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Gene Section

Review

SNCG (synuclein, gamma (breast cancer-specific protein 1))

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Abstract

Expression of synuclein-gamma (SNCG) protein is elevated in the advanced stages of many types of cancers, including breast, ovarian, lung, gastric, liver, esophagus, colon, prostate and others.
In breast carcinoma, SNCG is causatively linked to stimulated proliferation, metastasis and drug resistance.
A clinical follow-up study indicates that patients with an SNCG-positive breast cancer have a significantly shorter disease-free survival and overall survival than patients with SNCG-negative tumors.
Overexpression of SNCG compromises normal mitotic checkpoint controls, resulting in multinucleation as well as faster cell growth.
SNCG has also been shown to promote invasion and metastasis in in vitro assays as well as in animal models. SNCG overexpression also interferes with drug-induced apoptotic responses. Expression of SNCG in cancer cells results in a more malignant phenotype with increased cell motility, enhanced transcriptional activity of steroid receptors and accelerated rate of chromosomal instability.
Two closely located AP1 binding sites residing in the first intron of the SNCG gene are important regulators of the promoter activity. Other factors regulating SNCG expression are methylation-demethylation of exon and post-transcriptional regulation by microRNAs.

Keywords
Invasion, metastasis, cancer, tumorigenesis, transcriptional regulation, microRNA

Identity

Other names: BCSG1, gamma-synuclein, PERSYN, PRSN, Synoretin

HGNC (Hugo): SNCG

Location: 10q23.2

Note
Synuclein-gamma is a member of the synuclein family of proteins which are believed to be involved in the pathogenesis of neurodegenerative diseases. High levels of SNCG have been identified in several types of cancer suggesting the association of its overexpression and cancer development.

DNA/RNA

Description

Human SNCG gene consists of five exons that span about 5 kbp. The intron 1 contains two closely located AP1 recognition sequences. Deletion of these motifs greatly diminished the SNCG promoter activity, suggesting that AP1 is an important transactivator for SNCG transcription SNCG transcription is primarily controlled by regulatory sequences located in intron 1 and exon 1 and in a lesser extent by 5' flanking region. Synuclein expression is regulated predominantly at the level

of SNCG gene transcription, SNCG mRNA stability and by micro-RNA (miRs).

Protein

Description

Encoded by human SNCG gene (synuclein family), the highly conserved 127-amino acid 13 kD cytoplasmic gamma-synuclein is similar to two other members of the family, alpha-synuclein and beta-synuclein. The gamma-synuclein protein is the least conserved of the synuclein proteins. The human gamma-synuclein is 87.7% and 83.8% identical to the mouse and rat proteins, respectively, which are 4-amino acids shorter. For all three members of the family the region of highest homology is the amino-terminal region. The synuclein proteins contain several repeated domains that display variations of a KTKEGV consensus sequence. This motif, repeated six to seven times in the amino-terminal portion of the protein, is reminiscent of the alpha-helical domains of the apolipoproteins and suggests lipid binding properties. The very high conservation between species for a specific repeated domain of a particular protein suggests that the repeated domains have arisen from the duplication of a single domain within an ancestral synuclein gene. Later, this ancestral gene may have undergone successive duplications to give rise to the three synuclein genes in which the repeated domains may still be able to diverge. The third domain, however, remained absolutely identical, KTKEGV, in all genes throughout all species. A similar type of domain is present in proteins of the rho family. However, as of today, the role of these domains remains unknown.

Expression

Mammalian gamma-synuclein was first identified as the so-called breast cancer-specific gene 1 (BCSG1) in a high-throughput direct differential-cDNA-sequencing screen for markers of breast cancer. Northern blot analysis showed that the gene is principally expressed in the brain, particularly in the substantia nigra. The protein is expressed in the peripheral nervous system, mainly in primary sensory neurons, sympathetic neurons, and motor neurons. A high level of synuclein gamma was also detected in several types of tumors, and in the olfactory epithelium. A sequence dubbed synoretin was independently isolated from ocular tissues in a screen for novel proteins regulating phototransduction and is now thought to represent the bovine ortholog of gamma-synuclein. SNCG is expressed in brain, heart, skeletal muscle, ovary, testis, colon, spleen, pancreas, kidney and lung. MicroRNAs (miRs) are implicated in the regulation of SNCG expression.

