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Gene Section
Review

GRM1 (glutamate receptor, metabotropic 1)

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Abstract

Review on GRM1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: GPRC1A, MGLU1, MGLUR1, SCAR13

HGNC (Hugo): GRM1

Location: 6q24.3

DNA/RNA

Description

The mGluR1 gene contains 10 exons, which span a region of 409953 bp.

Transcription

The transcribed matured mRNA is 6939 bps in length.

Protein

Note

GRM1 encodes five alternative splice variants (1a, 1b, 1c, 1d, and 1e) (Zhu et al., 1999). All five variants contain the same N-terminal, but differ in the amino acid composition of their C-terminal domains due to the alternative splicings (DiRaddo et al., 2013).

Description

mGluR1 is an 1194 amino acid seven-transmembrane domain G-protein coupled receptor normally expressed in neuronal and glial cells in the brain (Stephan et al., 1996; Hermans and Challiss, 2001).

Its natural ligand is the excitatory neurotransmitter, L-glutamate. Structurally, mGluR1 has various domains that are necessary for its functions.

The N-terminus forms two large extracellular lobes separated by a cavity where the ligand glutamate binds to and is referred to as the amino terminal domain (ATD) or "Venus Fly Trap" (O'Hara et al., 1993; Beqollari and Kammermeier, 2010).

ATD is separated from the trans-membrane region of mGluR1 by a 70 amino acid cysteine rich domain (CRD), which is essential for dimerization, and activation of the receptor (Huang et al., 2011).

The seven alpha-helical transmembrane domains (TMD) precede the cysteine rich region.

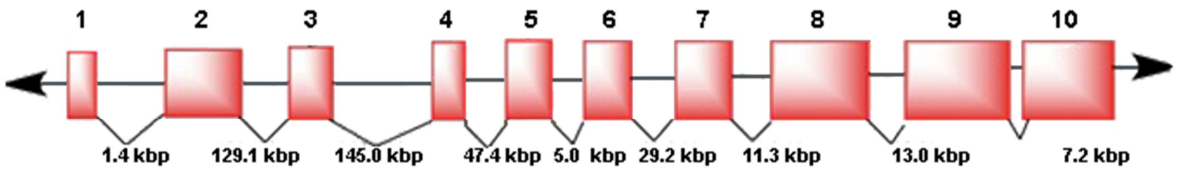

Figure 1. Human GRM1 has 10 exons, which are depicted by boxes and shown with the relative position to one another. Adapted from DiRaddo et al., 2013.

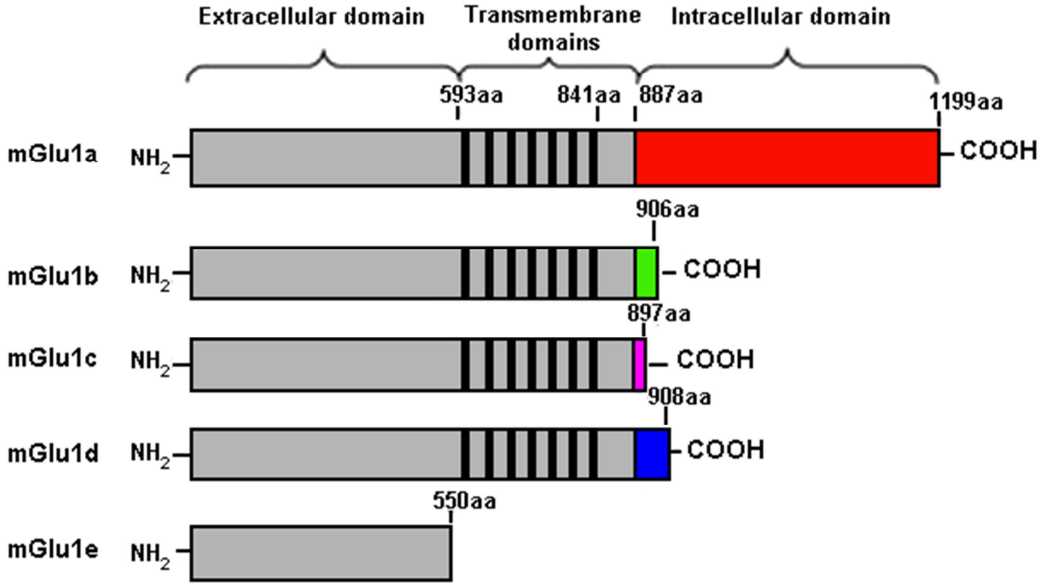

Figure 2. There are five human mGluR1 isoforms. The black boxes represent the seven-transmembrane domains of mGluR1. Alternative splicing of mGluR1 mRNA produces five mGluR1 isoforms each with a unique C-termini, which is highlighted by the different colors. The shortest isoform, mGluR1e, is truncated before the seven-transmembrane domains, which results in the expression of only the amino terminal fragment (Costantino and Pellicciari, 1996). Adapted from Hermans and Challiss, 2001.

