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Gene Section
Review

GPC1 (glypican 1)

Wael Awad, Derek T Logan, Katrin Mani

Dept. of Biochemistry & Structural Biology, Lund University, Box 124, S-221 00 Lund, Sweden (WA, DTL), Glycobiology, Dept. of Experimental Medical Science, BMC A13, S-221 84 Lund, Sweden (KM)

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Abstract

Review on GPC1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: glypican

HGNC (Hugo): GPC1

Location: 2q37.3

DNA/RNA

Description

The gene spans 32381 pb of DNA, comprising 9 exons.

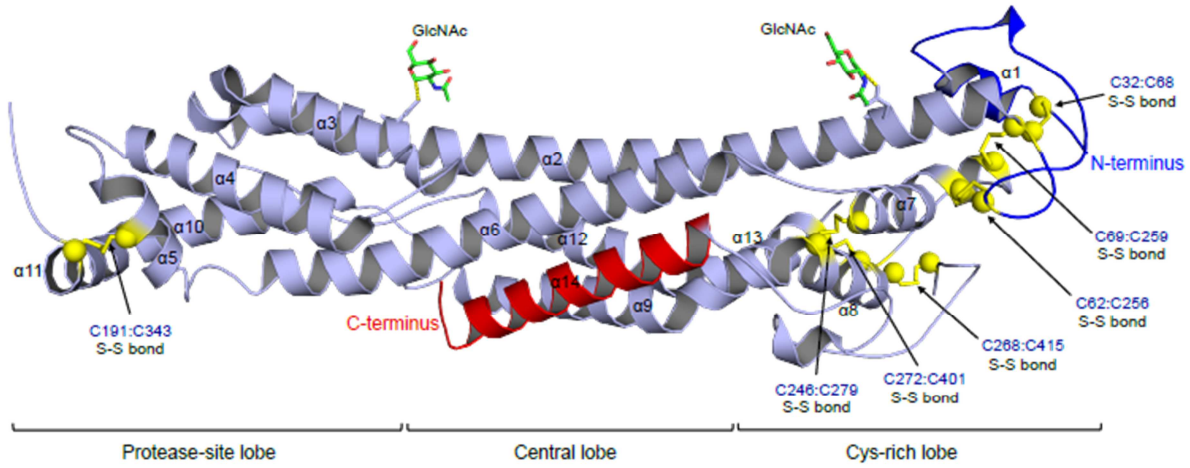
Transcription

1676 bp open reading frame.

Protein

Description

The glypican-1 gene codes for a protein of 558 amino acids with a predicted molecular weight of 62 kDa. It is a cell surface, lipid-raft-associated heparan sulfate proteoglycan (HSPG), composed of a glycosylphosphatidylinositol (GPI)-anchored core protein substituted with a three chains of heparan sulfate near its C-terminus. It shares, along with all other glypicans, an N-terminal secretory signal, heparan sulfate attachment sites, 14 evolutionary conserved cysteine residues and hydrophobic domain near the C-terminus for the addition of the glycosylphosphatidylinositol (GPI) anchor. Also, the glypican-1 core protein contains two N-glycosylation sites at Asn79 & Asn116, which are found to be invariably occupied. The N-linked glycans at these sites affect Gpc-1 protein expression and heparan sulfate substitution. Nevertheless the protein is folded correctly even in the absence of N-linked glycans (Svensson et al., 2011). Recently, the structure of C-terminally truncated human N-glycosylated Gpc-1 core protein was determined at 2.55 Å resolution (Svensson et al., 2012; Awad et al., 2013), which revealed a highly extended, cylindrical (dimensions 120 x 30 x 30 Å), stable all-α-helical fold. Its structural similarity to the Dally-like protein from Drosophila (Kim et al., 2011) confirmed a conserved overall fold for the glypican family. The Gpc-1 structure consists of 14 α-helices (α1- α14) and three major loops (L1-L3). The extended helix α2 (83Å) traverses the whole protein, carrying two N-linked glycans close to its ends. The Gpc-1 structure revealed the complete arrangement of the 14 Cys residues conserved across the glypican family, in 7 disulfide bonds, 6 of them located near the molecule N terminus at a region termed "Cys-rich lobe". This lobe is followed by a region forms the heart of the structure called the "central lobe". This lobe is stabilized by evolutionary conserved hydrophobic centers. The last region of the Gpc-1 molecule is termed the "protease site lobe" because of the presence of a protease site in this part. No additional electron density was observed in the electron density maps from crystals of non-truncated glypican-1 containing the HS attachment region near the C-terminus, which suggests that this part is highly disordered. This extended long C terminus (50 residues) might thus give the core protein a freedom in its orientation when Gpc-1 is anchored to the cell membrane (Svensson et al., 2012).



