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Gene Section
Review

GPX3 (Glutathione peroxidase 3)

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Abstract

Review on GPX3, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
GPX3; Glutathione peroxidase 3

Identity

Other names: GPX-P, GSHPX-3, GSHPX-P

HGNC (Hugo): GPX3

Location: 5q33.1

DNA/RNA

Transcription

Human GPx3 gene is transcribed to the GPx3 transcript of 1779 bp (NM_002084), consisting of exon 1 (1-304 bp), exon 2 (305-458), exon 3 (459-576), exon 4 (577-676), and exon 5 (677-1761).

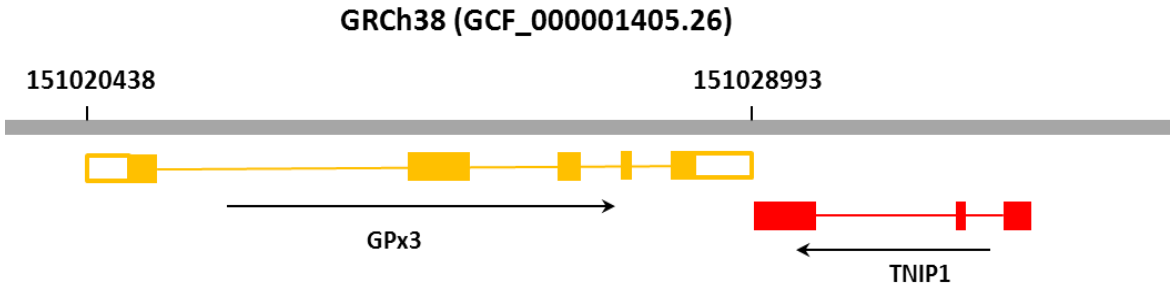
The coding DNA sequence (CDS) 218..898 bp, encodes for a protein of 226 aa, comprising a leading signal peptide sequence at 218..277 bp followed by the main coding sequence for GPx3. An OPAL codon (TGA) at 434-436 bp is translated to a Selenocycteine (Chambers et al. 1986; Fu et al. 2002; Fu et al. 2002).

Pseudogene

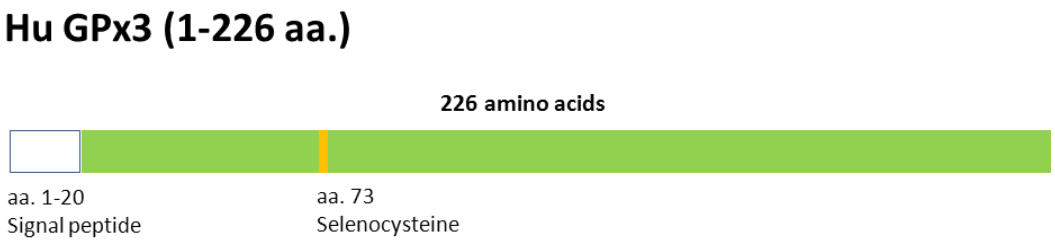
Unknown.

Description

Plasma glutathione peroxidase 3 is a member of glutathione peroxidase family, and is the only secretary glutathione peroxidase, accounting for the all glutatione peroxidase in extracellular compartment. Structurally, intracellular GPx3 has a leading signal peptide. GPx3, similar to other selenoproteins, contains a UGA OPAL codon at codon 73, which is coded for a selenocystein residue in the presence of selenium.



The human GPx3 gene is located at the forward strand of chromosome 5 in the region between 151,020,438 to 151,028,993 bps (GRCh38), comprising 5 exons and adjacent to TNIP1 gene. There are 10 to 11 variant transcripts of GPx3, but only 7 are processed as proteins, according Ensemble Genome Browser database (ENSG00000211445), of which only one with known function (NCBI database).



Protein

Expression

GPx3 is a plasma glutathione peroxidase, being secreted to extracellular compartment after synthesized in cells. GPx3 mRNA is expressed in different tissues, lung, heart, breast, prostate, placenta,and kidney. But majority (almost 70%) of plasma GPx3 is thought kidney originated(Avissar et al. 1994; Tham et al. 1998). GPx3 is transported through circulation and binds to the basement membrane of epithelia of GI (Burk et al. 2011). GPx3 mRNA is detected in a variety of tissues, while most of them are not joining in the plasma GPx3(Chu et al. 1992; Maeda et al. 1997; Tham, Whitin et al. 1998), implicating the unknown function of GPx3 in other tissues or organs.

