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Gene Section
Review

GBP1 (guanylate binding protein 1, interferon-inducible, 67kDa)

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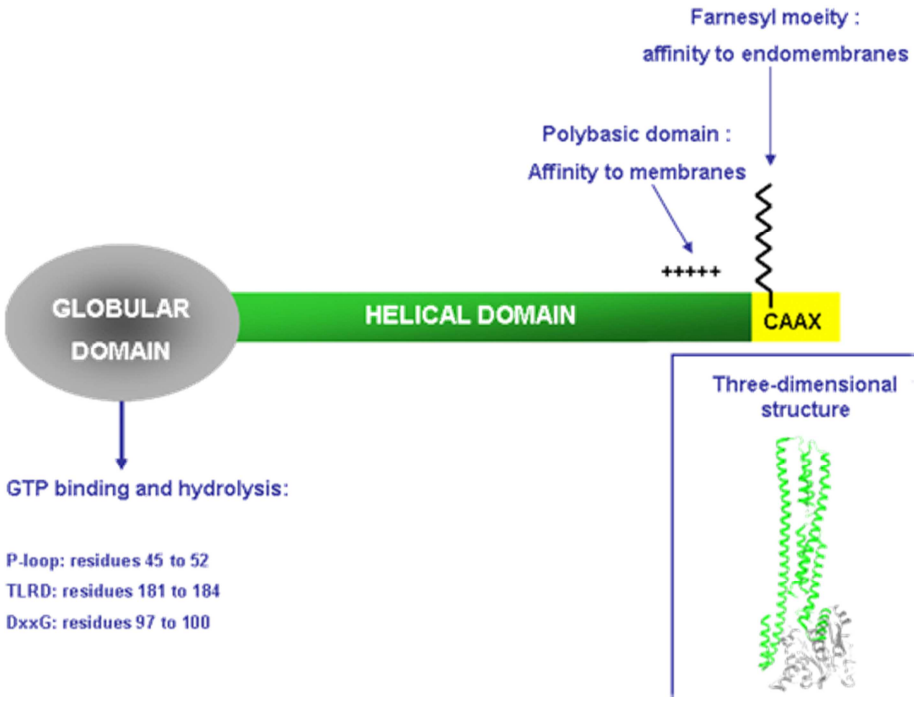
Identity

Other names: GBP-1; HuGBP-1

HGNC (Hugo): GBP1

Location: 1p22.2

Local order: Chromosome 1; starts at 89,290,575 bp from pter and ends 89,303,631 bp from pter;
size= 13,056 base pairs;
orientation: minus strand (according to hg18-Mar_2006).
The family of guanylate binding proteins (GBP) consists of 7 members.
All seven genes are located in 1p22.2.
The human GBP1 gene is telomeric to GBP2 and centromeric to GBP3.



A schematic representation of the domain structure and the three-dimensional structure of GBP-1. GBP-1 consists of a globular domain (residues 1 to 278), which contains the GTP binding and hydrolysis domains, and of a helical domain (residues 279 to 593) terminated by a polybasic sequence and an isoprenylation motif (CAAX). C= Cysteine, A= aliphatic acid, X= any amino-acid (here a serine, specifically recognized by a farnesyl-transferase).

DNA/RNA

Description

The GBP1 gene consists of 11 exons (ranging from 102 to 1164 bp) and 10 introns. The coding sequence starts in the second exon.

Transcription

Only one variant mRNA has been described for GBP-1 (Accession Number: NM_002053). This mRNA is 3050 bp long with a coding sequence of 1779 bp. Four polymorphisms have been described for GBP-1: c.232A>G (codon 78 Ile>Val), c.498G>C (codon 166 Glu>Asp), c.1046C>G (codon 349 Thr>Ser), c.1226C>G (codon 409 Ala>Gly).

Pseudogene

A pseudogene has been identified for GBP1 (LOC400759 alias FLJ17004) on chromosome 1 (1p22.2, chro 1: 89645826-89663081, according to hg18-Mar_2006). Two pseudogenes have also been described in the mouse (pseudomGbp1 and pseudomGbp2).

