**Gene Section**

**Review**

**RASGRF1 (Ras protein-specific guanine nucleotide-releasing factor 1)**

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**Identity**

Other names: CDC25; CDC25L; GNRP; GRF1; GRF55; H-GRF55; PP13187

HGNC (Hugo): RASGRF1

Location: 15q25.1

**DNA/RNA**

Note

Differential imprinted methylation of the paternal and maternal alleles in neonatal brain. The methylation of promoter of the paternal allele prevents the binding and gene silencing caused by CTCF in the unmethylated maternal allele.

**Description**

128.44 Kb, 28 exons.

**Transcription**

mRNA size: 4022 bases.

**Protein**

Note

In the early 90s, several groups identified in murine brain extracts, a protein of a molecular weight between 100-160 kDa, named Ras-GRF (Ras-Guanine nucleotide Releasing Factor) and Cdc25Mm, based on its ability to induce GDP release in p21ras and on its high homology with the Sacharomyces cerevisiae gene CDC25, whose deficiency it could rescue.

The diagram shows the functional modules present in Ras-GRF1. The flanking amino-acid limits shown correspond to the human protein. Arrows indicate the phosphorylation sites that have been characterized and, in brackets, the kinases responsible. It should be noted that Ras-GRF1 has approximately 83 predicted phosphorylation sites; 63 serines, 19 threonines and 11 tyrosines. The regions essential for inducing GDP/GTP release in Rac and Ras GTPases are underlined. Other interacting proteins and the regions involved in such interactions are shown by broken lines. PM, Plasma Membrane; CaM, Calmodulin. The descriptions of Ras-GRF domains can be found in the text.
**Description**

Ras-GRF1 is a protein that contains multiple modular motifs. The Ras-GEF region, includes the Cdc25 domain which exhibits guanine nucleotide exchange factor (GEF) activity towards the Ras family GTPases and a REM (Ras Exchange-stabilization Motif) domain, responsible for the stabilization of the core of the Cdc25 domain. Separating these domains, there is a region rich in proline, glutamic acid, serine and treonine aminoacids (PEST) that constitutes a hypothetical target for proteolysis. Ras-GRF1 also possesses: two pleckstrin-homology (PH) domains, which have been suggested to interact with polyphosphoinositides and other types of phospholipids and may play some role in Ras-GRF1 interactions with membranes: the α-helical coiled-coil (CC) motif plays a role in protein-protein interactions; a Isoleucine-Glutamin (IQ) domain, which binds Calmodulin and is responsible for the calcium-dependent activation of Ras-GRF1; and a dbl-homology (DH) region, which exhibits GEF activity towards Rho family GTPases, in particular Rac-1. The DH domain also mediates in Ras-GRF dimerization that ensues upon activation. The DH domain and the second PH domain constitute the catalytic module, archetypically present in all Rho-GEFs, which entails nucleotide exchange activity over Rho family GTPases. Ras-GRF1, along with Ras-GRF2 and Sos, are the only known exchange factors that combine Rho and Ras exchanger activity in the same protein.

**Expression**

Ras-GRF1 is fundamentally expressed in the central nervous system and, at a reduced level, also in the spinal cord. It is more abundant in hippocampus, some deep nuclei, neocortex, and the granule cell layer of the anterior lobules of the cerebellum. Its expression is low during embryonal development and increased drastically in the first days after birth. Its presence has also been reported in pancreatic beta cells. Alternative splicing variants are expressed in brain, lung, pancreas, as well as several tumour cell lines.

**Localisation**

By immunofluorescence, Ras-GRF1 exhibits a predominant cytoplasmic distribution, particularly at the perinuclear area, and mostly excluded from lamelipodia and peripheral structures. However, significant amounts are also associated to the plasmamembrane and in the endoplasmic reticulum, but not the Golgi apparatus. Such a distribution can be ascertained by biochemical fractionation, which shows Ras-GRF1 in both soluble and particulate fractions, its proportions vary depending on the cell type. Its association with membranes does not increase upon activation. In addition, it is also remarkably present in the synaptic junctions of mature neurons.