Function

Glutathione peroxydase 3, as other tetrameric GPx enzymes using reduced glutatione as electron donor, catalyses the oxydation of reduced glutathione and the simultaneous reduction of a variety of hydrogen peroxide and organoperoxides. As a result, the GPx3 functions in the system to relieve oxidative stress as an antioxidant enzyme. The catalytic residues in GPx3 have been mapped to the location of U73, Q107 and W181(Ren et al. 1997). U73 codes for selenocycteine, a residue that is involved in the reduction of hydrogen peroxide in a catalytic cycle of its atom, from reduced selenolate anion (R-se) to oxidized selenic acid (R-Se-OH). Latter regenerates selenolate anion by GSH. In physiological PH, selenole forms anion, a good reducing source in the system(Ren, Huang et al. 1997). However, electron donor GSH is limited in the extracellular space, implicating a rate limiting factor in the antioxidative function of GPx3. Conserved domain analysis classifies glutathione peroxidase as thioredoxin-like-superfamily protein (Conserved domains database[gi|6006001|ref|NP_002075|]).
In recent studies, GPx3 protein expression was found in a variety of normal tissues or cells, while down-regulated in a number of cancers.

Through Yeast Two-Hybrid analyses, GPx3 was found interacting with several proteins in cells. One of such proteins is a TP53 transactivated protein, PIG3, which positively regulates apoptosis and mediates UV-induced cell death. The interaction between GPx3 and PIG3 leads to apoptotic cell death. GPx3 with mutated OPAL codon retains its capabilities in promoting cell death, suggesting that GPx3 contains pro-apoptotic activity independent of its peroxidase function(Wang et al. 2012).

Homology

Glutathion peroxidase activity of GPx3 is conserved in other seven GPx selenocysteine containing proteins. Though encoded from different genes, all contain a common UGA OPAL codon, encoding a selenocysteine residue in coding region, an active site of enzyme activity(Tosatto et al. 2008). GPx3 sequence, if excluding signal peptide, has the highest homology (84%) and identities (72%) with GPx5 encompassing 200 out of 226 aa in the coding region; while 60% homology with GPx1, GPx2 ; but low, 46-47% with GPx4,6,7,and 8.
GPx3 is expressed in other species. Human GPx3 shares sequece homology (94%) and identities (89%) with mouse GPx3 over 226 aa including signal peptide sequence; 95-96% homology and 91-92% identities with rat(NP_071970.2)and dog (NP_001157926.1) of full coding region, but is of only limited homology to GPx3 in Xenopus Laevis (NP_001085319.2)and Zebra fish (NP_001131027.1).

Mutations

Note
Not known.

Cancer cell lines or primary tumor	Down-regulation	Methylation
HNSCC	6/10	7/10
Lung cancer		
NSLC	2/6	-
SLC	4/7	-
Adenocarcinoma	2/6	-
Melanoma	3/6	-
Ovarian cancer	4/9	3/8
Bladder cancer	6/7	5/6
Esophageal cancer	2/4	-
Breast cancer	-	4/8
Prostate cancer	3/3	3/3

*down-regulated or methylated cell lines/total tested cell lines

Expression and methylation of GPx3 gene in multiple cancer cell lines(Yu et al. 2004; Yu, Yu et al. 2007; Chen, Rao et al. 2011)

Implicated in

Prostate cancer

Oncogenesis

Silencing of GPx3 gene with hypermethylation of GPx3 promoter was first found in a microarray study of three prostate cancer cell lines, in which treated with 5-aza-2' deoxycytidine, GPx3 expression was induced in these cells originally silenced in GPx3 (Lodygin et al. 2005). GPx3 down-regulation was subsequently confirmed in several gene expression-array analyses of a large number of human prostate cancer specimens with high rate of occurrence (LaTulippe et al. 2002; Luo et al. 2002; Yu, Landsittel et al. 2004; Yu, Yu et al. 2007). Complete inactivation of GPx3 was closely correlated with the poor clinical outcome of prostate cancer. Hemizygous and homozygous deletion of GPx3 gene occurs in a subset of prostate cancer samples(39%). CpG island hypermethylation in GPx3 promoter occurs in over 90% of prostate cancer samples (Lodygin, Epanchintsev et al. 2005; Yu, Yu et al. 2007). The frequent CpG hypermethylation in GPx3 in cancer suggests that hypermethylation plays a significant role in GPx3 down-regulation in cells. Down-regulation of GPx3 increases these cell's vulnerability to oxidative damages. Conditions predisposed to prostate cancer, such as high animal fat diet in TRAM mice and loss of tumor suppressor Nkx3.1, has been found accompanied with decrease in GPx3 expression in animal (Chang et al. 2014), (Ouyang et al. 2005).