Crystal structure of the N-glycosylated human Gpc-1 core protein (PDB entry 4ACR). Cartoon diagram of Gpc-1 in which the body of the structure is coloured light blue, the N-terminal helix and loop in dark blue and the C-terminal helix in red. Important loops (L1:L3) and all of the α-helices (α1:α14) are labelled. The seven disulphide bonds common to all glypicans are indicated in yellow. The assignment of different lobes in the Gpc-1 structure (Svensson et al., 2011) is displayed on the bottom line.

Expression

GPC1 is expressed mainly in the central nervous system (CNS) and skeletal system during development but also in many other tissues in the adult.

Localisation

GPC1 is a cell surface HSPG that can be internalized via a caveolin-1 associated pathway. GPC1 undergoes a recycling from cell surface to endosomes and back to the cell surface via Golgi. During recycling, the HS chains of GPC1 are degraded by heparanase and further on by a novel copper, nitric oxide and vitamin C-dependent deaminative cleavage. New HS chains are synthesized on the stubs remaining on the core protein (Cheng et al., 2002; Fransson and Mani, 2007).

Function

Many of the functions of GPC1 are dependent on the HS side chains, which are capable of binding and/or activating and/or transporting a variety of growth factors (FGF2), cytokines, enzymes, viral proteins, and polyamines. It is known that both the core protein and the HS chains of GPC1 are important for brain function, as knock-out of GPC1 gene expression results in reduction of brain size by 30% (Jen et al., 2009) and errors in HS metabolism result in neurodegeneration and mental retardation accompanied by accumulation of amyloid β in human brain (Ohmi et al., 2011). A role for GPC1 in axonal guidance and regeneration via Slit has been proposed (Bloechlinger et al., 2004; Lau and Margolis, 2010). Several studies indicate involvement of Gpc1 in prion conversion and scrapie infection (Löfgren et al., 2008; Taylor et al., 2009; Hooper, 2011).

Homology

GPC1 belongs to the glypican family. To date, six different glypicans have been identified in vertebrates (GPC1, GPC2, GPC3, GPC4, GPC5, and GPC6), two in Drosophila melanogaster (Dally and Dally-like protein), two in C. elegans (Gpn-1 and Lon-2) and one in zebrafish (knypek). Based on sequence comparisons, vertebrate glypicans fall into two subfamilies: glypicans 1, 2, 4, 6 and glypicans 3 and 5, with approximately 25% amino acid identity between the groups.

Implicated in

Various cancers

Note

Many studies have shown that GPC1 is crucial for efficient cancer cell growth, metastasis, and angiogenesis of many human and mouse cancer cell types (Ding et al., 2005; Kayed et al., 2006; Aikawa et al., 2008; Whipple et al., 2012). GPC1 is up-regulated in human cancer cells such as glioma, pancreatic and breast cancers and supports and maintains the mitogenic effect of several HS-binding growth factors (Matsuda et al., 2001; Kayed et al., 2006; Su et al., 2006). Downregulation of GPC1 results in prolonged doubling times and decreased growth of cancer cells in vitro, as well as attenuated tumor growth, angiogenesis, and metastasis in vivo.

Neurodegenerative diseases

Note

A number of studies indicate involvement of GPC1 in the pathogenesis of several neurodegenerative diseases including Alzheimer's disease (van Horssen et al., 2001; Watanabe et al., 2004; Cappai

et al., 2005; O'Callaghan et al., 2008; Timmer et al., 2009; Cheng et al., 2011), prion disease (Cheng et al., 2006; Löfgren et al., 2008; Taylor et al., 2009; Hooper, 2011), and Niemann-Pick type C1 disease (Mani et al., 2006). GPC1 has been localized to the amyloid plaques of Alzheimer's disease. Both nitric oxide- and heparanase-induced degraded GPC1 HS have found to be associated with amyloid deposits, including the toxic amyloid β peptide aggregates in brain of human Alzheimer's patients and transgenic Alzheimer's mice (Sandwall et al., 2010; Cheng et al., 2011). Further, it has been shown that the HS oligosaccharides released from GPC1 by Cu/NO-vitamin C form conjugates with amyloid β peptides, thereby modulating and suppressing oligomerization of amyloid β and dissolving toxic amyloid β oligomers in hippocampal slices from Alzheimer's mice (Cheng et al., 2011). Other studies have shown that amyloid β toxicity is attenuated in cells overexpressing heparanase, suggesting that HS oligosaccharides generated by cleavage with heparanase could also have a protective effect (Sandwall et al., 2010; Zhang et al., 2012).

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