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Research progress of regulatory factor 6 of G protein signaling pathway and tumor

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Abstract

The RGS protein controls the magnitude and duration of GPCR signaling by acting as a GTPase-activating protein of the G subunit, and this activity is governed by the RGS structural domain. RGS6's GAP function is prominent in the circulatory and cerebral nervous system domains, and RGS6 was found to achieve its apoptosis-promoting and growth-inhibiting pathways via non-G protein pathways in several tumor-related experiments. RGS6 was found to promote tumor cell apoptosis and growth inhibition pathways via non-G protein pathways in several tumor-related assays and to play a similar role in breast tumor tissue.

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Introduction

Regulator of G protein Signaling pathway (RGS) protein is an important valve to regulate the G Protein-Coupled Receptor (GPCR)-mediated cellular response induced by activation of heterotrimeric G protein. The RGS protein determines the size and duration of GPCR signaling through GTPase activator protein, a Gα subunit. This activity is determined by its RGS domain. The R7 RGS protein subfamily has two distinct domains, DEP/DHEX (Dishevelled, Egl-10 and Pleckstrin domain/DEP helically extended) and GGL (G protein gamma subunit-like), that mediate the membrane targeting and stability of these proteins. RGS6, a member of R7 subfamily, specifically regulates the activity of G protein. Interestingly RGS6 is the only protein with a signal regulation mechanism independent of G protein within the RGS family. In addition it has been found in multiple tumor-related experiments where RGS6 is promoting tumor cell apoptosis and growth inhibition through a non-G protein pathway, and similar effects where discovered in breast tumor tissues.

G protein and G protein-coupled receptor

G Protein Coupled Receptors (GPCRs) consist of one peptide chain containing seven α-helix transmembrane domains, which divide the receptors into extracellular N-terminal, three extracellular rings, intracellular C-terminal, and three intracellular rings [1]. Two highly conservative cysteine residues on the outer ring play a key role in the stability of the spatial structure through disulfide bonds, and a site on the inner ring binds to G protein. GPCRs participate in many physiological processes, such as sensitization, behavioral and emotional regulation, immune system regulation, autonomic nervous system regulation, and maintenance of a steady state. It is one of the important pathways for information transmission inside and outside of cells [2-4]. GPCRs, with a special seven-transmembrane α-helix structure, are regarded as the protein with the largest molecular weight in the human body. It receives a series of extracellular signals, such as hormones in the blood, neurotransmitters between synapses, and some cytokines, through the structural domain exposed to the surface of the cell membrane, trans-

mitting the signals from the outside to the inside of the cell, which regulates the activities of relevant enzymes inside the cell through coupling with G protein.

The heterotrimeric guanine nucleotide binding protein (G protein) is an uncoupling protein located between the GPCRs and the effector substrate. The G protein is composed of three different subunits, named Gα, Gβ, and Gγ, with a total molecular weight of about 100 KDa. The Gβ and Gγ subunit exist as dimers, and the dimers of Gα and GβGγ subunit are anchored to the plasma membrane by covalently bonded lipid molecules, respectively. Gα subunit has a GTP enzyme activity, and the dimer of GβGγ subunit acts as the anchor point of Gα subunit on the cell membrane. When the spatial conformation of GPCRs is changed after combining with an extracellular ligand, the corresponding heterotrimer G protein is dissociated from the C-terminal of GPCRs located inside the cell and the linked fifth and sixth transmembrane segment. At the same time the Gα subunit is also dissociated from the GβGγ subunit, exposing the binding site with nucleotide cyclase (AC). The Gα subunit further binds to AC, and the free Gα-GTP is in the activated open state, resulting in binding and activation of effector proteins, followed by signal transduction. At the end of signal transduction, both GTP on Gα subunit are hydrolyzed by GTP enzyme to GDP, and Gα subunit and GβGγ subunit are affinity converted into heterotrimer G protein, which is reset into a resting state before the next signal regulation transmission accrues [5]. G protein has a variety of regulatory functions, including the activation and inhibition of adenylate cyclase by Gs and Gi, the regulation of cGMP phosphodiesterase activity, the regulation of phospholipase C, and the regulation of intracellular Ca^{2+} concentration. GPCRs act as Guanine nucleotide Exchange Factors (GEFs) on the Gα subunit, transforming extracellular stimuli into intracellular signaling cascades. Based on this cycle, the duration of the heterotrimeric G protein signal is considered to be controlled by the lifetime of the Gα subunit in its GTP-binding state [6].