Cervical cancer

Oncogenesis

GPx3 is down-regulated in cervical cancer tissues when compared with normal cervical tissues, and the down-regulation is closely correlated to lymph node metastasis and prognosis in cervical cancer patients. Promoter methylation is the major cause of GPX3 down-regulation(Zhang et al. 2014).

Esophageal squamous cell carcinoma(ESCC) and Barrett's adenocarcinomas (BA)

Oncogenesis

Down-regulation of GPx3 expression in ESCC was revealed in a DNA micro-array study and GPx3 gene methylation was indicated by demethylation treatment of ESCC tissues with 5-aza-2'-deoxycytidine, where GPx3 expression was restored in 71.4% of tumor samples and 10.7% of adjacent normal tissues(He et al. 2011). The GPx3 gene methylation was significantly correlated with the downregulation of GPx3 mRNAs in tumors.

In Barrett's adenocarcinomas (BA), quantitative RT-PCR revealed 91% of tumor samples with reduced levels of GPx3 mRNA. Similarly, GPx3 promoter hypermethylation was detected in 88% of BA samples with the mostly bi-alleles hypermethylation(Lee et al. 2005; Peng et al. 2009).

Gastric cancer

Oncogenesis

Down-regulation of GPx3 expression in gastric cancer was identified in gastric cancer tissues, which displayed a high occurrence rate of 8/9 cancer cell lines, and 83% (90/108) of gastric cancer samples. Hypermethylation of GPx3 promoter in 6 out of 9 cancer cell lines and 60% of gastric cancer samples significantly contributed to the silencing of GPx3 gene(Zhang, Yang et al. 2010; Peng et al. 2012), although loss of copy number of GPx3 gene was also detected in the cancer samples. Silencing of GPx3 was correlated to the lymph node metastasis of gastric cancer and was also detected in the adjacent normal gastric tissue samples, suggestive of cancer field effects in gastric tract. In addition, a study

showed that two intronic SNPs in GPx3 significantly altered gene expression, a possible link to the increasing risks of gastric cancer (Wang et al. 2010). Wound healing analyses showed that retoring GPx3 expression in cells decreased cell motility, a possible feature involved in cancer metastasis.

Breast cancer

Oncogenesis

Down-regulation of GPX3 expression in breast cancer was identified through immunohistochemistry (IHC) analyses of breast cancer samples by comparing with the normal tissues. The inflammatory breast cancer (IBC), with higher frequency of GPx3 promoter methylation, had GPx3 expression significantly lower than those in non-inflammatory breast cancer (non-IBC)(Mohamed et al. 2014).

Ovarian carcinoma

Oncogenesis

Similar to breast cancer, abberation of GPx3 expression in ovarian cancer distinguishes cancer stage and cell type of ovarian cancer ; Decreased levels of serous glutathione peroxidase 3 were associated with late stages of papillary serous ovarian cancer or disease progression(Lau et al. 2014), while clear cell subtype showed elevated GPx3 expression(Hough et al. 2001).

Colorectal Carcinoma

Oncogenesis

Tumor suppression of GPx3 in the inflammatory colonic tumorigenesis (colitis associated carcinoma) model was suggested in the GPx3-knockout mice as the manifestation of the increased number of tumor with higher degree of dysplasia in colon. Knockdown of GPx3 in the colon cancer cell line resulted in increase of inflammation, proliferation, DNA damage and apoptosis following the exposure to oxidative stress (Barrett et al. 2013). Genotype analyses of three SNPs in GPx3 indicates that the genetic variations in GPx3 contribute to the risk of rectal cancer (Haug et al. 2012)

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