

## Gene Section

### Mini Review

# GRB10 (growth factor receptor-bound protein 10)

Sébastien Degot

I.G.B.M.C., BP 163, 1 rue Laurent Fries, 67404 Illkirch, France

Published in Atlas Database: August 2002

Online updated version : <http://AtlasGeneticsOncology.org/Genes/GRB10ID278.html>

DOI: 10.4267/2042/37919

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.

© 2003 Atlas of Genetics and Cytogenetics in Oncology and Haematology

## Identity

**Other names:** RSS; IRBP; Grb-IR; MEG-1

**HGNC (Hugo):** GRB10

**Location:** 7p12-11.2

**Local order:** Between two potential genes LOC221982 (in telomeric position) and LOC222987 (in centromeric position).

## DNA/RNA

### Description

At least 16 exons spanning approximately 50 kb.

### Transcription

Four splicing variants are known for human Grb10 gene:

- hGrb10 beta alias Grb-IR (accession number U34355)

- hGrb10 gamma alias Grb10/IR-SV1 or hGrb-IRbeta/hGrb10

- hGrb10 epsilon alias KIAA0207 (accession number D86962)

- hGrb10 zeta alias hGrb10 gamma.

This nomenclature is a new nomenclature for Grb10 splice variants that was agreed by several researchers.

Grb10 gene has a broad expression profile with different size of transcripts depending on the isoforms. Moreover, Grb10 is imprinted in a highly isoform- and tissue-specific manner.

## Protein

### Description

- Isoform beta: 548 aa, 62 kDa (aa: amino acids)

- Isoform gamma: 536 aa, 61 kDa

- Isoform epsilon: 588 aa, 66 kDa

- Isoform zeta: 594 aa, 67 kDa

The different splice variants share a similar structure with:

- A small proline-rich sequence (11 aa) close to the amino-terminus that can interact with SH3 domain of c-Abl in vitro (domain named Pro on the figure above);

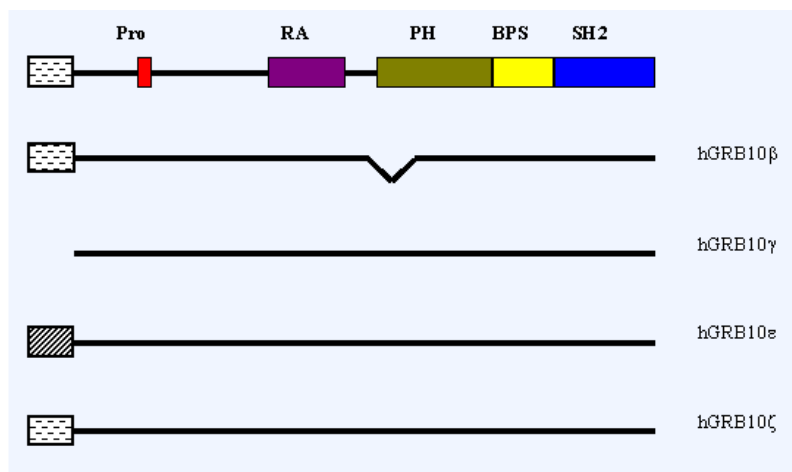
- A Ras-associated-like domain (84 aa) homologous to the *C. elegans* MIG-10 protein raising the possibility that Grb10 could directly interact with Ras-like GTP-binding protein (domain named RA on the figure above);

- A central Pleckstrin homology domain of 124 aa except for the isoform alpha which contains only 85 aa (domain named PH on the figure above). This domain was proposed to play an important role in targeting Grb10 to the mitochondria.

- The BPS (Between PH and SH2) domain is composed of 48 aa and binds to the activated insulin and/or IGF-1 receptors;

- An SH2 domain (104 aa) which interacts with phosphotyrosine of several proteins.

- PH domain, BPS domain and SH2 domain compose a region of 300 aa termed GM (Grb/Mig). Grb10 is able to dimerize/oligomerize through interaction between the N-terminal domain of one molecule and the GM region of another one.



### Expression

Grb10 protein has been detected in most human cell lines using a highly specific antibody.

### Localisation

Most of the endogenous Grb10 is peripherally associated with the mitochondria where it interacts with pools of Raf-1. Treatment with serum or IGF-I is able to induce the relocalization of a small proportion of the endogenous Grb10 to the plasma membrane.

### Function

Grb10 is able to interact with a lot of proteins (Insulin receptor, IGF-1 receptor, ELK receptor, PDGFRB, GHR, EGFR, RET, HGFR, FGFR, RAF-1, MEK1, JAK2, BCR-Abl TEC kinase, NEDD4, cABL, AKT, c-KIT).

Several studies suggest a role for Grb10 in cell proliferation. However, despite the clear involvement of Grb10 in pathways activated by IR and IGF-R, there is still some controversy about whether its effect is inhibitory or stimulatory. One report showed that stable overexpression of mGRB10 alpha inhibits IGF-1 mediated cell proliferation, whereas another report demonstrated that overexpression of the same mGrb10 alpha increased DNA synthesis upon growth factor stimulation (PDGFBB, IG-1, or insulin). These contradictions might be explained by the use of different cell lines or experimental procedures.

