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Gene Section
Review

RAPGEF1 (Rap guanine nucleotide exchange factor (GEF) 1)

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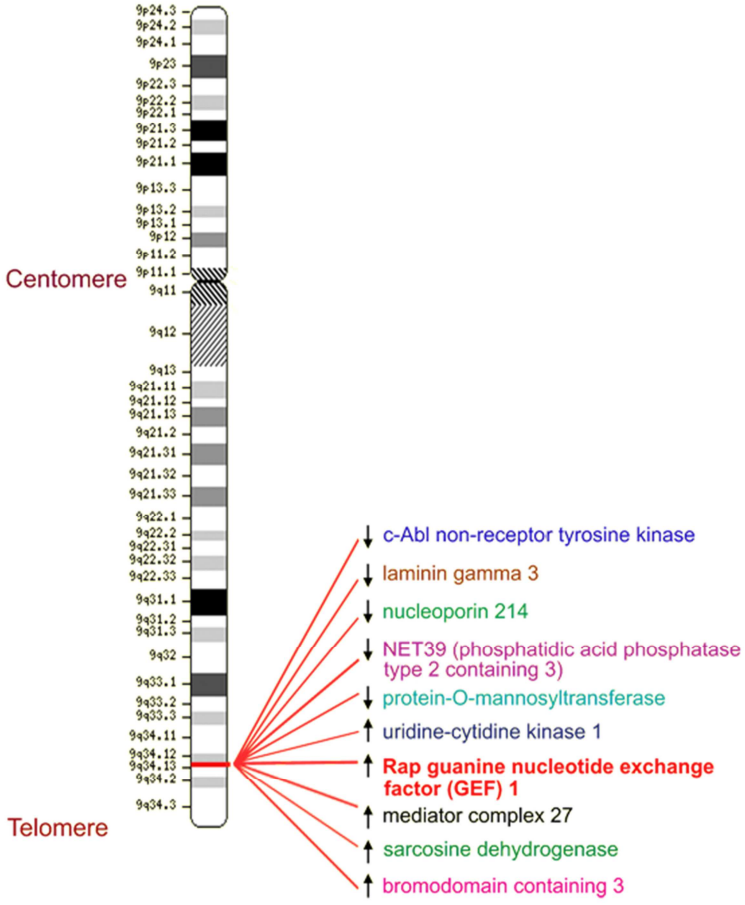
Identity

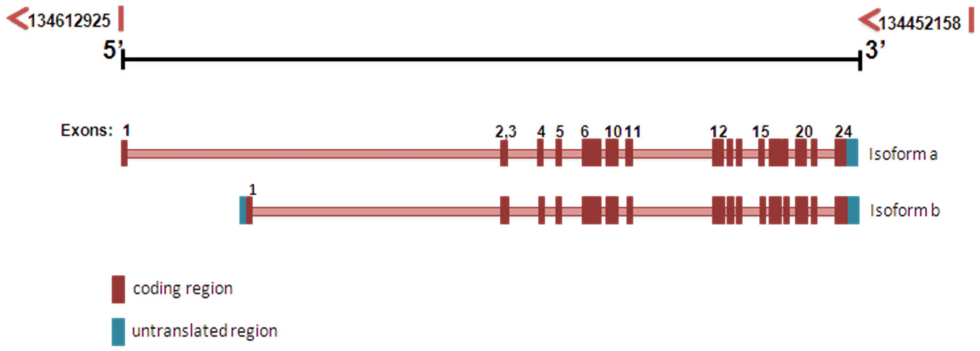
Other names: C3G, DKFZp781P1719, GRF2
HGNC (Hugo): RAPGEF1

Location: 9q34.13

Local order: c-Abl non-receptor tyrosine kinase, RapGEF1, sarcosine dehydrogenase, bromodomain containing 3, ADP-ribosylation factor 4 pseudogene.



Human chromosome 9 map showing the position of C3G (RapGEF1).



Schematic showing the genome organization of C3G gene.

DNA/RNA

Description

The human RAPGEF1/C3G gene is comprised of 24 exons, spanning 163 kb on chromosome 9q34.13.

Transcription

Expression is ubiquitous, with some tissues like the heart, uterus and skeletal muscle showing higher expression.

