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Regulator of G Protein Signaling 10: Structure, Expression and Functions in Cellular Physiology and Diseases

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Abstract

Regulator of G protein signaling 10 (RGS10) belongs to the superfamily of RGS proteins, defined by the presence of a conserved RGS domain that canonically binds and deactivates heterotrimeric G-proteins. RGS proteins act as GTPase activating proteins (GAPs), which accelerate GTP hydrolysis on the G-protein α subunits and result in termination of signaling pathways downstream of G protein-coupled receptors. RGS10 is the smallest protein of the D/R12 subfamily and selectively interacts with Gαi proteins. It is widely expressed in many cells and tissues, with the highest expression found in the brain and immune cells. RGS10 expression is transcriptionally regulated via epigenetic mechanisms. Although RGS10 lacks multiple of the defined regulatory domains found in other RGS proteins, RGS10 contains post-translational modification sites regulating its expression, localization, and function. Additionally, RGS10 is a critical protein in the regulation of physiological processes in multiple cells, where dysregulation of its expression has been implicated in various diseases including Parkinson's disease, multiple sclerosis, osteopetrosis, chemoresistant ovarian cancer and cardiac hypertrophy. This review summarizes RGS10 features and its regulatory mechanisms, and discusses the known functions of RGS10 in cellular physiology and pathogenesis of several diseases.

Keywords

RGS10; RGS proteins; GPCR; G-protein; regulatory mechanisms; ovarian cancer

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Authorship Contributions

F.A. wrote the original draft and prepared the figures. F.A., J.K.L., and B.R. edited and revised the manuscript. All the authors read and approved the final version of the manuscript.

Competing Interests

The authors declare that they have no conflicts of interest.

1- Introduction

1.1. GPCR/G-protein signaling

G protein-couple receptors (GPCRs) and the transduced heterotrimeric G-proteins, which modulate a cascade of intracellular effector proteins and chemical second messengers, are essential in the regulation of various physiological functions of cells and organ systems. They represent the largest family of FDA-approved targeted drugs for the treatment of a wide range of disorders caused by dysregulation of GPCR/G-protein signaling [1]. In the resting state, GPCRs are bound to inactive heterotrimeric G-proteins, consisting of the Gα-GDP and Gβγ dimer. In response to a variety of extracellular stimuli, GPCRs undergo conformational changes and act as guanine nucleotide exchange factors (GEFs) by promoting the exchange of GDP for GTP on Gα. As a result, activated GTP-Gα dissociates from Gβγ dimer, and thereby both can regulate downstream effector proteins [2] (Figure 1), such as enzymes, RhoGEFs, and ion channels that in turn initiate diverse signaling pathways mediating cellular responses [3–7]

The amplification and duration of signaling activity by Gα-GTP and Gβγ are tightly modulated by the intrinsic GTPase activity of Gα, in which the Gα subunit hydrolyzes GTP to GDP and promotes reassembly with the Gβγ dimer to reform the inactive Gαβγ protein complex. This, in turn, results in the deactivation of G-protein cycle. Even though Gα functions as a molecular switch and turns itself off by hydrolyzing its bound GTP to GDP, its intrinsic rate of GTP hydrolysis measured *in vitro* is very slow and does not account for the fast deactivation kinetic of G-proteins observed *in vivo* [8]. This observation has led to the discovery of proteins, named as regulators of G protein signaling that modulate the Gα-GTP hydrolysis rate, and thereby fine-tune the activation of G-proteins that mediate cellular signaling events.

1.2. RGS protein family

Regulator of G protein signaling (RGS) proteins that were initially discovered via genetic analysis in yeast and worm models [9–11], represent a diverse family of structural and multifunctional intracellular proteins that canonically regulate GPCRs and heterotrimeric G-protein signal transduction. RGS proteins control the lifetime of signaling pathways mediated by G-proteins. They act as a guanosine triphosphatase (GTPase) activating proteins (GAPs), which accelerate GTP hydrolysis of the active Gα-GTP form and, in turn, convert it back to the inactive Gα-GDP form. Consequently, this results in the termination of downstream G-protein signaling pathways (Figure 1).

To date, 20 canonical RGS proteins and 19 RGS-like proteins have been identified with various regulatory roles [12–14]. All canonical RGS proteins contain the conserved, approximately 120 amino acids long RGS domain, consisting of nine α helices that are subdivided into two sub-domains. The first subdomain forms a smaller helix bundle and is comprised of helices αI, II, III, VIII, and IX, while the larger bundle subdomain comprises helices αIV, V, VI, and VII [15]. The RGS domain selectively binds and stabilizes the Gα subunit in its transition state for GTP hydrolysis, mimicked by ($GDP+AlF4^{-}$), resulting in GDP production and turning off signaling cascades regulated by G-proteins [15, 16].

The structure of canonical RGS proteins ranges from small proteins comprised solely of an RGS domain responsible for GAP activity to more complex proteins containing multiple motifs and domains with functions in subcellular localization, protein stability, and protein-protein interactions. Based on the homology of the RGS domain and the presence of other common structural domains, canonical RGS proteins are categorized in four main subfamilies, consisting of A/RZ, B/R4, C/R7, and D/R12 (Figure 2). As negative regulators of G-protein signaling, RGS proteins mainly exert their GAP function on α subunits of the Gi/o and Gq families of G-proteins. Although there are no confirmed reports on GAP activity of any RGS domain toward Gαs, RGS proteins indirectly regulate Gαs downstream signaling through interaction with subtypes of adenylate cyclase (AC) [17, 18].

1.3. RGS D/R12 proteins subfamily

RGS D/12 subfamily is composed of three distinct structural proteins (Figure 2), containing RGS10, RGS12, and RGS14, which share high sequence identity within a conserved RGS domain (Figure 3A) and act as GAP for the Gi family Gα subunits. Whereas RGS10, at 20 kDa, is a relatively simple RGS protein, RGS12 and RGS14 are much larger and more complex than RGS10, and have multiple common structural and regulatory motifs and functional domains, including a pair of tandem Ras-binding domains (RBDs) and a C-terminal G-protein regulatory (GPR) motif, also known as the GoLoco motif. Through their first RBD domain, both RGS12 and RGS14 interact with activated small G-proteins, such as H-Ras-GTP and Rap-2-GTP [19–21], while the two tandem RBDs of RGS14 mediate interactions with Raf kinases [21] and calcium dependent-calmodulin (CaM) [22]. The GPR motif plays a role in subcellular localization and selectively binds inactive Gα proteins-GDP, thereby inhibiting the exchange of GDP toward GTP through its guanine nucleotide dissociation inhibitor (GDI) activity [23].

Unlike RGS14, RGS12 is expressed as multiple isoforms. The longest RGS12 isoform is called trans-spliced-RGS12TS-L, is a 156 kDa protein that possesses two additional domains, including PTB and PDZ domains, making RGS12 the largest member of the RGS protein family. The PTB domain is involved in interacting with neuronal N-type calcium channels [24, 25], while the PDZ domain binds the C-terminal of the CXCR2 receptor [26], and both PTB/PDZ domains significantly attenuate ERK phosphorylation downstream of PDGFβ receptor activation [27]. RGS12 is abundant in the brain [28], heart [29] and osteoclasts [30], and is implicated in neuronal differentiation [31], bone disorders [32], cardiac hypertrophy [33] and lung and prostate cancers [34, 35].

RGS14, at 61 kDa, is expressed in the brain with a high enrichment in CA2 hippocampal neurons, where RGS14 naturally suppresses synaptic plasticity and limits learning and spatial memory [36]. Further, RGS14 is associated with cardiac remodeling [37], Parkinson's disease (PD) [38], and kidney diseases [39–41]. This review primarily focuses on the small RGS protein RGS10, and discusses, in-depth, its characterization, regulatory mechanisms, and the physiological and pathological roles of RGS10 in several cells and mouse models.