Localisation

The three human synuclein genes are expressed in the thalamus, the substantia nigra, the caudate nucleus, and the amygdala. Only gamma-synuclein appears strongly expressed in the subthalamic nucleus. Although gamma-synuclein is not present in senile plaques, Lewy bodies or neurofibrillary tangles, a high level of gamma-synuclein immunoreactivity is detectable in dot-like structures and other deposits which are characteristic lesions in the brains of patients with neurodegenerative diseases, as well as in the retina and optic nerve. SNCG mRNA and gamma-synuclein protein were also detected in unstimulated and phytohaemagglutinin (PHA)-stimulated cultured lymphocytes from peripheral blood of normal donors. It has been shown previously by in situ hybridization that SNCG/BCSG1 mRNA is not expressed in normal adult breast tissue, but high levels of this mRNA are present in advanced infiltrating breast tumours. In paraformaldehyde fixed cells, SNCG displayed punctuate cytoplasmic staining, a pattern that is usually associated with markers of the endoplasmic reticulum or vesicular structures.

Function

The normal cellular function of gamma-synuclein is as yet unclear, but interestingly exogenous expression of the protein increases the invasive and metastatic potential of breast tumors. The highly conserved N-terminal region is known to be important for the lipid interactions of the synucleins and the highly acidic C-terminal region has been suggested to possess chaperone-like activity, to regulate the aggregation of synucleins and to mediate protein-protein interactions. It seems that gamma-synuclein plays a role in neurofilament network integrity and may modulate axonal architecture, also, it may increase the susceptibility of neurofilament-H to calcium-dependent proteases and may also modulate the keratin network in skin. Phosphorylation by GRK5 appears to occur on residues distinct from other kinase target residues. Synuclein gamma is likely involved in the pathogenesis of neurodegenerative and ocular diseases, for example, glaucoma and SNCG is expressed at very high level in advanced infiltrating breast cancer. The dual role of SNCG in neurodegeneration and malignancy could involve common mechanisms. Changes in organization of the cell cytoskeleton are among the most prominent characteristics of both processes. The involvement of gamma-synuclein in regulating neurofilament network integrity raises the possibility that it may also affect the intermediate filament network in malignant breast epithelial cells. In addition, gamma-synuclein regulates the level of expression

of several genes, for example matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9). Gamma-synuclein is readily oxidized at methionine-38 and after oxidation it aggregates and induces the aggregation of alpha-synuclein.
The binding of gamma-synuclein to phospholipase C β2 (PLCβ2) results in inhibition of enzymatic activity and therefore may regulate the intracellular level of second messenger phosphatidylinositol 4,5 bisphosphate (PI(4,5)P2).
Gamma-synuclein is a novel regulator of lipid metabolism in adipocytes and the deficiency of this protein has a significant effect on whole body energy expenditure.

Homology

There are currently almost 200 DNA and protein sequences in the sequence databases with high homology to the synuclein gene or protein.
All synuclein sequences available to date from Homo sapiens, Mus musculus, and Rattus norvegicus can be assigned to three distinct protein groups: alpha beta and gamma-synuclein. Synuclein proteins have also been identified in other organisms: synelfin is the alpha-synuclein ortholog in Serinus, phospho-neuroprotein 14 (PNP14) is the beta-synuclein ortholog in Bos taurus, and the first synuclein protein described in Torpedo californica corresponds to the human gamma-synuclein. Interestingly, synucleins are identified only in vertebrate and no homologous proteins have been revealed in invertebrate or lower organisms.
Each of the three family members is composed of an N-terminal lipid-binding domain, containing a series of 11-residue imperfect repeats, and an acidic C-terminal domain.
Among the human family members, gamma-synuclein 50% identical and 74% homologous to alpha-synuclein and 47% identical and 66% homologous beta-synuclein.
The highly conserved N-terminal region is known to be important for the lipid interactions of the synucleins and the highly acidic C-terminal region has been suggested to possess chaperone-like activity, to regulate the aggregation of synuclein and to mediate protein-protein interactions.
The very high degree of conservation in the lipid-binding N-terminal domains of all three synucleins strongly suggests that both beta and gamma-synuclein like alpha-synuclein bind to lipid membranes and adopt a highly helical structure. Nevertheless, differences in the sequences of the three proteins in both their central parts and C-terminal domains must be responsible for those differences that do exist in their individual functions, as well as for their different roles in disease.

