

Gene Section

Review

GRN (granulin)

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Identity

Hugo: GRN

Other names: GEP; GP88; PCDGF; PEPI; PGRN; acrogranin; granulin-epithelin; proepithelin; progranulin

Location: 17q21.32

DNA/RNA

Description

13 exons, including 12 protein encoding exons and a further 5' non-coding exon.

Transcription

Major mRNA: 2323bp

Protein

Description

Granulins are a family of secreted, glycosylated peptides; Granulins are cleaved from a single precursor protein with 7.5 repeats of a highly conserved 12-cysteine granulin/epithelin motif. The 88 kDa precursor protein, progranulin, is also called proepithelin and PC cell-derived growth factor. Cleavage of the signal peptide produces mature granulin which can be further cleaved into a variety of active, 6 kDa peptides. These smaller cleavage products are named granulin A, granulin B, and granulin C, etc.

Expression

Granulins are widely expressed. Normally, high levels of GRN expression on rapidly proliferating cells, such as skin cells, deep crypts of gastrointestinal tract,

kidney, and immune cells; Low levels of GRN expression on muscle and liver cells. However, over-expressing on some kinds of tumor cells, such as breast cancer, prostate cancer, ovarian cancer.

Localisation

Nucleus.

Function

Progranulin stimulates cell proliferation, migration and survival. It activates conventional growth factor signaling pathways including the p44/42 MAPkinase and phosphatidylinositol 3-kinase pathways and the Focal Adhesion Kinase pathway. Many experiments show that increasing the expression of progranulin can stimulate the tumor growth on immortalized but otherwise non-tumorigenic cells. SW13 cells overexpress progranulin (high PGRN), so, they produce large tumors in nude mice; cells that express less progranulin (basal PGRN), do not grow as tumors. However, progranulin is necessary for tumor growth. Attenuating progranulin (PCDGF) expression in mammary cancer cells MDA-MB-468 and human hepatocellular carcinoma cell lines (HepB3) led to a dramatic reduction (90% and 87%, respectively) in the size of tumors when the cells were grown in nude mice. Also, some experiments indicated that progranulin caused an increase of the motility and the invasiveness of tumor and played an important effect on apoptosis of tumor cells, reduced the rate of cell death.

Mutations

Note: Mutations in the progranulin (PGRN) gene have been identified in frontotemporal lobar degeneration with ubiquitin inclusions linked to chromosome 17q21.

There are two novel frameshift mutations and three possible pathogenic missense mutations in the PGRN gene, and PGRN mutations in familial cases recruited from a large population-based study of frontotemporal lobar degeneration carried out in the Netherlands. However, no mutation was found in the development of different cancers.

Implicated in

Breast cancer

Disease

Progranulin has been shown to play a major role in breast tumorigenesis by stimulating proliferation, mediating survival and conferring resistance to some chemicals such as tamoxifen and doxorubicin, and its overexpression account for the resistance to therapeutic agents. PCDGF/GP88 has metastatic potential in breast cancer, and tumor cells (such as MCF-7 cells) with a PCDGF over-expression or treated exogenously with PCDGF both stimulated anchorage-independent cell growth and accelerated cell migration through matrigel. Furthermore, PCDGF/GP88 also can up-regulated the expression of matrix metalloprotease-9, and stimulated VEGF expression in some tumor cells. So, PCDGF/GP88 could act to promote metastasis and angiogenesis in human breast cancer cells in addition to stimulating their proliferation and survival.

PCDGF/GP88 activated mitogen-activated protein kinase (MAP kinase Erk1/Erk2) as well as phosphatidylinositol 30-kinase (PI-3 kinase) pathways leading to the stimulation of several cyclins including Cyclin D1 and Cyclin B. In the adrenal carcinoma SW-13 cells, progranulin expression was also a major determinant of focal adhesion kinase signaling pathway in addition to MAP kinase and PI-3 kinase.

Prognosis

GRN might play an important role in deciding the behavior of node-positive breast cancer, so, GRN maybe provide valuable information for the prognosis of breast cancer patients. Since all the in vitro studies indicated the importance of PCDGF/GP88 in breast tumorigenesis. PCDGF/GP88 expression was then examined in pathological samples. Correlation studies between PCDGF expression and prognostic markers such as ER/PR expression, proliferation index Ki67, p53, and erbB2 were also conducted. Normally, PCDGF staining was observed in breast carcinoma, whereas it was not detected in benign breast epithelium. In breast carcinoma, PCDGF expression was more common in ductal carcinoma than in invasive lobular carcinoma. Moreover, PCDGF staining was almost never observed in lobular carcinoma in situ, whereas most of ductal carcinoma in situ (DCIS) expressed PCDGF. PCDGF expression in DCIS correlated strongly with nuclear grade in DCIS and histological grades in IDC. Both ER positive and ER