2- Characterization of RGS10 protein

2.1. Gene and protein organization

RGS10 is a small RGS protein that resembles the structure of R4 subfamily members. However, based on RGS domain sequence similarity, RGS10 is classified as a third member of the D/R12 subfamily which also includes the proteins RGS12 and RGS14 (Figure 3A) [42–44]. Despite the homology within their RGS domains, RGS10 is one of the smallest proteins of the entire RGS protein family and shares only a single conserved RGS domain in common with both RGS12 and RGS14 that contain more accessory domains. In addition to its conserved and functional RGS domain, RGS10 contains short disordered amino and carboxy-terminal extensions, harboring regulatory modification sites (Figure 3B).

RGS10 is highly conserved in humans and rodents and is encoded by a single gene (*Rgs10*) located at the position 10q26 on chromosome 11 in humans and on murine chromosome 7 [45, 46]. Alternative splicing of the first exon of the *Rgs10* mouse gene results in two transcripts isoforms that share the last four exons and correspond to human transcripts with conserved exon structures. These two transcript variants yield two proteins, differing only by a few amino acids in their N-terminal sequences (Figure 3C). The long isoform, called RGS10A (RGS10–1/RGS10L), is a 181 amino-acid peptide, while the short isoform, termed RGS10B (RGS10–2/RGS10S), consists of 167 amino acids (Figure 3B). The third human isoform (173 aa), arising from an alternative start site upstream of the first shared exon, has been reported and shown to have GAP activity, but its homolog in mouse has not found yet [42, 45].

RGS10A (RGS10–1/RGS10L) is the predominant and functional isoform that is naturally expressed in osteoclasts [47], microglia [48], and ovarian cancer cells [49], while RGS10B (RGS10–2/RGS10S) lacking 14 amino acids at the N-terminus has impaired GAP function [50].

2.2. Tissue distribution

RGS10 is ubiquitously expressed; it has been detected in several tissues of humans and other mammals. Our results shown in Figure 4 confirm the wide tissue distribution of RGS10 protein expression and its lack in RGS10$^{-/-}$ mice. In human, the RGS10 mRNA is predominately expressed in the brain [51, 52], as well as subsets of immune cells, including CD4^{+} T cells [53], and monocyte-derived dendritic cells [54]. Also, the RGS10 transcript is highly expressed throughout the mouse and rat brains, with specific enrichment in the hippocampus, dorsal raphe, and striatum, regions of the brain that are implicated in mood disorders and anti-depressant treatment response [43, 55]. Further, RGS10 is found in peripheral tissues, including the cornea [56], heart, lung, testis and immune organs including the bone marrow, lymph nodes, and spleen, but its expression is not detectable in liver, kidney, and muscles [45]. Using an antibody ([C-20, sc-6206], Santa Cruz Biotechnology) raised against a synthetic peptide identical to the last 20 residues (EEDLPDAQTAAKRASRIYNT) at the C-terminus of RGS10 [55], protein expression of RGS10 was confirmed in our laboratory by western blotting in multiple parts of the brain including the cortex, hippocampus, cerebellum, and striatum (Figure 4A), and in several

peripheral tissues including the heart, lung, spleen, stomach and intestine (Figure 4B). RGS10 expression is absent in the liver and the kidney (data not shown).

2.3. Subcellular localization

Instead of localizing to the plasma membrane, where the canonical G protein targets reside, numerous RGS proteins are primarily accumulated in the nucleus [57–60]. The nucleus as a cellular storage compartment may serve to restrain RGS proteins' availability from regulating G-protein signaling or may allow them independently of their canonical function to regulate nuclear signal transduction through undefined nuclear interacting proteins [61]. Several reports (summarized in Table 1 and described below) demonstrated the localization of RGS10 to both the nucleus and the cytoplasm, with no significant plasma membrane localization. Chatterjee and Fisher (2000) first reported that RGS10 that is ectopically expressed in COS-7 cells and endogenously is expressed in H4-neuroglioma cells, is mainly localized to the nucleus [62]. In contrast to this finding, Burgon *et al.* (2001) demonstrated a predominant distribution in the cytoplasm of HEK-293 cells expressing RGS10-GFP fusion protein [63], while Lee and her colleagues observed endogenous RGS10 throughout cytoplasmic and nuclear cellular compartments in primary microglia [48]. Collectively, these findings suggest that the subcellular localization of RGS10 is cell type-specific.

Indeed, the cytoplasmic/nuclear translocation of RGS10 is a highly dynamic process. RGS10 can shuttle between the cytoplasm and the nucleus in response to cellular stimuli or signal-induced covalent modifications (Table 1). In microglia, RGS10 appears to be evenly distributed between the cytoplasm and nucleus under resting conditions. However, following lipopolysaccharide (LPS) stimulation, RGS10 is robustly enriched in the nucleus [48]. Furthermore, activation of Gαi signaling by melatonin promotes RGS10 translocation from the nucleus to the cytoplasm in PC3-AR prostate cancer cells [64]. Importantly, nuclear localization of RGS10 is induced through the cyclic AMP-dependent protein kinase A (PKA)-mediated phosphorylation of RGS10 on serine 168 [63], a residue located outside of its common RGS domain that contains a defined putative nuclear localization sequence [62]. Therefore, further sequence and deletion analyses are required to identify the potential nuclear localization sequences outside of the RGS domain and to elucidate the molecular mechanism underlying RGS10 nuclear localization in response to phosphorylation by PKA.

2.4. Gα binding and GAP activity

Many RGS proteins selectively target and negatively regulate a particular type of activated Gα protein signaling, while others have an affinity to interact with different Gα subtypes. RGS10 is selective to bind and terminate Gi family Gα subunits, including Gαi, Gαo, and Gαz [42, 44, 65]. Previous studies have defined and described the structure of RGS10 in an uncomplexed form compared to the structure of RGS10 complexed with Gαi3 [66, 67]. Soundararajan *et al.* (2008) demonstrated that RGS10 possesses a shorter flexible αVI helix and an extended αV-αVI loop containing 18 residues compared to typical 14 residues of αV- αVI loop for RGS domains of R4, R7, and Rz subfamilies [66].

Generally, the interaction between RGS10 and Gαi3 (critical residues highlighted in Figure 3C) is similar and consistent with R4 subfamily members-Gαi complexes with observed

differences in the αVI helix. Due to the disorder of the entire RGS10 αVI helix in its complex with Gαi3, a conserved arginine residue in the αVI helix (R113(99), a putative modulatory residue in RGS domain highlighted in Figure 3C) does not make a direct interaction with Gαi3 switch III region as R4 subfamily members do interact with Gαi complexes through this conserved residue [66]. The RGS10 RGS domain exhibits a higher GAP activity toward Gαi1 and Gαz compared to RGS domains of RGS4 and RGS19 (GAIP) [44] and approximately the same GAP activity similar to RGS domains of RGS4 and RGS16 against Gαo [68]. However, the GAP activity of RGS10 is lower toward Gαi1 and Gαo compared to higher GAP RGS proteins, such as RGS4 and RGS16 [69], where they localize to the plasma membrane through their N-terminal amphipathic domain, efficiently contributing to their GAP activity with Gαz. Interestingly, replacement of the N-terminal domain of RGS10 with the N-terminal domain of RGS4 enhances its GAP activity toward Gαi and Gαz [50, 70], suggesting that plasma membrane targeting is essential for its GAP activity. Moreover, unlike RGS4 and RGS16, RGS10 contains putative disruptor residues (highlighted in Figure 3C) including Q111(97), K139(125), and Y140(126) that disrupt the contact with both Gαi1 and Gαo and consequently result in reduced GAP activity [69].