Mutations

Note
No tumor-specific mutations of the SNCG gene were found in breast tumors and tumor cell lines, but two linked polymorphisms in the coding region were detected, both in mRNA and in exons III and IV of the gene from G243C and T377A.
These results reflect the absence of two G--A (and consequently Glu--Lys) in tumor cell lines, tumors and control tissues.
The above mentioned two linked polymorphic sites discriminate two alleles of the human persyn gene. The frequencies of the two alleles were the same in genomes of breast cancer and normal cells (20% G243/T377 and 80% C243/A377).
Both alleles are transcriptionally active and are expressed with similar efficiency in heterozygotes.

Epigenetics

Sequence analysis identified a CpG island in exon 1 of SNCG that contains 15 CpG sites, covering the region -169 to +81, relative to the translation start codon. CpG sites within the CpG island and its vicinity were partially and heterogeneously methylated in SNCG-negative breast cancer cell lines but unmethylated in SNCG-positive cells. SNCG expression correlates with complete demethylation of the exon 1 region. Specific methylation at the CpG sites 2, 5, 7, and 10-15, was sufficient to block the expression of SNCG gene in breast cell culture. Genomic sequencing and methylation-specific PCR assays have shown that SNCG CpG island is fully methylated in normal tissues of liver, esophagus, prostate, cervix, stomach, colon, and lung, but only partially methylated in breast tissue. Tumors from these tissues contain completely demethylated SNCG. Universal loss of the epigenetic control of SNCG gene expression in tumors and further demonstrating that the demethylation of SNCG CpG island is primarily responsible for the aberrant expression of SNCG protein in cancerous tissues have suggested an important role of gamma-synuclein-related epigenectic events in various malignancies. Reactivation of SNCG gene expression by DNA demethylation is a common critical contributing factor to malignant progression of many solid tumors and its expression in primary carcinomas is an effective molecular indicator of distant metastasis.

Implicated in

Note
The possible involvement of gamma-synuclein in tumorigenesis first came to light when a gene

named BCSG1 (breast cancer-specific gene 1) was shown to be overexpressed in advanced infiltrating carcinoma of the breast. In fact, BCSG1 and gamma-synuclein appear to be the same protein. SNCG protein is highly expressed in diversified cancer types, including the female hormone-sensitive cervical and breast cancers, male hormone-sensitive prostate cancer, four cancer types of the digestive system, and lung cancer. These cancers are currently the leading cause of mortality in both men and women. How SNCG induces disease progression in different cancer types remains elusive. Oncogenic activation of gamma-synuclein contributes to the development of breast and ovarian cancer by promoting tumor cell survival under adverse conditions and by providing resistance to certain chemotherapeutic drugs. Overexpression of gamma-synuclein leads to constitutive activation of extracellular signal-regulated protein kinases (ERK1/ERK2) and down-regulation of c-Jun N-terminal kinase 1(JNK1) in response to environmental stress signals. Gamma-synuclein is found in a wide variety of transformed cells and its overexpression leads to a significant increase in proliferation, motility, invasiveness and metastasis. Cells expressing gamma-synuclein are significantly more resistant to the chemotherapeutic drugs paclitaxel and vinblastine as compared with the parental cells. Activation of JNK1 and its downstream caspase-3 by paclitaxel or vinblastine is significantly down-regulated in gamma-synuclein-expressing cells, indicating that the apoptosis pathway activated by vinblastine or paclitaxel is blocked by gamma-synuclein. In breast cancer cells, SNCG has been shown to act as a chaperon for estrogen receptor and stimulate estrogen receptor-a signaling pathway that leads to cell proliferation. On the other hand, the inhibitory effects of SNCG on mitotic checkpoint function are mediated through the mitotic checkpoint kinase BubR1 and are independent of the expression status of estrogen receptor-alpha. The inhibitory effects of SNCG on mitotic checkpoint can be overthrown by enforced overexpression of BubR1 in SNCG-expressing cells. SNCG intracellularly associates with BubR1 together. This observation suggests that SNCG expression compromises the mitotic checkpoint control by inhibition of the normal function of BubR1, thereby promoting genetic instability, a recognized and important contributing factor in tumorigenesis. Because all synucleins have chaperone-like activities, they may interact with different proteins in different cellular background. Identifications of specific cellular targets of SNCG in different tumor types will provide insight to delineate its oncogenic functions in human malignancies.