negative tumors had moderate to strong PCDGF expression. Positive correlation was found between PCDGF staining and Ki67 proliferation index. Similarly, a larger percentage of tumors with moderate/strong PCDGF expression were p53 positive. In contrast, PCDGF expression was independent of *cerbB-2* overexpression. This study provides evidence of the high incidence of PCDGF expression in human breast cancer with positive correlation with clinicopathological variables such as tumor grade, proliferation index, and p53 expression. These characteristics the absence of expression in benign breast tissue suggest an important role of PCDGF in breast cancer pathogenesis and make it a potential novel target for the treatment of breast cancer.

Prostate Cancer

Disease

Normal prostate tissue did not express, or expressed low levels of PCDGF. PCDGF expression could be detected in more than 50% of cells in all specimens of prostatic intraepithelial neoplasia (PIN) and invasive prostate cancer. The expression of PCDGF in normal prostate tissue was much less intense and in a smaller fraction of cells than in PIN and invasive adenocarcinoma (P less than 0.0001). There was no correlation of PCDGF expression with age, Gleason score, pathological stage, status of lymph node metastasis, extraprostatic extension, perineural invasion, surgical margins, and vascular invasion. So, the induction of PCDGF expression occurs during the development of PIN. PCDGF may be a new molecular target for the treatment and prevention of prostate cancer.

Ovarian Carcinoma

Disease

The GEP/PCDGF has been shown to be an important growth and survival factor induced by low-malignant-potential (LPA) and ET-1 and cAMP/EPAC through ERK1/2 for ovarian cancer cells, and its expression is a predictor of patient survival in metastatic ovarian cancer cells. The prosurvival function of GEP is important in ovarian cancer tumor progression and chemoresponse. Overexpression of GEP increased capacity to migrate and invade their substratum, and was associated with cisplatin chemoresistance. Meantime, GEP overexpression increased tumor formation and protected cells from tumor regression in response to cisplatin treatment in vivo.

Prognosis

Several experiments discovered and validated the differential expression of GEP between noninvasive LPA tumors and invasive epithelial ovarian cancers in an effort to define a molecular basis for the pathologic differences between these epithelial tumor subtypes. Low malignant potential tumors share cytologic

similarities with invasive ovarian cancers but have epithelial cells that lack the capacity to invade their underlying stroma. These tumors are slow growing and rarely metastasize and patients with LMP tumors present most often with disease limited to the ovary. This presentation translates into a marked improved clinical outcome over patients with invasive ovarian cancers, with over 95% of patients alive at 10 years. In contrast, patients with invasive ovarian cancers more commonly present with, and die of, disseminated disease and have a 40% overall 5-year survival.

GEP expression also was observed in primary and metastatic epithelial ovarian carcinoma specimens, with down-regulated expression in tumor cells of malignant effusions. The poor outcome associated with stromal GEP expression suggests a prognostic role for this growth factor in ovarian carcinoma.

Endometrial cancer

Disease

The majority of endometrial cancers arise as a result of estrogen stimulation, the molecular targets of which remain incompletely defined. GEP may be one such target. GEP co-expression with ER was observed in most of cancers examined. A two to fivefold increase in GEP expression with estradiol and/or tamoxifen treatment was observed in KLE cells. Silencing of GEP in HEC-1-A cells using shRNA resulted in a decrease in proliferation among transfected cells. However, co-expression of GEP and ER in endometrial cancer cells, and the regulation of GEP by estrogen, suggests a role for GEP in steroid-mediated endometrial cancer cell growth. Further, characterization of GEP as a steroid-mediated growth factor in these cells may help me to understand endometrial cancer biology very well.

Teratoma

Disease

The PC cell line is a highly tumorigenic, insulin-independent, teratoma-derived cell line isolated from the nontumorigenic, insulin-dependent 1246 cell line. Studies of the PC cell growth properties have led to the purification of an 88-kDa secreted glycoprotein called PC cell-derived growth factor (PCDGF), which has been shown to stimulate the growth of PC cells as well as 3T3 fibroblasts. Since PCDGF was isolated from highly tumorigenic cells, its level of expression was examined in PC cells as well as in nontumorigenic and moderately tumorigenic cells from which PC cells were derived, and the levels of PCDGF mRNA and protein were very low in the nontumorigenic cells and increased in tumorigenic cell lines in a positive correlation with their tumorigenic properties. An inhibition of PCDGF expression resulted in a dramatic inhibition of tumorigenicity of the transfected cells when compared with empty-vector control cells. These data demonstrate the importance in tumor formation of overexpression of the novel growth factor PCDGF.