RGS10 has been shown to modulate Gαi-mediated receptor signaling. Adenoviral gene delivery-mediated RGS10 expression in CHOK1 cells stably expressing the human serotonin 5-HT1A receptor results in a significant reduction of Gαi-mediated inhibition of AC and inhibition of forskolin-stimulated cAMP production [71]. Consistent with its effect on 5-HT1A signaling, RGS10 overexpression attenuates the inhibition of AC activity mediated by μ (mu)-opioid receptor [72]. Further, RGS10 blocks CXCL12- stimulated chemokine CXCR4 receptor-mediated signaling in T cells [53]. Together, these findings support the selectivity of RGS10 in regulating GPCR-coupled Gαi signaling.

3- Regulation of RGS10 function and expression

3.1. Epigenetic mechanisms

Numerous studies (summarized in Table 2) have shown the regulation of RGS10 expression in response to various stimuli in several cell types and disease models. Unlike other RGS proteins, RGS10 is regulated at the transcriptional level via epigenetic mechanisms. Typically, the transcription of genes is epigenetically regulated through alteration of chromatin structure, containing nucleosomes formed by DNA coiled around histones proteins [73]. Modification of DNA and histones leads to chromatin remodeling, which either facilitates or impedes the transcriptional machinery's access to DNA. This results in the initiation or repression of gene expression [73]. Common mechanisms underlying chromatin modifications are DNA methylation and histone acetylation/deacetylation. DNA methylation is carried out by DNA methyltransferases (DNMTs) that add a methyl group directly to the fifth carbons of cytosine residues at CpG dinucleotides and mainly leads to gene silencing [74]. Histone acetylation is generally associated with transcriptional activation, and is mediated by adding acetyl groups on lysine residues of histone tails by histone acetyltransferases (HATs). In contrast, histone deacetylation involves the removal of

acetyl groups from histone residues by histone deacetylases (HDACs) and is linked to transcriptional repression [75].

Several studies have demonstrated that DNA hypermethylation and histone deacetylation are critical epigenetic mechanisms mediating the regulation of RGS10 transcription in cancer cells, as well as neurons and macrophages. RGS10 expression is suppressed in chemoresistant ovarian cancer cells due to an increase in DNA methylation and histone deacetylation at its promoter compared to chemosensitive counterparts [49]. Suppression of either DNA methyltransferase 1 (DNMT1) or histone deacetylase 1 (HDAC1) using siRNA knockdown significantly increases the expression of RGS10 in chemoresistant A2780-AD ovarian cancer cells [76]. In addition, pharmacological inhibition of the activity of DNA methyltransferase with 5-Aza deoxycytidine (5-Aza) enhances the RGS10 transcript level in human neural progenitor cells [77]. In contrast, LPS-mediated activation of microglia, where RGS10 is highly enriched in the central nervous system [55], suppresses RGS10 expression by histone deacetylation with no significant effect in DNA methylation [78]. The suppression of RGS10 expression following microglia activation involving HDAC recruitment to the RGS10 promoter is blocked by Trichostatin A (TSA), a pharmacological inhibitor of HDAC enzyme activity [78]. Collectively, these studies provide evidence that RGS10 is regulated in a cell type-specific manner in response to distinct epigenetic mechanisms.

The previous studies have demonstrated a dynamic regulation of RGS10 expression by epigenetic mechanisms, suggesting that modified RGS10 could be used as a biomarker. Wen *et al.* (2015) use a method called Methylated CpG Tandems Amplification and Sequencing (MCTA-Seq) to detect DNA methylation in freely circulating DNA in the blood of hepatocellular carcinoma (HCC) patients and their control subjects. Strikingly, the study finds that RGS10 is among only four biomarkers that have strongly hypermethylated CpG islands in the blood of hepatocellular carcinoma patients compared to healthy individuals. Therefore, hypermethylated RGS10 may potentially aid in detecting the early stage of hepatocellular carcinoma [79].

In addition to chromatin-modifying mechanisms regulating RGS10 expression, miRNAs, which are short non-coding RNAs, control the expression of genes via binding and degrading their transcripts and thus subsequently resulting in repression in protein translation [80]. They have been implicated in the pathogenesis of numerous diseases through the dysregulation of their target genes including RGS genes [81]. A microarray study in multidrug-resistant (MDR) laryngeal cancer followed by miRNA Target Prediction Analysis has revealed that RGS10 is a putative target of has-miR-93 [82]. Although RGS10 is suppressed in various types of chemoresistant ovarian cancer, its expression is upregulated and inversely correlated with down-regulation of has-miR-93 expression in MDR laryngeal cancer Hep-2/v resistant cells compared to chemosensitive Hep-2 cells [82]. Taken together, these findings suggest that dysregulation of RGS10 expression could contribute to an acquired chemoresistant phenotype depending on the cancer cell type and its regulation by epigenetic mechanisms.

3.2. Post-translational modifications

Several RGS proteins are subjected to a wide range of post-translational modifications (PTM), which have profound impacts on their stability, GAP activity, interaction with binding partners, and subcellular localization [81, 83]. Despite the lack of multiple defined regulatory domains found in RGS12 and RGS14, RGS10 has various defined regulatory PTM sites, including phosphorylation, palmitoylation and ubiquitination (Figure 3C).

Phosphorylation of RGS10 on serine 168 at its C terminus by cAMP-dependent PKA triggers RGS10 localization from the cytosol to the nucleus. It thus results in attenuation of RGS10 availability at the plasma membrane needed to regulate G-protein-dependent activation of the G-protein-coupled inwardly-rectifying potassium (GIRK) channels without affecting its GTPase activity against the Gα protein [63]. Furthermore, a proteomic approach has identified RGS10 phosphorylation in human platelets following thrombin receptor activating peptide (TRAP) stimulation [84]. However, the site of RGS10 phosphorylation and the kinase activated by TRAP was not determined. The effects of RGS10 phosphorylation on its GAP activity and platelet activation are also unclear.

Unlike other RGS subfamily members that have the N-terminal amphipathic helix or cysteine string to localize to the cell membrane [85], RGS10 targets the plasma membrane by palmitoylation, which is a reversible reaction involving the attachment of a 16-carbon fatty acids palmitate to cysteine residues via a thioester linkage [86]. RGS10 is palmitoylated on a conserved cysteine 66 residue buried inside helix 4 within the RGS domain, which influences its GAP activity based on the assay used. Palmitoylation of this residue inhibits RGS10 GTPase activity in the single turnover-GTP hydrolysis assay in detergent solution but substantially potentiates steady-state GAP activity in receptor/G-protein reconstituted proteoliposomes [70, 87, 88]. Consistent with the previous positive impact of palmitoylation on RGS10 GAP activity in *Spodoptera frugiperda* (Sf9) insect cells, Castro-Fernandez *et al.* (2002) show constitutive palmitoylation of RGS10 on a conserved cysteine 60 in mammalian GH3 cells stably expressing the GnRH receptor (GGH3). This constitutive palmitoylation results in the inhibition of GnRH agonist-induced inositol phosphate (I.P.) and cAMP production, while the elimination of the palmitoylation effect by substitution of cysteine 60 by alanine abolishes RGS10 GAP activity on GnRH signaling [89].

In addition to phosphorylation and palmitoylation, a recent study using quantitative proteomics has identified RGS10 as a substrate for ubiquitination by the E3 ubiquitin ligase tripartite motif protein 32 (TRIM32). Degraded RGS10 is detected in lateral/medial ganglionic eminence (L/MGE) progenitors and results in promoting Rheb-GTP/mTOR hyperactivity that is required for GABAergic interneuron generation via enhancing L/MGE proliferation. On the other hand, the accumulation of RGS10 in response to TRIM32 deficiency or the MG-132 proteasome inhibitor inhibits mTOR signaling and thus causes L/MGE autophagy, a feature of autism-like behaviors [90]. Since RGS10 contains undefined functional domains outside of its RGS domain, it will be interesting to determine if the RGS domain mediates the TRIM32-RGS10 interaction and whether TRIM32 also interacts with other RGS proteins.