Breast cancer

Note

Patients whose tumors expressed SNCG had a significantly shorter disease-free survival and overall survival. They also had a high probability of death when compared with those whose tumors did not express SNCG. Multivariate analysis demonstrated that SNCG is an independent predictive marker for recurrence and metastasis in breast cancer progression. SNCG is expected to be a useful marker for breast cancer progression and a potential target for breast cancer treatment. In one study it has been show that responses of 12 breast cancer cell lines to paclitaxel-induced mitotic arrest and cytotoxicity highly correlated with SNCG expression status. SNCG-positive cells exhibited a significantly higher resistance to paclitaxel-induced mitotic arrest than SNCG-negative cells. Down-regulation of SNCG expression directly increased the effectiveness of anti-microtubule drug-induced cytotoxicity in breast cancer cells without altering cell responses to doxorubicin. These new findings suggest that SNCG expression in breast carcinomas is probably a causal factor contributing to the poor patient response to paclitaxel treatment.

Ovarian cancer

Note

Several studies indicated that SNCG expression was not detectable in normal ovarian epithelium but was highly expressed in the vast majority of advanced staged ovarian carcinomas. Eighty-seven percent of ovarian carcinomas were found to express at least 1 type of synuclein, and 42% expressed all 3 synucleins (alpha, beta, and gamma) simultaneously. Highly punctate gamma synuclein expression was also observed in 20% of preneoplastic lesions of the ovary, including epithelial inclusion cysts, hyperplastic epithelium, and papillary structures, suggesting that synuclein gamma up-regulation may occur early in the development of some ovarian tumors. Demethylation is an important event in abnormal synuclein-gamma expression. The methylation pattern in ovarian cancer cells is different from that in breast cancer cells. In one of the studies that examined SNCG-nonexpressing ovarian cancer cells, all of the CpG sites were completely methylated instead of selective methylation at certain sites shown in breast cancer cells, thereby suggesting a tissue-specific methylation pattern. Recent studies indicated that the detection of SNCG mRNA in tumor-positive tumors was strongly associated with demethylation or hypometylation of SNCG gene. Methylation status was not correlated with FIGO stage or histological type of tumor. Tumor grading was strongly associated with

methylation status but due to relatively small group of studied samples (43 cases) this observation requires further confirmation.
Another interesting observation was that in 21% of samples both products of amplification were present and all these cases were SNCG mRNA-positive.
This observation could suggested that partial methylation of SNCG probably does not influence on synuclein expression in ovarian cancer tissue.
Comparison of the methylation status of SNCG and the expression of synuclein-gamma in breast and ovarian cancer cells lines in another study indicated a strong correlation between hypomethylation of the CpG island and SNCG expression in cancer cell lines.
The methylation pattern in ovarian cancer cells was different from that in breast cancer cells.
The analyzed CpG sites in ovarian cancer cells were all methylated in contrary to a selective methylation at certain sites shown in breast cancer cells, thereby suggesting a tissue-specific methylation pattern. Moreover, when exon 1 was partially and heterogeneously methylated, then SNCG expression in breast cancer cells was not detected.

Lung cancer

Note

SNCG is not expressed in normal lung tissues, but it is highly expressed in lung tumors. It has been demonstrated that cigarette smoke extract (CSE) has strong inducing effects on SNCG gene expression in lung cancer cells through demethylation of SNCG CpG island. CSE treatment also augments the invasive capacity of cells in an SNCG-dependent manner. These new findings demonstrate that tobacco exposure induces the abnormal expression of SNCG in lung cancer cells through downregulation of expression levels of DNA methyltransferases.

Gastric cancer

Note

For the gastric cancer cell lines, SNCG mRNA expression strongly correlated with demethylation of SNCG exon 1 CpG islands. Whereas SNCG was not expressed in non-neoplastic gastric mucosal tissues obtained at autopsy, partial demethylation was present in these tissues. Demethylation occurs before malignant transformation and that only partial demethylation does not result in up-regulated SNCG mRNA expression. Thus, it appears that partial SNCG demethylation can occur in normal gastric mucosa, which then extends in some cases to become to fully demethylated, resulting in up-regulated SNCG mRNA expression.