**Function**

The main function of Ras-GRF1, relays in its ability to activate GTPases in response to signals emanating from G protein-coupled receptors and from calcium fluxes. Ras-GRF1 also plays an important role linking signals from AMPA and NMDA receptors to the MAPK/ERK cascade in mature neurons. Initially, it was believed that Ras-GRF1 was unresponsive to signals generated by tyrosine kinase receptors, but lately, it has been demonstrated that Trk-family receptors can phosphorylate and directly associate to Ras-GRF1. Ras-GRF1 acts as a bifunctional protein with the ability to activate both Ras and Rac-1 GTAPses. In vitro, Ras-GRF1 can activate H-Ras, K-Ras and N-Ras GTAPses, but in vivo, its specificity is reduced to H-Ras, probably as a consequence of microlocalization processes taking place. Ras-GRF1 can also activate the R-Ras subfamily GTAPses, namely: TC21 and M-Ras. On the other hand, Ras-GRF1 acts as a Rac-GEF when activated in a Gβγ-dependent fashion. Another Rho-family GTAPse, Cdc42, exhibits a functional relationship with Ras-GRF1 activity, by being capable of negatively regulating Ras-GRF1 Ras-GEF functions. The mechanisms whereby such a regulation is achieved are yet unknown.

Ras-GRF1 knock-out mice are viable and show no major developmental alterations. They do show some mental restraints: they are severely impaired in amygdala-dependent long-term synaptic plasticity and show higher basal synaptic activity at both amygdala and hippocampal synapses, showing faults in the process of memory consolidation. They also show a higher neuronal excitability, are more susceptible to convulsionant drugs and do not exhibit tolerance to chronic exposure to cannabinoids. It has also shown a protective role in the stroke-associated neuronal degeneration. With respect to non-CNS effects, Ras-GRF1 knock-out mice exhibit body weight loss, hypoinsulinemia and glucose intolerance, owing to a reduction of pancreatic beta-cells.

As a regulator of the activation of Ras GTAPses, Ras-GRF1 could, conceptually, participate in all the processes regulated by those, including proliferation, survival and transformation. However, its restricted expression to the brain and localization in the synaptic junctions, suggest a more specific role. By regulating the activation state of the Rac GTAPses, Ras-GRF1 could participate in processes that require cytoskeletal reorganization. Thus, by coordinating the activation of Rac and H-Ras, it can control neuronal morphology and neurite outgrowth in PC12 cells, in response to NGF. Experiments in Knock-out mice also demonstrate that Ras-GRF1 controls synaptic plasticity by regulating a Rac- and p38-dependent long-term depression. Through its association with the p38 scaffold protein IB2/JIP2, Ras-GRF1 leads to a Rac-dependant activation of the p38 cascade. Moreover, it
has been demonstrated that the microtubule-destabilizing factor SCLIP can interact with Ras-GRF1, reducing its ability to activate the Rac/p38 cascade while not affecting the Ras/ERK pathway. The splice variant p75-Ras-GRF1 plays a role in the c-jun-dependent non-adherent growth in Rat1A cells. Recently, it has been shown that, in human melanoma cells, the protein Filamin-A regulates the ubiquination and destabilization of Ras-GRF1 that correlated with a decrease in the expression of MMP-9, a matrix metalloproteinase associated with different biological processes such as growth, invasion and angio-genesis.

**Homology**

Ras-GRF1 has a highly homologous protein: Ras-GRF2 (86% homology), which, unlike Ras-GRF1, is more ubiquitously expressed. This protein is similar in its structure to Ras-GRF1, thus also functioning as a signal transducer protein. It has been also described in pancreatic beta cells, a protein of 178 aminoacids whose C terminus is unrelated to known proteins (GRF β). Further, Ras-GRF1 has a highly homologous protein: Ras-GRF2 (86% homology), which, unlike Ras-GRF1, is more ubiquitously expressed. This protein is similar in its structure to Ras-GRF1, thus also functioning as a signal transducer protein. It has been also described in pancreatic beta cells, a protein of 178 aminoacids whose C terminus is unrelated to known proteins (GRF β).

**Mutations**

**Note**

No Ras-GRF1 mutations have been reported hitherto in human tumours. Even though overexpression of Ras-GRF1 can induce trans-formation of murine fibroblasts and morphological changes resembling transformation processes in other cellular types, no direct associations with human malignancies have been reported as far.

**Cancers**

**Note**

See above.

**Glucose homeostasis**

**Disease**

Role in maintaining glucose homeostasis by regulating pancreatic beta-cells mass. Ras-GRF1 knock-out mice show a phenotype similar to manifestations of preclinical type 2 diabetes.

**Neurodegenerative diseases**

**Disease**

Role in learning and memory processes in mature neurons. Possible link to neurodegenerative diseases such as Alzheimer disease (AD) or Creutzfeldt-Jacobs disease (CJD).

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