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Gene Section

Review

TGFBR3 (transforming growth factor, beta receptor III)

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Identity

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

DNA/RNA

Description

The TGFBbetaR3 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 superfamily signaling pathways, which have essential roles in mediating cell proliferation, apoptosis, differentia-tion, 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 TbetaRIII 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.

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-zygosity) 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 Unites 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

Blobe GC, Liu X, Fang SJ, How T, Lodish HF. A novel mechanism for regulating transforming growth factor beta (TGF-beta) signaling. Functional modulation of type III TGF-beta receptor expression through interaction with the PDZ domain protein, GIPC. J Biol Chem. 2001 Oct 26;276(43):39608-17

Esparza-Lopez J, Montiel JL, Vilchis-Landeros MM, Okadome T, Miyazono K, López-Casillas F. Ligand binding and functional properties of betaglycan, a co-receptor of the transforming growth factor-beta superfamily. Specialized binding regions for transforming growth factor-beta and inhibin A. J Biol Chem. 2001 May 4;276(18):14588-96

Chen W, Kirkbride KC, How T, Nelson CD, Mo J, Frederick JP, Wang XF, Lefkowitz RJ, Blobe GC. Beta-arrestin 2 mediates endocytosis of type III TGF-beta receptor and down-regulation of its signaling. Science. 2003 Sep 5;301(5638):1394-7

Copland JA, Luxon BA, Ajani L, Maity T, Campagnaro E, Guo H, LeGrand SN, Tamboli P, Wood CG. Genomic profiling identifies alterations in TGFbeta signaling through loss of TGFbeta receptor expression in human renal cell carcinogenesis and progression. Oncogene. 2003 Sep 11;22(39):8053-62

Stenvers KL, Tursky ML, Harder KW, Kountouri N, Amatayakul-Chantler S, Grail D, Small C, Weinberg RA, Sizeland AM, Zhu HJ. Heart and liver defects and reduced transforming growth factor beta2 sensitivity in transforming growth factor beta type III receptor-deficient embryos. Mol Cell Biol. 2003 Jun;23(12):4371-85

Elliott RL, Blobe GC. Role of transforming growth factor Beta in human cancer. J Clin Oncol. 2005 Mar 20;23(9):2078-93

Criswell TL, Arteaga CL. Modulation of NFkappaB activity and E-cadherin by the type III transforming growth factor beta receptor regulates cell growth and motility. J Biol Chem. 2007 Nov 2;282(44):32491-500

Dong M, How T, Kirkbride KC, Gordon KJ, Lee JD, Hempel N, Kelly P, Moeller BJ, Marks JR, Blobe GC. The type III TGF-beta receptor suppresses breast cancer progression. J Clin Invest. 2007 Jan;117(1):206-17

Hempel N, How T, Dong M, Murphy SK, Fields TA, Blobe GC. Loss of betaglycan expression in ovarian cancer: role in motility and invasion. Cancer Res. 2007 Jun 1;67(11):5231-8

Turley RS, Finger EC, Hempel N, How T, Fields TA, Blobe GC. The type III transforming growth factor-beta receptor as a novel tumor suppressor gene in prostate cancer. Cancer Res. 2007 Feb 1;67(3):1090-8

You HJ, Bruinsma MW, How T, Ostrander JH, Blobe GC. The type III TGF-beta receptor signals through both Smad3 and the p38 MAP kinase pathways to contribute to inhibition of cell proliferation. Carcinogenesis. 2007 Dec;28(12):2491-500

Finger EC, Turley RS, Dong M, How T, Fields TA, Blobe GC. TbetaRIII suppresses non-small cell lung cancer invasiveness and tumorigenicity. Carcinogenesis. 2008 Mar;29(3):528-35

Gordon KJ, Dong M, Chislock EM, Fields TA, Blobe GC. Loss of type III transforming growth factor beta receptor expression increases motility and invasiveness associated with epithelial to mesenchymal transition during pancreatic cancer progression. Carcinogenesis. 2008 Feb;29(2):252-62

Hempel N, How T, Cooper SJ, Green TR, Dong M, Copland JA, Wood CG, Blobe GC. Expression of the type III TGF-beta receptor is negatively regulated by TGF-beta. Carcinogenesis. 2008 May;29(5):905-12

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