Following the TMD is the carboxyl terminus of mGluR1, also known as the intracellular cytoplasmic tail domain (CTD). CTD is involved in modulating G-protein coupling and selectivity (Pin et al., 2003; Seebahn et al., 2013).

The CTD is also the region subjected to alternative splicings, regulated by phosphorylation, and modulatory protein-protein interactions (Niswender and Conn, 2010).

The CRD is consisted of three beta-pleated sheets and nine cysteine residues. CRD plays a key role in facilitating the allosteric coupling between the ATD and the TMD regions during ligand binding and receptor activation (Niswender and Conn, 2010). Upon activation of mGluR1 by glutamate, the signal induced is transmitted from the ATD through the CRDs, by way of a disulfide bridge formed between the 9th cysteine of the CRD and a cysteine residue in lobe 2 of the ATD (Rondard et al., 2006; Muto et al., 2007).

As a result, a conformational change takes place that brings the C-terminal regions of the CRDs closer to one another and elicits cysteine-cysteine interaction in the e2 loop of the TMD (Muto et al., 2007). This conformational change produces a shift in the TMD to induce G-protein activation (El Moustaine et al., 2012).

Expression

mGluR1 is normally expressed in the central nervous system and is activated by its natural ligand, L-glutamate (Teh and Chen, 2012a). Upon activation, mGluR1 couples to Gα/q11 proteins to induce phosphatidylinositol (4,5)-biphosphate (PIP2) hydrolysis leading to the formation of two-second messengers, inositol 1,4,5-triphosphate (IP3) and diacyglycerol (DAG) (Conn and Pin, 1997; Hermans and Challiss, 2001). These second messengers stimulate intracellular calcium release from the endoplasmic reticulum (ER) stores and activate protein kinase C (PKC), resulting in the stimulation of G-protein-independent signal transduction pathways (Hermans and Challiss, 2001; Goudet et al., 2009).

Such pathways include the mitogen activated protein kinase pathway (MAPK) and the phosphatidylinositol-3-kinase (PI3K)/AKT pathway (Marín, et al., 2006; Shin et al., 2010).

Localisation

Cell membrane of neurons.

Function

mGluR1 activation is involved in mediating neuronal excitability, synaptic plasticity, and feedback inhibition of neurotransmitter release (Speyer et al., 2012).

All of which promotes learning and memory formation in the central nervous system (Hermans and Challiss, 2001).