In addition to the defined and functional regulatory modification sites mentioned above, Squires *et al.* (2018) have identified and reported a list of PTM sites found on human RGS10 (highlighted in Figure 3C), including K53(39) and K148(134) (Ubiquitination), K78(64) (Acetylation), and S24(10), S27(13), Y94(80), Y143(129), and Y179(165) (Phosphorylation). The majority of these regulatory sites are found within the canonical RGS domain, and half of these sites overlap with reported human variants in RGS10 [91]. Therefore, further studies are needed to characterize the functional roles of these sites in regulating RGS10 GAP activity, subcellular localization, protein stability, and their implications in disease models.

4- RGS10 functions in physiology and pathological diseases

Given its broad expression in diverse cells and tissues, RGS10 has emerged as an essential regulator involving cellular processes, physiological responses, and pathological conditions. This section reviews and discusses the results from biochemical, cellular, and *in vivo* studies that have revealed the physiological roles of RGS10 and its implications in pathological states. The overview of phenotypes and disease links arising from loss of RGS10 expression is present in Table 3.

4.1. Neuroinflammation

RGS10 is normally expressed at high levels in the central nervous system, with particular enrichment in microglia [55, 92]. Microglia are the brain's resident macrophages, which generally engulf pathogens and cell debris. However, chronic microglia activation leads to an amplified release of proinflammatory and neurotoxic mediators that eventually enhance inflammation-induced neurotoxicity. Injured neurons, in turn, produce danger signals that ultimately augment inflammatory microglial responses. This interplay between microglia and neurons results in an uncontrolled and persistent neuroinflammation, which is known to drive the progression of neurodegenerative pathogeneses, such as Alzheimer's disease and PD [93, 94]. Microglia are mainly activated in response to bacterial LPS, tumor necrosis factor α (TNF-α), neurotoxins, extracellular ATP and 6-OHDA.

A polymorphism in the *Rgs10* gene has been associated with age-related maculopathy [95] and schizophrenia [96]. Interestingly, activation of microglia by LPS or TNF-α triggers suppression of RGS10, which could directly amplify microglial inflammatory responses mediating neurotoxicity. Furthermore, RGS10-deficient mice exhibit enhanced CNS microglia burden, and activation. Interestingly, these mice are hypersensitive to systemic exposure of LPS-mediated substantia nigra pars compacta (SNpc) DA neuron degeneration, a phenotype of PD [48]. Activated primary microglia isolated from RGS10-deficient mice produce higher levels of inflammatory mediators, which consequently elevate media toxicity toward MN9D (mesencephalon DA neuroblastoma) cells, compared to WT mice [48, 97]. Similarly, dwon-regulation of RGS10 via siRNA in BV2 mouse microglia cells upregulates inflammation-related gene expression following LPS activation of TLR4, including TNF-α and IL-1β. Also, knockdown of RGS10 enhances MN9D cell death in response to activated BV2 cultural media incubation, which could be prevented by etanercept-mediated neutralization of TNF-α neurotoxic effects [48]. In primary microglia exposed to TNF-α or

LPS, RG10 deficiency leads to enhanced expression and transcriptional activity of NF-κB, a major transcription factor mediating inflammatory signaling. Reciprocally, re-expression of RGS10 in RGS10-deficient primary microglia suppresses microglia activation, NF-κB activity, proinflammatory cytokines release, and inflammatory neurotoxicity. In addition, virus-mediated gene delivery of RGS10 into SNpc of rats significantly decreases 6-OHDA neurotoxin-induced microglia activation and DA neuron degeneration [97]. Consistent with these data, knockdown of RGS10 in BV2 cells enhances LPS-induced cyclooxygenase-2 (COX-2) expression and the release of its downstream effector, PGE2. Interestingly, amplification of LPS-stimulated TNF-α and COX-2 following microglial RGS10 suppression does not require Gαi activity [98]. Despite the importance of these results, the molecular mechanism underlying RGS10 regulation of microglial inflammatory signaling has not been clearly defined.

In addition to its higher microglial expression, RGS10 is also high and detectable within the nuclei of neurons [55]. MN9D cells transfected with direct siRNA-targeting RGS10 are more sensitive to the toxic effects of activated BV2 cultural media [48]. Due to the direct role of RGS10 in promoting DA neuron survival and regulation of microglial inflammatory responses, specifically TNF-α, and the fact that TNF-α/TNFR1 signaling is involved in DA neurons loss, the prosurvival function of RGS10 in DA neurons against TNF-α-induced cytotoxicity has been addressed. Treatment of MN9D cells with TNF-α suppresses RGS10 protein expression. As discussed RGS10 subcellular localization in the above sections, phosphorylation of RGS10 at serine 168 triggers its translocation to the nucleus. The overexpression of WT RGS10, but not of RGS10 S168A mutant which is resistant to PKA phosphorylation, reduces the neurotoxic effects of TNF-α in MN9D cells, through the inhibition of PARP-1 and caspase 3 cleavages and potentiation of PKA/CREB-mediated Bcl-2 anti-apoptotic expression. Consistent with these data, blocking PKA-induced RGS10 phosphorylation and the subsequent nuclear translocation limit the protective effect of RGS10 against TNF-α toxicity [99]. Together, these results suggest that phosphorylation of RGS10 by PKA is required for RGS10's neuroprotective effect against cytotoxicity induced by TNF-α. In the context of aging, as a major risk factor for neurodegenerative diseases, RGS10 expression is decreased within $Iba1^+$ cells in the brains of aged mice, which possibly causes changes in inflammatory responses or age-related cellular functions that could predispose to neurodegeneration [100]. Collectively, these findings provide evidence of the anti-inflammatory and neuroprotective roles of RGS10 in the CNS.

4.2. Immune system

Various types of leukocytes express RGS10. Within the immune system, RGS10 is strongly expressed in monocytes/macrophages [101], T lymphocytes [53], dendritic cells [54], and mast cells [102], with relatively low expression in B lymphocytes [103] and neutrophils [104].

In peripheral macrophages, RGS10 is the most highly expressed RGS protein and has a central role in macrophage polarization. RGS10 suppresses classical M1 activation through the downregulation of NF-κB activation and inflammatory cytokines release, and promotes markers of the alternatively activated M2 phenotype [101]. RGS10 also modulates NLRP3

and NLRC4 inflammasome activity in activated BMDM [105]. Interestingly, long-term, but not short-term, Gαi inhibition by PTX treatment during macrophage growth and differentiation suppresses LPS-induced M1 markers and upregulates IL-4-induced M2 markers [105]. Thus, it will be interesting to test whether amplification of inflammatory M1-related genes seen in RGS10-deficient, activated BMDMs is affected by long-term PTX treatment. Therefore, RGS10 acts as an anti-inflammatory protein and a critical modulator in the regulation of peripheral macrophage activation and differentiation.

In addition to macrophages, high expression of RGS10 has been detected in human monocyte-derived dendritic cells and murine BM-derived dendritic cells [54]. Although RGS10 expression is downregulated following LPS treatment in macrophages [101], LPS-mediated dendritic cell activation does not affect RGS10 expression [54]. Dendritic cells are professional antigen-presenting cells, mainly inducing T cell activation. Similar to dendritic cells of wild-type mice, antigen presentation and induction of $CD4^+$ T cell proliferation are also observed in dendritic cells derived from RGS10-deficient mice [106].

A previous study has shown that RGS10 is found in human and mouse T cells, where its expression is upregulated in response to the activation of the chemokine receptor CXCR4 [53]. Functionally, loss of RGS10 enhances chemokine-induced Vav1–Rac1 activation mediating α4β1 and αLβ1 integrin-dependent T cell adhesion, while overexpression of RGS10 reduces this adhesion response triggered by chemokine treatment. In addition, the silencing of RGS10 amplifies Cdc42 activation mediating T cell migration following chemokine stimulation [53]. Collectively, these findings demonstrate that RGS10 is an efficient regulator that desensitizes signaling pathways controlling cellular immune responses.