However, although the Gα subunit can hydrolyze GTP and inactivate itself, this process is rather slow and does not account for the rapid inactivation kinetics observed under physiological conditions. In 1996, many scholars found and identified RSG as an RGS family, which combined with G protein subunits through an "RGS box" domain of about 120 amino acids, significantly accelerated its internal GTP enzyme activity, thus performing negative feedback regulation on GPCRs [7-15]. The RGS protein is capable of accelerating GTP enzyme activity up to 1000 times [16]. The discovery of RGS protein and its GTP enzyme Accelerating Protein (GAP) activity on G subunit not only solves the obvious timing conflict between the known GPCRs-mediated physiological response and the *in vitro* activity of related G proteins but also helps reveal the hitherto unrecognized role of G protein subunits in cellular processes outside the GPCRs signaling domain through the discovery of new functional domains in members of the RGS protein family.

G protein receptor regulatory factor

In the mid-1990s, through the integration of studies by multiple scholars, RGS proteins were found as a family. First, the findings in *S. cerevisiae* identified a new factor, Sst2, which regulates the sensitivity of the pheromone, as a modulator of GPA1, the yeast Gα subunit [8,17]. Koelle and Horvitz demonstrated that a functional deletion mutation in the egl-10 gene results in reduced oviposition and locomotor behavior in *C. elegans* [10]. This effect was in contrast to the functional deletion mutation of G protein GOA-1 in *C. elegans*. The authors assumed that the two proteins might play a role in a common signaling pathway, with one positively regulated and the other negatively regulated. They subsequently demonstrated a high degree of sequence similarity between EGL-10 and the yeast protein Sst2, as well as several mammalian proteins we now call RGS proteins, including RGS1 (formerly BL34 and 1R20), RGS2 (formerly G0S8) and the closest RGS7 [10]. Over the same period, Gilman's laboratory described the first biochemical function of mammalian RGS proteins, demonstrating that protein RGS4 and GAIP (now called RGS19) can be used *in vitro* as a complement to certain Gα subtypes, including all members of the Gαi subfamily [18]. In 1997, Doupnik et al. demonstrated that the heterologous expression of RGS4 in *Xenopus* oocytes replicates the time-dependent inactivation of the G protein-coupled inward rectifier potassium channel [19]. Based on the research by various scholars, it has been summarized that (1) RGS protein directly interacts with G protein α subunit; (2) The interaction of RGS with these α subunits increases the rate of hydrolysis (GAP activity) of GTP by Gα; (3) different RGS proteins pair different Gα subunits [13,20,21]. Further studies on the mechanism of RGS protein activity explored how these proteins established their typical GTP enzyme activation or GAP activity by stabilizing the transition state of GTP hydrolysis. With the research on the activity mechanism of RGS protein, others have begun to pay attention to the structure of RGS protein. To clarify the key structural determinants of the interaction between RGS and Gα and the structural basis of its GAP activity [22]. At the same time, the study focused on the cellular effects of RGS protein as a family and explored the downstream effectors of RGS protein. The in-depth study of RGS protein not only revealed the number of mammalian RGS proteins (and genetic variants) present but also the diversity of the protein family itself. Moreover, the activity of RGS protein is usually regulated by controlling expression, stability, and localization, rather than by ligand binding. Therefore, RGS protein is not directly regulated by small molecules like GPCRs. Since the discovery of RGS proteins, they have been divided into structural and functional families. The RGS protein family was established and named after its prototypical members: A/RZ, B/R4, C/R7, D/R12, E/RA, F/GEF, and G/GRK [23].