Brain tumor-glioblastoma multiforme

Disease

The 2.1-kb granulin mRNA was expressed predominantly in glial tumors, whereas expression was not detected in non-tumor brain tissues. Granulin may be a glial mitogen, as addition of synthetic granulin peptide to primary rat astrocytes and three different early-passage human glioblastoma cultures increased cell proliferation in vitro, whereas increasing concentrations of granulin antibody inhibited cell growth in a dose-dependent manner. The differential expression pattern, tissue distribution, and implication of this glioma-associated molecule in growth regulation suggest a potentially important role for granulin in the pathogenesis and/or malignant progression of primary brain neoplasms.

Multiple Myeloma

Disease

PCDGF mRNA and protein expression was detected in human MM cell lines such as ARP-1 and RPMI 8226, and PCDGF added exogenously stimulated cell growth and sustained cell survival of both ARP-1 and RPMI 8226 cells in a dose- and time-dependent fashion. When treated with neutralizing anti-PCDGF antibody, RPMI 8225 cells growth was inhibited. This indicated that PCDGF acts as an autocrine growth factor for MM cells. Studies of signal transduction pathways showed PCDGF stimulated mitogen-activated protein kinase and phosphatidylinositol 3'-kinase pathways but not the Janus-activated kinase-signal transducer and activator of transcription pathway. Immunohistochemical analysis of bone marrow smears obtained from MM patients indicated that PCDGF expression was associated with myeloma cells from MM patients and correlated with the presence of MM disease.

Laryngeal carcinoma

Disease

The PC cell-derived growth factor protein levels and mRNA levels of the laryngeal squamous cell carcinomas were significantly higher than those of normal laryngeal tissues. Simultaneously, the difference in the levels of mRNA and protein between those of laryngeal precancerous lesions (papilloma/leukoplakia) and those of normal tissues was significant, whereas those of laryngeal precancerous lesions (papilloma/leukoplakia) were significantly lower than those of laryngeal squamous cell carcinomas. Strong PC cell-derived growth factor expression was associated with lymph node metastases in laryngeal squamous cell carcinoma. Functional studies on Hep-2 cell lines demonstrated that the attenuation of PC cell-derived growth factor expression levels led to diminished cell proliferation rates, anchorage-independent growth in vitro, tumor forming in vivo and resistance to apoptosis. PC cell-derived

growth factor is a pivotal autocrine growth factor in the tumorigenesis of laryngeal squamous cell carcinoma. In the future, PC cell-derived growth factor may be a logical and potential target for early diagnosis, specific therapy and prognosis of laryngeal squamous cell carcinoma.

Bladder Cancer

Disease

Proepithelin is overexpressed in bladder cancer cell lines and clinical specimens of bladder cancer. Proepithelin did not appreciably affect cell growth, but it did promote migration of 5637 bladder cancer cells and stimulate in vitro wound closure and invasion. These effects required the activation of the mitogen-activated protein kinase pathway and paxillin, which upon proepithelin stimulation formed a complex with focal adhesion kinase and active extracellular signal-regulated kinase. However, proepithelin plays a role in stimulating migration, invasion of bladder cancer cells, and establishing of the invasive phenotype.

Prognosis

So far, it is unclear if proepithelin has a significant effect on the prognosis of patient with bladder cancer.

Renal epithelium

Disease

Acrogranin levels were low in benign renal tissue and increased in malignant renal tissue. In addition, high-grade RCC exhibited higher levels of expression than low-grade RCC and normal tissue. So, acrogranin may be a functional important growth factor in RCC and a potential molecular marker for high-grade RCC.

Hepatocellular carcinoma

Disease

In hepatocellular carcinoma, there is a closed relationship between p53 and GEP protein. Studies revealed an overall positive association between the two protein expression patterns, and the association of p53 and GEP protein expression was found to be highly significant only in HCCs with wild-type p53; there was no association in HCCs with p53 mutation. The GEP levels in the HepG2 hepatoma cell line with a wild-type p53 background were modulated by transfection experiments. Overexpression of the GEP protein resulted in an increased p53 protein level and suppression of the GEP protein resulted in a decreased p53 protein level in HepG2 cells. In summary, p53 wild-type protein nuclei accumulation is associated with GEP protein expression in human HCC specimens, and GEP modulates p53 wild-type protein levels in vitro.

Gastric cancer

Disease

Granulin was expressed in gastric cancer cells, and may be considered as a tumor associated antigen.

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