Protein

Description

GBP-1 belongs to the class of large GTPases that contains, in addition to the GBPs, three further groups of proteins, which share structural and biochemical properties: the dynamins, the Mx proteins and the atlastins. GBP-1 has a molecular weight of 67 kDa and its crystal structure has revealed the presence of two domains: (1) a N-terminal globular alpha/beta domain harbouring the GTPase activity and (2) a long C-terminal part organized in an index finger-like domain composed exclusively of seven alpha-helices (alpha7 - alpha13). The domains are connected by a short intermediate region consisting of one alpha-helix and a short two-stranded beta-sheet. In addition, GBP-1 harbours a C-terminal CAAX isoprenylation motif. GTPases typically harbour three classical GTP-binding domains: the phosphate-binding P-loop GXXXXGK(S/T), the phosphate- and Mg^{2+}-binding DXXG motif (G, glycine; K, lysine; S, serine; D, aspartic acid; T, threonine; and X, any amino acid) and the guanine nucleotide-specificity providing (N/T)KXD motif (N, asparagine). In GBP-1 the classical (N/T)KXD motif is substituted by a conserved arginine-aspartic acid (RD)-motif (TLRD, with L, leucine and R, arginine).

Expression

GBP-1 was initially shown to be among the most highly induced proteins in human fibroblasts exposed to interferon (IFN)-gamma. Subsequently, it was reported that in vitro hGBP-1 expression can be induced by IFN-gamma in many different cell types including endothelial cells, fibroblasts, keratinocytes, B-cells, T-cells or peripheral blood mononuclear cells. In vivo expression of hGBP-1 has been predominantly detected in inflammatory tissues and has been found to be associated almost exclusively with endothelial cells and monocytes. It has been shown subsequently that hGBP-1 expression in endothelial cells is also induced by other pro-inflammatory cytokines such as IFNalpha, TNFalpha and IL1alpha/IL1beta. Many other cytokines (IL-4, IL-6, IL-10, IL-18), chemokines (MCP-1, PF4) or growth factors (angiopoietin-2, PDGF B/B) tested did not affect GBP-1 expression in these cells. Interestingly, the two major angiogenic growth factors (AGF: bFGF, VEGF) are able to inhibit the expression of GBP-1 induced by inflammatory cytokines.

Localisation

The localization of GBP-1 is primarily cytosolic and its distribution is granular. Plasma membrane association at the level of tight junctions has also been described. In addition, GBP-1 has been shown to be secreted from IFN-gamma-stimulated endothelial cells through a non-classical secretion pathway.

Function

GTPase activity.

GBP-1 can bind the three nucleotides GTP, GDP and GMP with a relative low affinity ($Kd_{mant\text{-}GMP}$=0,53 µM, $Kd_{mant\text{-}GDP}$=2,4 µM, $K_{dmant\text{-}GppNHp}$=1,1 µM). GBP-1 has however the ability to hydrolyse GTP to both GDP and GMP with a high hydrolysis rate (max 95 min^{-1}). At physiological temperature GMP is the major product (90%) of hGBP1. On the contrary to small GTPases like Ras, GBP-1 does not require the presence of GEF (GTP exchange factor) or GAP (GTPase activating protein) proteins for its GTPase activity. In the case of GBP-1, the GTP hydrolysis is self-stimulated by oligomerization of the protein.

GBP-1 is involved in IFN-gamma response, either in infection or in inflammation.

Homology

The human GBP family comprises 7 highly homologous members, all located on the chromosome 1. GBP-1 is to 77% similar to GBP-2, 88% to GBP-3, 56% to GBP-4, 68% to GBP-5, 54% to GBP-6 and 56% to GBP-7. Homologues have been found in various species like zebrafish, chimpanzee (99% homology), rat, dog or mouse. GBP-1 shares 59% of homology with murine GBP-1 and murine GBP-2.

Mutations

Note

No somatic or germline mutations have yet been reported for human GBP-1.

Implicated in

Infection

Note

GBP-1 exhibits antiviral activity against vesicular stomatitis virus and encephalomyocarditis virus. The

expression of GBP-1 is also elevated in the blood of patients with a chronic active Epstein-Barr virus infection. Furthermore GBP-1 and GBP-2 can potentiate the inhibitory effects of IFN-gamma on Chlamydia trachomatis growth. Finally, elevated concentrations of GBP-1 have been detected in the cerebrospinal fluid of patients with bacterial meningitis.

Inflammation

Note

As GBP-1 is mainly expressed in endothelial cells in vivo in a context of inflammation, its effects have been extensively studied in these cells. It has been showed in endothelial cells that GBP-1 mediates the effects of inflammatory cytokines and inhibits proliferation, spreading, migration or invasion. GBP-1 is also involved in the regulation of apoptosis and senescence in endothelial cells stimulated with IFN-alpha. Evidence for an implication in cancer has been found for GBP-1 (see below).

Colorectal carcinomas

Note

GBP-1 protein is strongly expressed in the stroma of about one third of colorectal carcinomas in association with an IFN-gamma dominated Th-1-like angiostatic immune response.

Prognosis

This expression correlates with an increased cancer-related 5-year survival.

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