G protein receptor regulatory factor R7 family

R7 RGS protein members include RGS6, RG7, RGS9, and RGS11. These RGS proteins all contain four domains, RGS+GGl+DEP/DHEX, with binding between the three components, and R7 RGS protein is generally considered to be a heterotrimeric complex consisting of three subunits. The central element of this complex is formed by the RGS molecule itself, which shares a common domain tissue across all R7 RGS members. The key feature of all RGS proteins, namely the catalytic RGS domain, is located at the C- terminal end of the molecule and constitutes the only enzymatically active moiety in the complex. The RGS domain of all R7 RGS proteins is capable of stimulating GTP hydrolysis on Ga protein subunits [24,25]. From an enzymatic point of view, this process can be considered to be accompanied by the release of inorganic phosphates, the conversion of active Ga-GTP species to inactive Ga-GDP species, known as GAP function (GTP enzyme activator protein) [26]. The RGS domain of the R7 RGS protein acts as an effective gap even when isolated from other non-catalytic domains [27,28]. Upstream of the RGS domain, the R7 RGS protein carries a second conservative feature, the G protein gamma-like (GGL) domain. This domain is structurally homologous to the

conventional C subunit of the G protein [29]. Like all G protein subunits, the GGL domain binds to its essential partner, the Gβ subunit. However, unlike conventional Gc subunits, this interaction of the GGL domain is incredibly specific because it can only form a coiled interaction with Gβ5(5, a distant member of the G protein B subunit family (type 5 G protein β subunit)) [30-32]. The recently resolved crystal structure of the RGS9 Gβ5 complex revealed that the interaction between GGL and Gβ5 closely follows the same configuration and binding mechanisms observed in conventional dimers [33]. Finally, the N- terminal region of the R7 RGS protein consists of the DEP(Dishelved, Egl-10, Pleckstrin) and DHEX (DEP helically extended) domains [33,34]. The DEP domain is found in many signaling proteins, whereas the DHEX domain is specific to the R7 RGS protein. Two crystal structures and chimeric mutagenesis studies indicated that the DEP and DHEX domains form a single functional domain in the molecule. Recent studies have shown that the DEP/DHEX module of the R7 RGS protein is responsible for their interactions with two novel membrane proteins R9AP (RGS9 ankyrin) and R7BP (R7 family binding protein) [35]. There is increasing evidence that alternative splicing is a powerful mechanism that affects three members of the R7 RGS family: RGS6 [36], RGS9 [37], and RGS11 [38].

In conclusion, the R7 RGS protein consists of three building blocks: (1) A catalytic RGS domain, (2) a GGL domain that recruits Gβ5 subunits, and (3) a DEP/DHEX domain that mediates receptor interactions.

G protein receptor regulatory factor 6

Gene structure of RGS6

Human RGS6 is located on chromosome l4. The RGS6 gene consists of 629,635 base pairs, including 19 introns and 20 exons, with the exons between bases 51 and 332, encoding 36 different transcriptional fragments, which are composed of long-chain or short-chain N-terminal domains, complete or incomplete GGL domain, 7 different C-terminal domains and a common internal RGS domain combination. The first RGS6 mRNA expression was initially found in the mammalian brain [39]. The transcription product is also remarkably expressed in the heart, and RGS6 immunostaining is strongest in mouse myocardium compared with other co-cultured cells (such as endothelial cells) [39]. In addition to brain and heart, the expression of RGS6 in human tissues can also be found in a variety of peripheral tissues, such as lung, bladder, omental adipose tissue, and gastrointestinal tract [40].