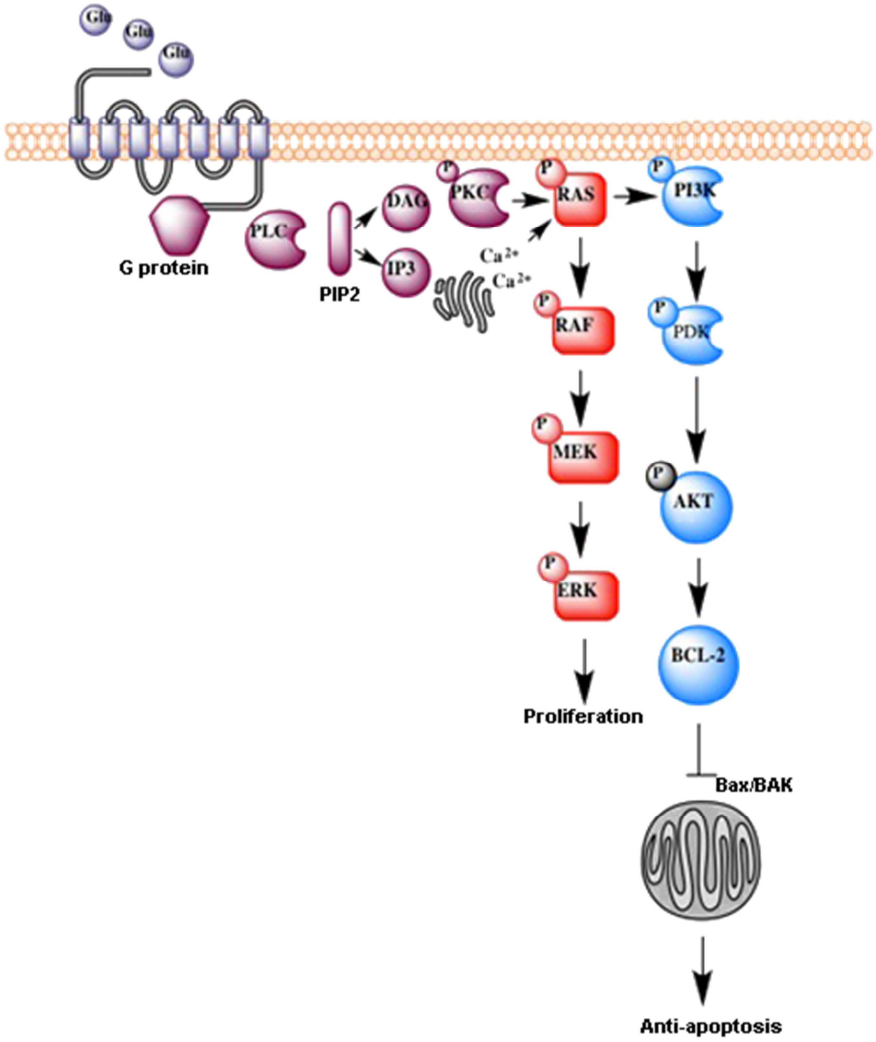

Figure 3. Diagram of the proposed signal transduction pathways elicited by stimulated mGluR1. Adapted from Teh and Chen, 2012b.

Mutations

Note

Over 20 somatic missense mutations in the ligand binding and intracellular regulatory domains of mGluR1 have been identified in various tumors types (Sjöblom et al., 2006; Kan et al., 2010; Esseltine et al., 2013). A number of these mutations result in irregular mGluR1 stimulation of G protein coupling, biased ERK1/ERK2 phosphorylation, and intracellular retention in the endoplasmic reticulum (ER) (Esseltine et al., 2013). Such changes in mGluR1 signaling lead to abnormal receptor activity in numerous human cancers.

Implicated in

Melanoma

Disease

Melanoma is the most severe form of skin cancer and arises from the aberrant transformation of melanocytes. The most common mutations identified as drivers of melanomagenesis include B-RAF and N-RAS activating mutations as well the tumor suppressors INK4a/ARF and PTEN (Teh and Chen, 2012a).

Oncogenesis

Glutamate signaling via mGluR1 has been shown to affect cell survival, cell differentiation and cell proliferation of non-neuronal tissues (Skerry and Genever, 2001; Shin et al., 2008). Chen and colleagues demonstrated the ectopic expression of mGluR1 in mouse melanocytes was sufficient to induce spontaneous metastatic melanoma development in transgenic mouse models, TG3 and Tg(Grm1)EPv (E) (Pollock et al., 2003). The ectopic expression of human mGluR1 was also detected in human melanoma cell lines and biopsy samples. To date, ~175 melanoma biopsy samples from primary to metastatic lesions have ben examined and found GRM1 mRNA and protein to be expressed in ~ 60% of the samples (Pollock et

al., 2003; Namkoong et al., 2007). Moreover, expression and activation of mGluR1 in melanoma cells has been shown to activate the MAPK and P13K/AKT pathways, two of the most frequently stimulated signaling cascades in melanoma (Marín et al., 2006; Shin et al., 2010).

Breast cancer (triple-negative breast cancer)

Disease

Triple-negative breast cancer, are malignant tumors in breast tissue that lack estrogen receptor and progesterone receptor and amplification of the HER2 gene (Engebraaten et al., 2013).

Oncogenesis

Speyer and colleagues described mGluR1 expression as a potential oncogene in mammary breast pathogenesis.

They detected mGluR1 expression in multiple triple-negative breast cancer cell lines (TNBC) (Speyer et al., 2012). This group also provided evidences that the growth of TNBC cells was inhibited when mGluR1 expression was reduced by an shRNA or treatment with mGluR1 antagonist, Bay36-7620 (Speyer et al., 2012).

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