Alternative spliced forms: Human RAPGEF1/C3G has two isoforms - isoform a and b which differ in the N-terminal (3 aa of Isoform a replaced by 21 aa in isoform b). Isoform-a has 6085 bps of transcript length whereas isoform-b has 6256 bps of transcript length.

An alternate isoform in rat has a 153bp insertion which is expressed only in testis and brain.

A truncated isoform is expressed in CML cells (K562) named p87C3G which has 4.5 kb of transcript length.

Pseudogene

None.

Protein

Description

This 140 kDa protein is a guanine nucleotide exchange factor for some members of Ras family GTPases.

Size: isoform a: 1077 amino acids; isoform b: 1095 amino acids.

Domains: C-terminal catalytic domain: homologous to CDC25, exchange factor activity.

Central protein interaction domain: contains poly-proline tracts, with the ability to bind to SH3 domains of various proteins.

N-terminal non-catalytic domain contains an E-cadherin binding domain.

Catalytic activity: Activates downstream GTPases like Ras family members Rap1, Rap2, R-Ras, TC21 and Rho family member TC-10.

Expression

Expression is ubiquitous. Higher levels of RAPGEF1/C3G are seen in differentiated human neuroblastoma cells compared to undifferentiated cells.

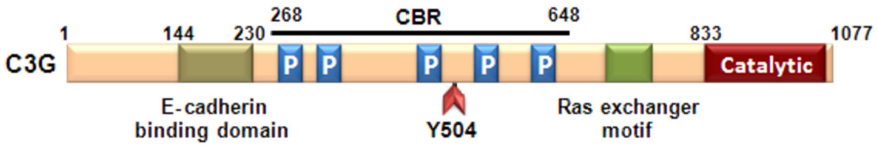
Interacting partners: p130Cas, Crk, Crk-L, Grb2, Hck, PDGF, Cas-L, Shc, Rap1, c-Abl, PP2A and E-cadherin.

Tyrosine phosphorylation: phosphorylated predominantly at Y504; phosphoryaltion also at other tyrosine residues. Kinases known to phosphorylate RAPGEF1/C3G are Hck, Src, c-Abl and Fyn. Rat and mouse isoforms show changes in sequence surrounding Y504.

Membrane anchoring: Constitutive association with Crk enables the complex to interact with phospho-tyrosine motifs upon stimulation of growth factor receptors in the cell membrane.

Actin cytoskeleton binding: Binds to actin cytoskeleton; phosphorylation at Y504 enhances F-actin binding.

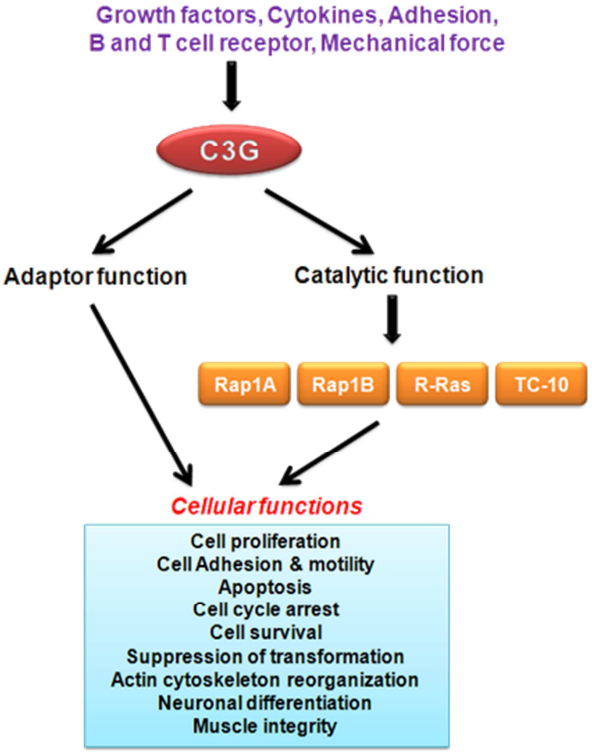
Downstream effectors: Ras family members Rap1, Rap2, R-Ras, TC21, Rho family member TC-10.