Functions of RGS6

RGS6 is a member of the R7 subfamily of RGS proteins (RGS6, RGS7, RGS9, RGS11), which shares the RGS domain, GGL and DEP/DHEX. These three regions together regulate the stability, localization and function of RGS6 protein. As being a member discovering the R7 family, Fisher Lab first identified and cloned RGS6, further demonstrating the presence of complex alternative splicing of RGS6 in the brain; Splicing of the two primary RGS6 transcripts resulted in 36 different subtypes, each with a different protein structure, affecting its stability and subcellular localization. All RGS6L subtypes have the signature RGS and DEP/DHEX domains, distinguished by nine different C- terminal sequences and the presence or absence of a complete GGL domain [36]. The interaction between GGL domain and the atypical Gβ subunit Gβ5 is a basic condition for the stability of the entire R7 protein subfamily, and also a necessary condition for the stability of RGS6 protein [30,41]. Genetic ablation of the Gβ5 gene (GNB5) is strongly associated with loss of the R7 protein subfamily in the retina and striatum, as evidenced by [42]. Moreover, the ability of Gβ5 to stabilize RGS6 may not only depend on its interaction with GGL domains, but may require the simultaneous formation of specific domains with DEP/DHEX. It could be demonstrated that Gβ5 interacts with the DEP/DHEX domains of RGS7 and RGS9, members of the R7 family, and the Gβ5 residue mutations that mediate this interaction and thus can lead to instability of the two RGS proteins [43-45]. In addition to promoting protein stability, the GGL and DEP/DHEX domains are responsible for regulating the targeting function of RGS6 cells. The transfection of COS-7 cells with GFP-labeled RGS6 splicing variant has revealed that the GGL domain could stabilize the expression of RGS6 in the cytoplasm. The entry of GFP-labeled RGS6 into the nucleus may be noted when the GGL domain is lost due to alternative splicing, or when Gβ5 is overexpressed to produce the RGS6:Gβ5 complex [36]. Similarly, DEP/DHEX domain also has the function of regulating the cytoplasmic nuclear entry of RGS6. Further studies on subcellular localization of GFP-labeled RGS6 protein variants in COS-7 cells have shown that RGS6 splicing variants containing DEP/DHEX domain are mainly expressed in the cytoplasm, while those RGS6 lacking this domain are mainly expressed in the nucleus [36]. This differential subcellular localization of RGS6 may be related to its biological function. For example, immunohistochemical analysis of RGS6 protein localization in the mouse cerebellum using Fisher's laboratory-generated antibodies against the N-terminal protein domains common to all RGS6L isoforms revealed that subtypes of RGS6 have different cytoplasmic and nuclear localization patterns [36]. To further support the functional relevance of this differential subcellular localization, other R7 family members, in particular RGS7, RGS9, and Gβ5, were also shown to have different cytoplasmic and nuclear localization patterns [46]. Therefore, the localization of RGS6 on the plasma membrane is crucial to its function, and its co-expression with Gβ5 affects the nuclear localization of RGS6. The expression of RGS6 mRNA was first found in mammalian brain and that level of transcription was also evident in the human heart [47,48]. Using antibodies to the unique N- terminal of RGS6, nervous system expression with multiple bands of RGS6 immunoreactive bands were confirmed in multiple brain regions, including the cortex, hippocampus, cerebellum, striatum, and ventral tegmental area. RGS6 expression was also found in multiple peripheral tissues including the heart and lung [49].

GAP function of RGS6

RGS6 plays a role in the signaling of negatively regulated heterotrimeric G proteins. The RGS domain is responsible for the GAP activity of RGS6 and other RGS proteins and allows it to negatively modulate Gαi/o proteins [50]. In neuron-like cells, RGS6 interacts with neuronal growth-related protein 2(stathmin-like 2, STMN2) to promote neurite growth and cell differentiation [51]. The RGS6-specific regulation of Gαi/o protein activity is associated with the regulation of several disease states, particularly in the central nervous system. Most neurotransmitters such as dopamine, 4-aminobutyric acid (GABA), opioids and 5- hydroxytryptamine interact with GPCRs, and RGS with G protein-dependent signaling may provide therapeutic targets for treatment [52-54]. Studies have shown that RGS6 has the ability to negatively regulate the GABA-B receptor signal in the cerebellum [55]. In addition, there is also evidence that RGS6 is capable of regulating the signaling of other GPCR, such as 5-HT and opioid receptors [56,57]. As the therapeutic target of GABA