4.3. Cardiac hypertrophy

Numerous recent studies have emerged that describe novel functions of RGS proteins in cardiovascular physiology and pathology [107]. Among various RGS proteins, RGS10 is expressed in normal human and mouse hearts, whereas RGS10 protein is significantly expressed at lower levels in failing human hearts and hypertrophic murine hearts. In addition, RGS10 protein expression is downregulated following Angiotensin II (AngII) treatment in neonatal rat cardiomyocytes [108]. However, the precise mechanism for the downregulation of RGS10 remains undefined.

Furthermore, the biological function of RGS10 in the heart has been proposed in the murine model of cardiac hypertrophy. Aortic banding mediated-pressure overload in RGS10-deficient mice displays cardiac hypertrophy, while overexpression of RGS10 alleviates this cardiac hypertrophy response [108]. Moreover, in RGS10-deficient neonatal cardiomyocytes, AngII induces hypertrophy, potentially through amplification of the MEK/ERK signaling pathway [108].

In addition, RGS10 has been reported to mediate the effect of β-adrenergic activation on endogenous G-protein-gated (GIRK) current deactivation in rat atrial myocytes [109]. Together, these findings strongly suggest that RGS10 is a cardioprotective protein through

inhibition of the signaling downstream of AngII receptor, while its suppression may contribute to cardiac remodeling pathogenesis.

4.4. Osteoclastogenesis

Substantial evidences have revealed critical roles of RGS proteins in modulating functions of osteoclasts, bone-resorbing cells that tightly regulate and contribute to the process of bone remodeling and related pathological diseases [110]. RGS10, like other RGS proteins, is highly expressed in human osteoclasts and murine osteoclast like-cells, whereas RGS10 expression is induced in osteoclasts precursors by RANKL stimulation [47, 111], a control step required for differentiation of osteoclasts precursors into mature osteoclasts.

More importantly, the silencing of RGS10 in preosteoclasts or BMMs treated with RANKL impairs osteoclast differentiation through blocking intracellular Ca^{2+} oscillation and loss of expression of NFATc1, a master switch transcription factor in the regulation of terminal differentiation of osteoclasts [47, 111]. In contrast, overexpression of RGS10 results in enhanced RANKL sensitivity leading osteoclastogenesis by regulating Ca^{2+} oscillation-NFATc1 signaling pathway. Consistent with its role in modulating osteoclast cell differentiation, RGS10-deficient mice exhibit severe osteopetrosis and osteoclast differentiation defects [111]. Interestingly, the reintroduction of either RGS10 or NFATc1 in BMMs derived from RGS10-deficient mice rescues osteoclastogenesis defects. Further elucidation of the mechanism reveals that RGS10 interacts in a competitive fashion with calmodulin (CaM) and phosphatidylinositol 3,4,5-triphosphate (PIP3) in a calcium-dependent manner leading to PLCγ activation and Ca^{2+} oscillation, which subsequently activate NFATc1 signaling required for osteoclast terminal differentiation [47, 111]. Therefore, RGS10 is a crucial factor of osteoclastogenesis through potential regulation of the crosstalk between G-protein signaling and RANKL-dependent signaling pathway.

Moreover, the inhibition of RGS10 mediated by adeno-associated virus (AAV) reduces osteoclast markers and regulates the immune response in a murine model of periodontal disease, which is associated with bone loss [112]. In addition to its role in osteoclasts differentiation, RGS10 is expressed in chondrocytes, the resident cells of the cartilage. Similar to RGS5 and RGS7, RGS10 promotes chondrocyte differentiation [113], suggesting that RGS10 is essential for chondrogenesis involved in the normal function and development of cartilage.

4.5. Platelet functions

Many GPCR agonists, such as thrombin, adenosine diphosphate (ADP), and thromboxane A2 (TxA2), regulate platelet activation, which is essential for physiological hemostasis or thrombosis [114]. In addition to RGS18, RGS10 is predominately expressed in quiescent platelets [115] and modulates platelet activation via binding to the spinophilin (SPL) scaffolding protein forming a complex with the SHP-1 protein tyrosine phosphatase [116]. Following exposure to platelet activators, SHP-1 is phosphorylated, which subsequently triggers the dephosphorylation of SPL and, in turn, the decay of this complex [116]. Dissociation of the complex increases free RGS10 levels and its availability to limit G-protein signaling and allows SPL to interact with PP1 phosphatase and inhibits its activity

[117], both of which regulate platelet activation. In addition to SPL/RGS10/SHP-1 complex, RGS10 interacts with 14–3-3γ scaffolding protein in resting platelets, whereas agonists of platelets induce RGS10 release from 14–3-3γ binding [118].

Furthermore, although RGS10 is a selective GAP for Gi family Gα subunits, platelets isolated from mice lacking RGS10 are hyperresponsive to stimuli that act via receptors coupled to Gi, Gq, and G12/13 proteins [118, 119]. In response to these stimuli, RGS10-deficient platelets exhibit aggregation, α-granule secretion, and integrin activation and enhance hemostasis and thrombogenesis [118, 119], without affecting platelet count and survival [120]. Along with more thrombosis formation, RGS10-deficient mice are more susceptible to ischemia [119]. Interestingly, RGS10 expression is higher in platelets of patients with aspirin resistance and metabolic syndrome compared to aspirin-sensitive patients [121], suggesting an indirect role for RGS10 in regulating platelet functions. Collectively, these studies indicate that RGS10 serves as a molecular brake on excessive activation of platelets and the process of pathological thrombosis.

4.6. Cancers

Given the enormous implications of GPCRs and cognate G-protein signaling in cancer initiation and progression [122], emerging evidences suggest a direct contribution of RGS proteins in tumor evolution, where dysregulation of RGS protein expression is observed and linked to many types of cancers [123]. RGS10 has been studied in ovarian cancer cells, where its expression is lower than normal ovary cells [49]. Interestingly, datasets comparing gene expression between multiple models of chemoresistant ovarian cancer cells and their parental, chemosensitive counterparts have demonstrated that the RGS10 transcript level is suppressed during the development of chemoresistance [124]. Further, RGS10 has been identified as a key modulator of ovarian cancer survival and chemoresistance, in which RGS10 knockdown via siRNA leads to enhanced ovarian cell viability and promotes chemotherapeutic drug resistance [124], potentially through activation of Rheb-GTP/mTOR signaling mediated ovarian cancer cell survival. Altman *et al.* (2015) have shown that RGS10 interacts with the monomeric GTP-binding Rheb protein, which is known to bind and activate the mechanistic target of rapamycin complex 1 (mTORC1). Elevated levels of active GTP-bound Rheb are observed in RGS10-deficient cells, which consequently amplify phosphorylation levels of AKT, mTOR, 4EB-BP1, p70S6 kinase, eIF2a, and ribosomal protein S6 [125].

A recent study has demonstrated RGS10-mediated regulation of Inflammatory signaling in SKOV-3 ovarian cancer cells, where the expression of TNF-α and COX-2 is robustly enhanced following RGS10 knockdown compared to control cells. Interestingly, the effects of RGS10 suppression on TNF-α and COX-2 expressions are independent of amplified Gαi signaling [98]. Given the finding that RGS10 modulates survival and chemoresistance of ovarian cancer and regulates inflammatory mediators' expressions that have recently linked to ovarian cancer chemoresistance [126–128], further work is needed to investigate whether amplification of inflammatory signaling accounts for the enhanced survival and chemoresistance observed in RGS10-deficient ovarian cancer cells.

In addition to the functional studies of RGS10 in ovarian cancer, there is a couple of correlative studies linking the change in RGS10 expression to poor prognosis of multiple cancers, including laryngeal cancer [82], hepatocellular carcinoma [79], and pediatric acute myeloid leukemia [122]. Therefore, these studies suggest that RGS10 may serve as a biomarker for cancer diagnosis and detection.