Esophageal cancer

Note

The examination of the serum γ-synuclein levels of patients with gastrointestinal and esophageal squamous cell carcinomas, benign disease and healthy controls by a sandwich ELISA demonstrated a positive correlation between serum γ-synuclein and the development of these types of cancer. From this study a conclusions was put forward that serum γ-synuclein is a promising diagnostic biomarker for early detection of gastrointestinal and esophageal cancer. Serum γ-synuclein SNCG may play an important role in invasion, infiltration and apoptosis of esophageal cancer and serve as target spots in the targeted therapy of esophageal cancer. However, the analysis of expression pattern of SNCG in another study including 27 cases of esophageal cancer (ESC) demonstrated that it is downregulated in 16 out of 27 cases of ESC. Overexpression of SNCG in ESC 9706 cell line has shown that the ectopic expression of SNCG in ESC cell line inhibits cell growth in dish and colony formation in soft agar. Therefore, unlike breast and ovarian cancers, a reversed correlation between SNCG expression and ESC development was found, which led to a hypothesis that SNCG may play a role of a tumor suppressor in the development of human ESC.

Prostate cancer

Note

A strong association between SNCG expression and prostate cancer development is found. By performing genomic sequencing and methylation-specific PCR assays, an inclusive demethylation of CpG sites within the CpG island of SNCG gene in prostate cancer samples was established. These results suggest a loss of the epigenetic control of SNCG gene expression in tumors and demonstrate that the demethylation of SNCG CpG island is primarily responsible for the aberrant expression of SNCG in prostate cancerous tissues. A conclusion is drawn that that reactivation of SNCG gene expression by DNA demethylation is a common critical contributing factor to malignant progression of tumors and its expression in primary carcinomas is an effective molecular indicator of distant metastasis. Therefore, the methylation status of SNCG gene can be used as a sensitive molecular tool in early detections of tumorigenesis. Silencing SNCG by siRNA in LNCaP cells contributes to the inhibition of cellular proliferation, the induction of cell-cycle arrest at the G1 phase, the suppression of cellular migration and invasion in vitro, as well as the decrease of tumor growth in vivo with the notable exception of castrated mice. SNCG is a novel androgen receptor (AR) coactivator.

It interacts with AR and promotes prostate cancer cellular growth and proliferation by activating AR transcription in an androgen-dependent manner.

Endometrial cancer

Note

SNCG expression is associated with poor outcome in endometrial adenocarcinoma. There is a positive association between SNCG expression and tumor grade, tumor stage, type II carcinomas, deep myometrial invasion and lymphovascular invasion. A correlation between SNCG and adverse outcomes, such as shorter overall survival and disease free survival is found.

The expression level of SNCG in endometrioid endometrial carcinoma is closely associated with International Federation of Gynecology and Obstetrics (IFGO) stages, the depth of myometrial invasion and lymph nodes metastases (p

SNCG is considered a useful marker for endometrioid endometrial carcinoma invasion, metastasis and prognosis in endometrioid endometrial carcinoma.

Gallbladder cancer

Note

SNCG is highly expressed in human gallbladder cancer, and its abnormal expression is associated with tumor aggressiveness. SNCG gene silencing in NOZ cells inhibited cell growth, colony formation, and invasion. In addition, it directly increased the effectiveness of paclitaxel in inducing G2/M cell-cycle arrest and cell apoptosis. A decrease in tumor growth and weight was found in mice injected with SNCG-silenced NOZ cells. Together, these findings suggest that SNCG plays an important role in the progression of human gallbladder cancer.

Colon cancer

Note

Abnormal expression of SNCG protein has been demonstrated in colon cancer. SNCG predicts poor clinical outcome in colon cancer with normal levels of carcinoembryonic antigen (CEA). SNCG levels in colon adenocarcinoma were closely associated with intravascular embolus and tumor recurrence but independent of preoperative serum CEA levels. SNCG expression was an independent prognostic factor of a shorter disease-free survival and overall survival ($P < 0.0001$). SNCG is a new independent predicator for poor prognosis in patients with colon adenocarcinoma, including those with normal CEA levels. Combination of CEA with SNCG improves prognostic evaluation for patients with colon adenocarcinoma.

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