receptor, the function of RGS6 lies not only in its ability to regulate alcohol addiction but also in its ability to inhibit the signaling pathway of alcohol-induced organ damage. RGS6 has been identified as a potential therapeutic target for the treatment of alcoholism [58,59]. Based on the hypothesis of the regulatory function of RGS6 on 5-HT, studies have found that by reducing the regulation of RGS-mediated 5-HT receptor, it can lead to the enhancement of 5-HT receptor signaling within a mouse model [56]. Further studies shown that RGS6 played a role as a key regulator of 5-HT receptor signaling, and RGS6-/- mice also show spontaneous anti-depressant and anti-anxiety behaviors [60]. Based on the hypothesis that RGS6 regulates the function of dopamine, some scholars have found in the study of Parkinson's disease that the loss of dopaminergic neurons is closely related to the down-regulation of RGS6 mRNA. Researchers have established the first animal model of Parkinson's disease and confirmed that the pathogenesis caused by the knock-out of the single gene RGS6 is very similar to human diseases [61]. Subsequently, more studies found that the Single Nucleotide Polymorphisms (SNP) in RGS6(rs4899412) was significantly correlated with the volume change of caudate nucleus in patients with Alzheimer's disease [62]. Another SNP in RGS6(rs2332700) is strongly associated with schizophrenia [63]. In the circulatory system, a study found that the heart expressed a large number of RGS proteins [64]. RGS6 is a major modulator of the parasympathetic nerve that stimulates the heart [65]. The expression of RGS6 is enriched in the sinoatrial node and atrioventricular node, the main pacemaker parts of the myocardium. The absence of RGS6 leads to the activation enhancement of M2R-dependent GIRK channel, the inhibition of action potential discharge in sinoatrial node and bradycardia [66].

Non-GAP function of RGS6

RGS6 is not dependent on the potential key signaling of G protein, and its regulation of G protein signaling is a previously unrecognized domain in the RGS6 protein subclass. Initial studies have shown that heat stress, protein toxicity stress, or transcription-related stress can induce the transport of RGS6 to the nucleus. The RGS domain of RGS6 is primarily responsible for promoting stress-induced nucleolus accumulation, which is one of the first proven functions of the RGS domain beyond the modulation of G protein [67]. Further studies have confirmed that RGS6 expression can be changed in diseases where the cellular stress pathway may be activated, such as ischemic stroke [68]. Many subsequent studies have revealed that the G protein-independent pathway of RGS6 is more closely related to the tumor. RGS6 is unique in that it is the only member in the R7 protein family that has been proven to regulate the G protein-independent pathway [69-71].(The non-GAP functions of RGS6 are described in detail in the next section on neoplasms).

RGS6 and tumor

GPCRs are overexpressed in many cancers and drive tumor cell growth and metastasis. Therefore, GPCR signal has become a target in cancer biology [72]. Given their ability to negatively regulate the GPCR signal, it is conceivable that the RGS protein may act as a tumor suppressor or regulate carcinogenesis. To support this hypothesis, RGS protein was first associated with cancer in 2004, when SNPs in the RGS6 gene (rs2074647) were found to be positively associated with a reduced risk of bladder cancer, particularly in smokers who found that RGS6 SNP promote the translation of RGS6 mRNA and enhance its stability, especially in those bladder cancers induced by carcinogens [73]. These findings for the first time revealed the critical role of RGS6 as a tumor suppressor and a signaling mediator for DNA damage. Initial studies have shown a positive correlation between SNP in RGS6 and a reduced risk of bladder cancer, and further studies have helped to solidify the role of RGS6 as a tumor suppressor. First, the same RGS6 SNP found in previous bladder cancer studies was also associated with a reduced risk in lung cancer [74,75]. Second, it was found that RGS6 expression was negatively correlated with human breast cancer progression [70,76]. In addition, RGS6-knockout mice showed accelerated carcinogenesis with carcinogen exposure and accelerated progression of spontaneous breast tumors [76]. Finally, a similar trend has been described in human pancreatic cancer where RGS6 expression was again found to be negatively correlated with tumor grade and prognosis [77]. It has been proven in a study of drug-resistant cell model of acute leukemia that the target gene inhibits the degradation of DNMT1 by down-regulating the GGL domain of RGS6, thereby inducing model cells to express multi-drug resistance characteristics [78]. Recent studies have found that RGS6 mRNA and protein levels are down-regulated in human lung cancer tissues compared to non-cancer patients. in non-small cell lung cancer. Low levels of RGS6 are more prominent in metastatic lung cancer tissues and are associated with poor prognosis in patients with lung cancer. Overexpression of RGS6 inhibits EMT induced by non-small cell cells through the TGF-β pathway *in vitro* and inhibits the metastatic mechanism of non-small cell lung cancer cells *in vivo* [78].