4.7. Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating autoimmune disorder affecting the CNS. Even though the exact etiology of this disease remains unknown, several hypotheses and a variety of factors have been proposed, involving the pathological role of autoreactive infiltrating T cells attacking myelin and initiating inflammatory processes mediated by proinflammatory cytokines release, which in turn exacerbate MS disease severity [129]. The global lack of RGS10 does not alter the distribution and baseline numbers of immune cells, including B cells, $CD4^+$ and $CD8^+$ T cells, and monocytes in the brain, blood, and lymphoid tissues [100]. In comparison to WT cells, naïve splenic $CD4^+$ T cells derived from RGS10-deficient mice exhibit intact TCR-induced proliferation, cytokine release, and *in vitro* Th1 or Th17 effector cell differentiation following activation by polarizing stimuli [106]. In contrast, in experimental autoimmune encephalomyelitis (EAE), a murine model of MS induced by myelin oligodendrocyte glycoprotein peptide fragment 35–55 (MOG35–55) immunization that mimics the immunopathological features of human MS, infiltration of both Th1 and Th17 cells in the CNS of RGS10-deficient mice (C57BL/6 background) is significantly reduced compared to WT counterparts (C57BL/6 background) [106].

Further, immunized RGS10-deficient mice have dramatically less clinical EAE symptoms associated with a significant reduction in T cell proliferation and cytokine production in response to *in vitro* MOG35–55 immunogen reexposure. Injection of *in vitro* differentiated RGS10-deficient Th1 cells (but not Th17 cells) into WT naïve recipient mice results in less EAE clinical phenotype compared to mice receiving *in vitro* Th1 cells from WT mice [106]. Due to its role in regulating T cell chemotaxis and its high expression in other immune cells, such as macrophages, further studies involving conditional knockout mice should aid in our understanding how RGS10 augments MS. Interestingly, in addition to the RGS1 protein, the transcript level of RGS10 is also higher in peripheral blood mononuclear cells (PBMCs) from MS patients compared to healthy individuals [130]. Therefore, this finding suggests that RGS10 modulates T cell functions that could contribute to this autoimmune disease.

4.8. Metabolic disorders

A high-fat diet (HFD), as one of the highly impactful environmental factors, induces body weight gain and central obesity, with various metabolic abnormalities. The role of RGS10 in metabolic changes related to HFD consumption has been studied in mice, where RGS10 expression is downregulated in the liver and upregulated in adipose tissues of WT mice fed with HFD compared to low-fat diet (LFD)-fed mice [131]. In comparison to WT, HFD-fed RGS10-deficient mice are more susceptible to the body weight gain associated with larger white adipose and liver tissue masses. More importantly, HFD-fed RGS10-deficient mice exhibit insulin resistance, while glucose intolerance and higher leptin levels are observed in

RGS10-deficient mice following either LFD or HFD feeding compared to WT mice [131]. Furthermore, since RGS10 serves as an anti-inflammatory protein in macrophage activation, RGS10-deficient mice fed with HFD are more susceptible to chronic inflammation, as evidenced by higher M1 inflammatory gene transcripts in the liver and adipose tissues and lower mRNAs of Fizz1 and YM1 anti-inflammatory M2 markers [131]. Thus, this study sheds light on the importance of RGS10 in managing HFD-induced body weight gain and related metabolic disorders.

5- Targeting RGS10 expression

Compelling evidence from several studies has shown that suppression of RGS10 in various cell types is linked to the pathogenesis of diverse diseases models, such as PD [48], cardiac hypertrophy [108], ovarian cancer chemoresistance [124], and osteopetrosis [47, 111]. More importantly, RGS10 expression is silenced in many of these cells, where the impact of RGS10 loss leads to these pathologies. For example, RGS10 expression is suppressed in microglia and neurons by inflammatory stimuli and in cardiomyocytes in response to AngII treatment. Likewise, RGS10 expression is significantly downregulated in multiple chemoresistant ovarian cancer cells compared to chemosensitive ones. As discussed above, both DNA methylation by DNMTs and histone deacetylation by HDACs mediate epigenetic silencing of RGS10 that could consequently contribute to the development of resistance to chemotherapy in ovarian cancer. Pharmacological inhibition of both enzymatic activities of DNMTs by 5-Aza and HDACs by TSA restore RGS10 expression and enhance the sensitivity of chemoresistant ovarian cancer cells to chemotherapy. Indeed, these inhibitors are not selective and have more side effects; thus, more work is needed to elucidate the molecular mechanisms and further protein targets that control RGS10 expression and function. Identification of these molecular mechanisms will provide valuable insight into the function of RGS10 and will facilitate strategies to target RGS10 in various disorders in which its function is implicated. Altogether, stabilizing RGS10 expression could potentially be a useful and promising strategy in the treatment of various ailments.

6- Conclusions and future perspective

Since its initial discovery, growing knowledge and considerable progress have been achieved in defining the canonical GAP functions, as well as regulatory mechanisms of RGS10 and its potential roles in a number of pathophysiological states. Despite its simple structure, the studies discussed herein suggest that RGS10 is a critical modulator of G-protein and inflammatory signaling and a wide range of physiological cellular processes, including survival, polarization, adhesion, chemotaxis, and differentiation in multiple types of cells. Together, these findings implicate RGS10 as an attractive and promising therapeutic target for the treatment of pathological conditions in various target cells, in which alteration in its expression and function is involved. Although RGS10 has many functions in these systems, the molecular mechanisms governing its functions have not been fully defined. Therefore, further research should focus on identifying binding partners of RGS10, which will be fundamental in understating both the mechanism underlying RGS10 function and the mechanism controlling RGS10 expression in different disease states. As discussed above, RGS10 expression is suppressed following different signals in several cellular and animal

models, which in turn impacts their pathophysiology. Thus, defining regulatory factors in a specific cellular environment will facilitate the development of therapeutic strategies to target RGS10 in all its implicated diseases. In addition, it will help future efforts to design and identify selective compounds that stabilize RGS10 expression using high-throughput screening libraries. Given the high expression of RGS10 in immune cells, particularly macrophages, and its role in the regulation of inflammatory responses in these cells, future studies could explore the role of RGS10 in infectious disease models in which immune and inflammatory responses have a significant influence.

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Abbreviations

AC	adenylate cyclase
AlF4	aluminum fluoride
AngII	angiotensin II
AR	androgen receptor
ATP	adenosine triphosphate
BMDMs	bone marrow-derived macrophages
CaM	calmodulin
CNS	central nervous system
COX-2	cyclooxygenase-2
DNMTs	DNA methyltransferases
ERK	extracellular signal-regulated kinase
GAP	GTPase-activating protein
GDP	guanosine diphosphate
GEFs	guanine nucleotide exchange factors
GFP	green fluorescent protein
GIRK	G protein-coupled inwardly-rectifying potassium channel
GPCR	G protein–coupled receptor
GTP	guanosine triphosphate
HATs	histone acetyltransferases

HDACs	histone deacetylases
6-OHDA	6-hydroxydopamine
HFT	high fat diet
kDa	kilodalton
KD	knockdown
KO	knockout
LFD	low-fat diet
L/MGE	lateral/medial ganglionic
LPS	lipopolysaccharide
MN9D	mesencephalon neuroblastoma cell
MS	multiple sclerosis
NFATc1	nuclear factor of activated T cells 1
NF-κB	nuclear factor kappa B
PGE2	prostaglandin E2
PD	Parkinson’s disease
PKA	protein kinase A
PTM	post-translational modifications
PTX	pertussis toxin
RANKL	receptor activator of nuclear factor (NF)-kB-ligand
RGS	regulator of G protein signaling
siRNA	small interfering RNA
SNP	single nucleotide polymorphism
SNpc	substantia nigra pars compacta
TLR	toll-like receptor
TNF-α	tumor necrosis factor-alpha
TSA	trichostatin A
WT	wild-type

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Highlights

- RGS10 is dysregulated in response to multiple stimuli and various disease models.
- Epigenetic and post-translational mechanisms regulate RGS10 expression and function.
- RGS10 has emerged functions in cellular physiology and pathology.
- Stabilizing RGS10 expression represents a promising therapeutic strategy.