Schematic showing the domain organization of RAPGEF1/C3G protein. The C-terminal catalytic domain of C3G is homologous to CDC25 and is responsible for target G protein activation. The N-terminal region has a domain which interacts with E-cadherin. The central protein interaction domain (also known as Crk binding region, CBR) contains multiple proline-rich sequences that bind SH3 domains of Crk, Cas, c-Abl and Hck. The non-catalytic sequences negatively regulate catalytic activity of C3G.

Localisation

Cytosolic.
Upon stimulation of growth factor receptors can be recruited to plasma membrane.
Upon phosphorylation by Src family kinases localizes to Golgi and sub-cortical cytoskeleton.
Also localizes to tips of filopodia and membranous ruffles.



Cellular functions involving C3G mediated signalling. C3G is involved in signalling pathways triggered by upstream activators like integrin binding, B cell receptor, T cell receptor, insulin, EGF, NGF, TXT: interferon-gamma, Hepatocyte growth factor, growth hormone, Reelin, mechanical force, Nectin, cadherin engagement, Erythropoietin and interleukin-3. Through its catalytic function it activates downstream G proteins by switching them from an inactive GDP bound state to an active GTP bound form. It targets the Ras family members Rap1, Rap2, R-Ras, and Rho family member TC-10, leading to activation of MAP kinases that play a role in cell proliferation and integrin-mediated signaling. C3G also has functions which are independent of its catalytic domain, where it behaves like an adaptor protein. Such functions include apoptosis and suppression of transformation.

Function

- **Suppression of transformation:** In cells expressing various oncogenes C3G shows transformation-suppression activity independent of its catalytic domain. This function is mediated by inhibition of ERK phosphorylation and cyclin A expression.
- **Cell survival and apoptosis:** C3G expression protects against serum starvation induced cell death in neuroblastoma cells through induction of p21. Co-expression of Hck with C3G induced high level of apoptosis in many cell lines. C3G is phosphorylated at Y504 in cells undergoing apoptosis as a consequence of c-Abl expression. C3G is required for c-Abl induced apoptosis.
Upon serum deprivation, C3G induces survival in MEFs through inhibition of p38alpha MAPK activity, which mediates apoptosis. In response to oxidative stress, C3G behaves as a pro-apoptotic molecule, as its knockdown or knockout enhances survival through up-regulation of p38alpha activity, which plays an anti-apoptotic role under these conditions.
- **Cell cycle arrest:** C3G expression induced the cell cycle inhibitor p21 in human neuroblastoma cells.
- **Filopodia formation:** C3G is required for c-Abl-induced filopodia during cell spreading on fibronectin. C3G expression induces actin cytoskeletal reorganization and promotes filopodia formation independent of its catalytic activity.
- **Neuronal differentiation:** C3G is induced during neuronal differentiation and is required for differentiation of human neuroblastoma cells.
- **Cell Proliferation:** Expression of membrane targeted C3G in Drosophila leads to cell fate changes and overproliferation during development, mediated by the RAS-MAPK pathway and RAP1.
- **Muscle integrity:** C3G is an accessory component of the Drosophila musculature, essential for the proper localization of integrins at muscle-muscle and muscle-epidermis attachment sites and important for maintaining muscle integrity during larval stages.
Knockout phenotype:
- Knockout mice show embryonic lethality with $C3G^{-/-}$ homozygous animals dying before embryonic day 7.5. Fibroblasts from knockout animals show impaired cell adhesion, delayed cell spreading and accelerated cell migration.
- Animals expressing hypomorphic allele of C3G show overproliferation of the cortical neuroepithelium, cortical neuron migration defects, and defects in blood vessel maturation.

Homology

C3G shares homology only in catalytic domain with other Ras family GTPases. It lacks multiple modular protein interaction domains seen in other family members.

Mutations

Note
Not known.

Implicated in

Various diseases

Note
p87 isoform of C3G lacking N-terminal 305 residues expressed in CML cell lines and Ph+ patients has been suggested to play a role in pathogenesis of CML. Decreased C3G expression due to hypermethylation was seen in cervical squamous cell carcinomas.

Amplification of C3G is associated with primary non-small cell lung carcinomas, which also show higher levels of protein expression in cancerous cells.
SNPs in the C3G gene have shown association with Type 2 diabetes in Korean and Finnish populations.

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