Grb10 seems to have also a role in apoptosis regulation. Grb10 SH2 domain is able to interact with Raf1 and MEK1. Transfection of SH2 domain Grb10 mutants induces apoptosis in HTC-IR and COS-7 cells suggesting that Grb10 may influence the equilibrium between ERK and JNK pathways and determine the choice between proliferation and programmed cell death. As Grb10 is located at the mitochondrial membrane it may be involved in communication between plasma membrane receptors and apoptosis regulators located on the mitochondrial outer membrane.

Grb10 interacts with Akt and is proposed to be a positive regulator of the Akt pathway downstream of PI3-K. By acting as an adaptor involved in the relocalization of Akt to the cell membrane, Grb10 may contribute to Akt activation and regulation of different biological processes such as proliferation, apoptosis and growth.

### Homology

Grb10 is a member of the Grb7 family of adapter molecules which contains three members Grb7, Grb10 and Grb14. Grb10 counterparts are found in mouse, rat, fly and worm.

## Implicated in

### Disease

The mapping of Grb10 gene to 7p made it a candidate gene for Russel-Silver Syndrome (RSS). But recent data suggest that Grb10 is unlikely to be the gene responsible for RSS.

## References

- Liu F, Roth RA. Grb-IR: a SH2-domain-containing protein that binds to the insulin receptor and inhibits its function. *Proc Natl Acad Sci U S A*. 1995 Oct 24;92(22):10287-91
- O'Neill TJ, Rose DW, Pillay TS, Hotta K, Olefsky JM, Gustafson TA. Interaction of a GRB-IR splice variant (a human GRB10 homolog) with the insulin and insulin-like growth factor I receptors. Evidence for a role in mitogenic signaling. *J Biol Chem*. 1996 Sep 13;271(37):22506-13
- Dong LQ, Du H, Porter SG, Kolakowski LF Jr, Lee AV, Mandarino LJ, Fan J, Yee D, Liu F. Cloning, chromosome localization, expression, and characterization of an Src homology 2 and pleckstrin homology domain-containing insulin receptor binding protein hGrb10gamma. *J Biol Chem*. 1997 Nov 14;272(46):29104-12
- Frantz JD, Giorgetti-Peraldi S, Ottinger EA, Shoelson SE. Human GRB-IRbeta/GRB10. Splice variants of an insulin and growth factor receptor-binding protein with PH and SH2 domains. *J Biol Chem*. 1997 Jan 31;272(5):2659-67
- Jerome CA, Scherer SW, Tsui LC, Gietz RD, Triggs-Raine B. Assignment of growth factor receptor-bound protein 10

(GRB10) to human chromosome 7p11.2-p12. *Genomics*. 1997 Feb 15;40(1):215-6

Morrione A, Valentinis B, Resnicoff M, Xu S, Baserga R. The role of mGrb10alpha in insulin-like growth factor I-mediated growth. *J Biol Chem*. 1997 Oct 17;272(42):26382-7

Dong LQ, Porter S, Hu D, Liu F. Inhibition of hGrb10 binding to the insulin receptor by functional domain-mediated oligomerization. *J Biol Chem*. 1998 Jul 10;273(28):17720-5

Nantel A, Mohammad-Ali K, Sherk J, Posner BI, Thomas DY. Interaction of the Grb10 adapter protein with the Raf1 and MEK1 kinases. *J Biol Chem*. 1998 Apr 24;273(17):10475-84

Nantel A, Huber M, Thomas DY. Localization of endogenous Grb10 to the mitochondria and its interaction with the mitochondrial-associated Raf-1 pool. *J Biol Chem*. 1999 Dec 10;274(50):35719-24

Wang J, Dai H, Yousaf N, Moussaif M, Deng Y, Boufelliga A, Swamy OR, Leone ME, Riedel H. Grb10, a positive, stimulatory signaling adapter in platelet-derived growth factor BB-, insulin-like growth factor I-, and insulin-mediated mitogenesis. *Mol Cell Biol*. 1999 Sep;19(9):6217-28

Wojcik J, Girault JA, Labesse G, Chomilier J, Mornon JP, Callebaut I. Sequence analysis identifies a ras-associating (RA)-like domain in the N-termini of band 4.1/JEF domains and

in the Grb7/10/14 adapter family. *Biochem Biophys Res Commun*. 1999 May 27;259(1):113-20

Yoshihashi H, Maeyama K, Kosaki R, Ogata T, Tsukahara M, Goto Y, Hata J, Matsuo N, Smith RJ, Kosaki K. Imprinting of human GRB10 and its mutations in two patients with Russell-Silver syndrome. *Am J Hum Genet*. 2000 Aug;67(2):476-82

Han DC, Shen TL, Guan JL. The Grb7 family proteins: structure, interactions with other signaling molecules and potential cellular functions. *Oncogene*. 2001 Oct 1;20(44):6315-21

McCann JA, Zheng H, Islam A, Goodyer CG, Polychronakos C. Evidence against GRB10 as the gene responsible for Silver-Russell syndrome. *Biochem Biophys Res Commun*. 2001 Sep 7;286(5):943-8

Jahn T, Seipel P, Urschel S, Peschel C, Duyster J. Role for the adaptor protein Grb10 in the activation of Akt. *Mol Cell Biol*. 2002 Feb;22(4):979-91

---

*This article should be referenced as such:*

Degot S. GRB10 (growth factor receptor-bound protein 10). *Atlas Genet Cytogenet Oncol Haematol*. 2003; 7(1):1-3.

---