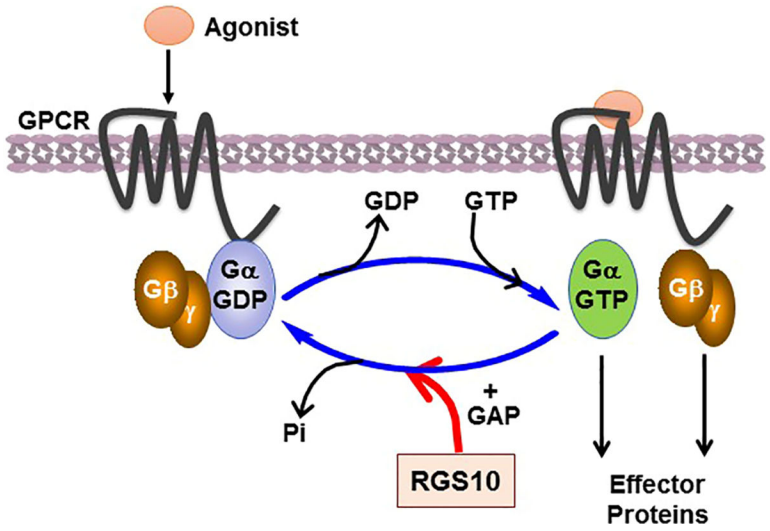

Figure 1: G-protein activation and RGS protein-mediated deactivation cycle.

In response to various agonists, the seven transmembrane GPCR undergoes a conformational change and induces the exchange of GDP to GTP on Gα and dissociation from Gβγ dimer, which, in turn, both activated GTP-Gα and Gβγ dimer regulate downstream effectors. This cycle is terminated by the GAP activity of RGS proteins, which accelerates hydrolysis of GTP to GDP and thus terminates GPCR signaling.

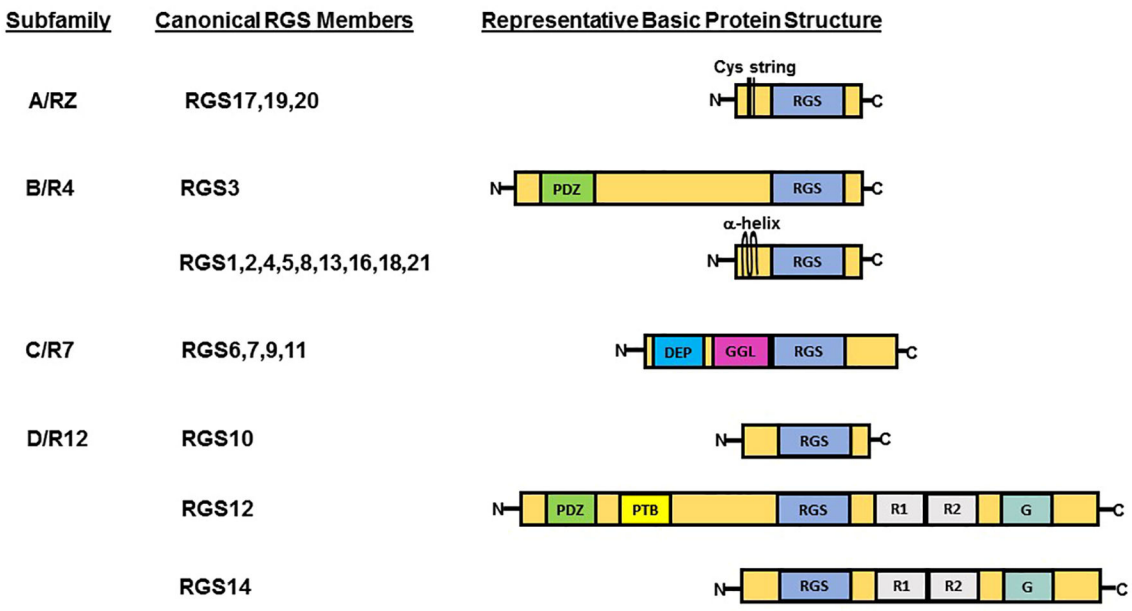

Figure 2: Classification and illustration of canonical RGS proteins based on the homology of the RGS domain and the presence of other common structural domains.

Protein domain and motif abbreviations are indicated as following: Cys string, cysteine string; α-helix, an amphipathic alpha–helix; RGS, regulator of G-protein signaling domain; DEP, disheveled EGL10-Pleckstrin homology domain; GGL, G protein gamma subunit-like domain; R1&R2, Ras/Rap-binding domain; G, G protein regulator motif; PTB, phosphotyrosine binding domain; PDZ, PSD95/Dlg/Z0-1/2 domain.

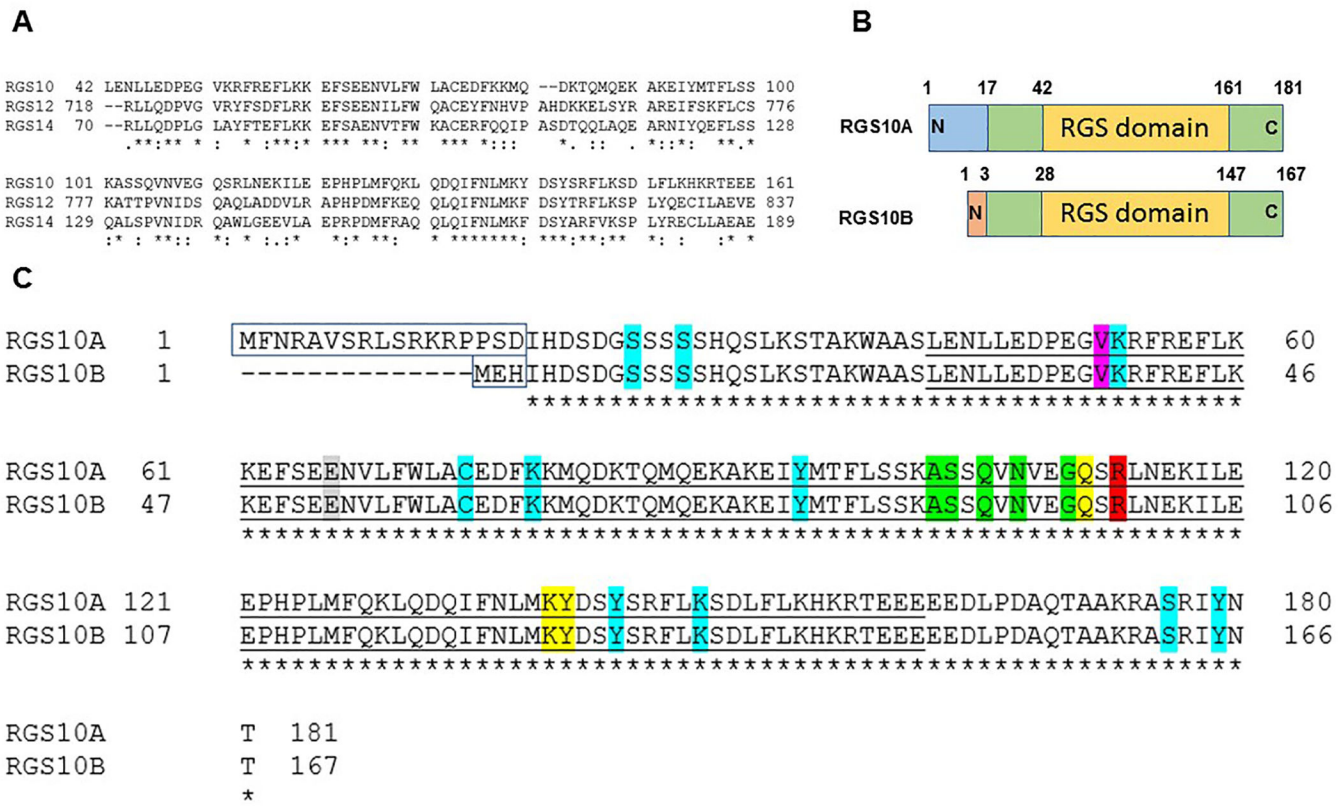

Figure 3: RGS10 isoforms: structure and analysis.

