 5 year survival rate for local disease is 20%. This low survival rate is due to delayed diagnosis caused by a lack of symptoms until the cancer is locally invasive or metastatic, a lack of effective screening tests, and ineffective treatments.

Oncogenesis
TbetaRIII may function as a tumor suppressor in pancreatic cancer. The genomic locus for TGFBR3 is deleted in 49% of human pancreatic cancers. Loss of TbetaRIII expression at the message and protein level correlates with worsening tumor grade in human pancreatic cancer specimens. In a pancreatic model of epithelial to mesenchymal transition (EMT), TbetaRIII expression is lost at the mRNA and protein levels. The loss of TbetaRIII protein expression occurs before the loss of E-cadherin and cytoskeletal reorganization, both markers of early EMT, and correlates with increased invasion and motility, hallmarks of EMT. The ability of TbetaRIII to suppress invasion and motility is partially mediated by sTbetaRIII.

Renal Cell Carcinoma (RCC)

Disease
RCC is the most common form of kidney cancer. There are several subtype of RCC including Clear Cell RCC, Papillary RCC, Chromophobe RCC, and Collecting Duct RCC.

Prognosis
The 5 year survival rate for all stages of renal cell carcinoma is 65.5%. There is a lack of effective treatments for metastatic RCC and the 5 year survival rate is 9.5% for metastatic disease.

Oncogenesis
Loss of TbetaRIII at both the mRNA and the protein level occurs in all RCC tumor stages. Loss of TbetaRIII RNA expression is an early event in RCC and leads to a partial loss of TGF-beta responsiveness and attenuation of TGF-beta signaling. The sequential loss of TbetaRII after TbetaRIII loss leads to complete TGF-beta resistance and a more aggressive, metastatic RCC phenotype. Restoring TbetaRIII expression in the presence of TbetaRII, leads to enhanced TGF-beta signaling, restoration of growth inhibition, and the loss of anchorage independent growth over that observed with TbetaRII alone.
References


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