(A) Clustal Omega as a multiple sequence alignment program was used to align the RGS domain sequences within the D/R12 subfamily of human RGS proteins. (B) Schematic of the RGS10 isoform structures. (C) Alignment of human RGS10 isoform sequences using Clustal Omega program. Unfilled boxed amino acids represent N-terminal splice variants. Conserved catalytic RGS domains are underlined. The bright green highlighted residues, including (A102(88), S103(89), Q105(91), N107(93), G110(96)) are critical residues of RGS10 for the interaction with Gαi3 according to RGS10:Gαi3-AlF4^{-} crystal structure (Protein Data Bank: 2IHB). The yellow-highlighted residues are putative disruptor residues, including Q111(97), K139(125), and Y140(126) that are predicted to impair the interaction with the Gα helical domain. The red-highlighted residue R113(99) is a conserved arginine residue within the RGS domain that does not contact the Gαi3 switch III region. The pink highlighted residue is a putative SNP that has been linked to schizophrenia. The gray-highlighted residue is the GAP dead mutation site based on the characterized GAP-dead mutation site in the RGS domain of RGS12 protein. Residue positions highlighted with turquoise are reported human RGS10 PTMs sites, including phosphorylation residues (S24(10), S27(13), Y94(80), Y143(129), S176(162), Y179(165)), ubiquitination residues (K53(39), K148(134)), palmitoylation C74(60) residue, and acetylation K78(64) residue.

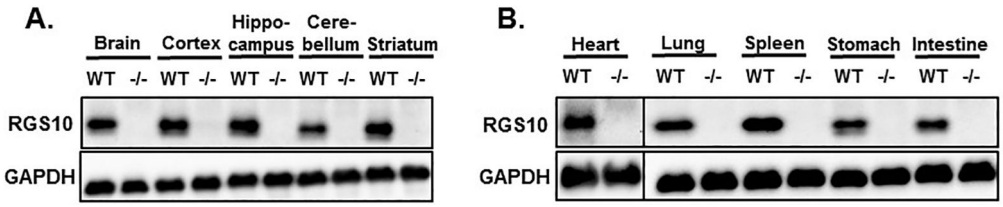

Figure 4: RGS10 protein expression in various tissues.

RGS10 protein expression was determined and compared by immunoblot analysis in (A) indicated brain regions, or (B) peripheral tissues (heart, lung, spleen, stomach, and intestine) of WT and RGS10-deficient mice. GAPDH was used as a loading control.

Table 1:

Subcellular localization of RGS10

Cells	Endogenous/ Ectopic expression	Predominant localization under resting condition	Stimulus/modification	Predominant localization after cellular stimulation	Reference
COS-7	Ectopic	Nucleus	ND	ND	[57]
Neurogliom a (H4)	Endogenous	Nucleus	ND	ND	
HEK293	Ectopic	Cytoplasm	Forskolin/ phosphorylation by PKA at (Ser 168)	Nucleus	[63]
PC3-AR	Ectopic	Nucleus	Melatonin or 8-bromo-cGMP	Cytoplasm	[64]
Primary microglia	Endogenous	Cytoplasm=Nucleus	LPS	Nucleus	[48]

ND indicates not determined.

Table 2:

Regulation of RGS10 expression

Cell/Tissue	Stimuli/Disease model	mRNA/ Protein	Expression	Reference(s)
BMDM cell	FSL-1 100 nM (2&6 h)	mRNA	Decrease	[132]
	LPS 10 ng/ml (3 h)	mRNA		
	LPS 100 ng/ml (48 h)	Protein	Decrease	[101]
Primary microglia cell	LPS 10 ng/ml (6 h)	mRNA	Decrease	[78]
	LPS 10 ng/ml (24,48&72 h)	Protein	Decrease	[48]
BV2 cell	LPS 10 ng/ml (4–72 h)	mRNA	Decrease	[78]
	LPS 10 ng/ml (48 h)	Protein		[48]
	TNF-α 10 ng/ml (24,48&72 h)	Protein		
	TSA 100,250,500 nM (24 h)	mRNA	Increase	[78]
	S1P 10 μM (48 h)	mRNA		
Spinal dorsal horn (L4-L5) tissue	pSNL model of inflammatory neuropathic pain (72 h)	Protein	Decrease	
MN9D cell	TNF-α 10 ng/ml (6&24 h)	mRNA/ Protein	Decrease	[99]
Phagocytic (MGdNΦ) microglia cell	Injection of apoptotic neurons (dN) into the cortex and hippocampus of WT mice	Protein	Decrease	[133]
Chondrocytes	Differentiation (9,12&15 days)	mRNA	Increase	[113]
Hippocampus	Acute electroconvulsive seizures ECS (24 h)	mRNA	Decrease	[134]
Ventral tegmental	Amphetamine (AMPH) self-administration	mRNA	Decrease	[135]
SKOV-3 cell	Cisplatin 100 μM (48 h)	mRNA	Decrease	[124]
	5-Aza (3,5,7&9 days)	mRNA	Increase	[49]
A2780-AD cell	TSA 500 nM (48&36 h)	mRNA	Increase	[76]
	5-Aza 10 μM&20 μM (3,5&7 days)	mRNA		
Caco-2 cell	Black tea polyphenol (Theaflavins TF-2) 50 μM (4–24 h)	mRNA	Increase	[136]
Striatum	Reserpine Acute treatment (30 min)	mRNA	Increase	[137]
	Daily reserpine (5 days)		Decrease	
Neonatal rat cardiomyocytes	Angiotensin II 50 μmol/L (24&48 h)	protein	Decrease	[108]
Human neural progenitor (hNP)	5-Aza 5 μM (5 days)	mRNA	Increase	[77]
Molt-4 cell	CXCL-12 (30&60 min)	protein	Increase	[53]
Osteoclast derived BMM	RANKL+M-CSF (10 ng/ml) (30 min-96 h)	mRNA	Increase	[111]
		protein		
RAW264.7 cell	RANKL+M-CSF (10 ng/ml) (30 min-96 h)	mRNA	Increase	[47]
Paw and spinal cord	Trimethylamine *N*-oxide (TMAO) (24 h)	Protein	Decrease	[138]

BMDM, bone marrow derived macrophage; FSL-1, Pam2CGDPKHPKSF, synthetic diacylated lipoprotein; LPS, lipopolysaccharide; MN9D, mesencephalon neuroblastoma cell line; RANKL, receptor activator of nuclear factor-κB-ligand; TNF-α, tumor necrosis factor-alpha; TSA, trichostatin A; 5-Aza, 5-Azacytidine; M-CSF, Macrophage colony-stimulating factor; S1P, sphingosine-1-phosphate; pSNL, partial sciatic nerve ligation.

Table 3:

RGS10-associated loss of function phenotypes and disease links

Phenotype(s)	Proposed disease links	Year	Reference(s)
Impaired osteoclasts differentiation	Osteopetrosis	2007	[47, 111]
Neuroinflammation and neurodegeneration	Parkinson's disease and a possible link to schizophrenia	2008	[48, 94, 96]
Reduced chemotherapy-induced cell death	Ovarian cancer chemoresistance	2010	[124, 125]
Hypertrophy following pressure overload	Heart failure	2015	[108]
Platelets aggregation and thrombogenesis	Aspirin resistance	2016	[119, 121]
Increased body weight with insulin resistance and glucose intolerance	Obesity and related metabolic syndromes	2019	[131]