In summary, these studies have described RGS6 as a potential tumor suppressor that is down-regulated as the tumor progresses. With one exception, RGS6 mRNA is expressed at a higher level in ovarian cancer cell lines compared to noncancerous cells, in contrast to the studies described above. Here, RGS6 can be used as a typical RGS protein, which has been proven to be related to the inhibition of lysophosphatidic acid receptor 2 signaling that drives the progression of ovarian cancer [79].

RGS6 and breast cancer

RGS6-mediated doxorubicin-induced cytotoxicity

Therapeutic strategies for breast cancer include surgery, hormone therapy, radiotherapy and adjuvant chemotherapy. Nevertheless, the treatment of breast cancer remains challenging, in part due to resistance to radiotherapy and conventional chemotherapy drugs [80]. Doxorubicin (Dox) is one of the most effective and widely used chemotherapeutic agents for the treatment of breast cancer [81]. The therapeutic effect of Dox depends on its ability to induce Double-Stranded DNA fragmentation (DSDBs) and activate DNA Damage Response (DDR) [82]. In view of the finding that SNP in RGS6 can increase its expression and prevent smoking-related cancers, assuming that RGS6 may promote DDR, the following experiments not only confirmed that RGS6 promotes DDR, but also confirmed that RGS6 is effective for detecting Dox-mediated ataxia telangiectasia mutant (ATM)-p53 apoptotic cells in Mouse Embryonic Fibroblasts (MEFs) and MCF-7 breast cancer cell lines [71]. First, Dox administration was found to result in simultaneous up-regulation of RGS6, accompanied by phosphorylation and up-regulation of p53. Moreover, in RGS6-deficient MEFs and MCF-7 cells, p53 response to Dox was almost completely absent, suggesting that RGS6 was necessary for p53 activation. Second, it was found that RGS6 was also necessary for autophosphorylation and activation of ATM. Once the DNA damage was too severe, the cells sensed and repaired it to initiate the p53-dependent apoptotic cascade. Finally, transient expression of RGS6 or its GAP-deficient mutants rendered MCF-7 cells susceptible to sub-

optimal doses of Dox, suggesting that RGS6 promotes the activation of the ATM-p53- apoptotic pathway through a G protein-independent mechanism. In fact, Dox-induced ROS production is RGS6 dependent, with both ATM activation and p53 phosphorylation mediated by ROS scavengers. Taken together, these findings reveal a novel mechanism of Dox treatment, namely, RGS6 mediated Dox-induced, RGS6-dependent ATM and p53 activation [71].

RGS6 as a tumor suppressor in breast cancer

Some scholars have found that RGS6 is restrictively expressed in human mammary duct epithelial cells and lost in these cells along with the progression of cancer, and proposed for the first time that RGS6 may have the function of tumor suppressor [70]. Therefore, in order to evaluate the potential of RGS6 as a tumor inhibitor, the effect of exogenous RGS6 expression on the proliferation of various cancer cell lines was studied. These experiments have demonstrated that RGS6 has strong anti-proliferative and apoptotic activity in breast cancer cells. In terms of its anti-proliferative effect, RGS6 inhibits growth by inducing G1/S phase cell cycle arrest and inhibits breast cancer colony formation. In addition, RGS6 is also able to induce the inherent apoptotic pathway in breast cancer cell lines by promoting ROS production. Importantly, the experiment confirmed that RGS6' s ability to promote apoptosis was not related to its GAP activity against G protein. Another feature described by other scholars is that RGS6 deletions are generally associated with an increase in breast cancer tumor grade and are not related to the tumor state, i.e., Estrogen Receptor (ER)/ Progesterone Receptor (PR)/ Human Epidermal growth factor Receptor 2 (HER2) state [76].

Outlook

Future studies of the mechanisms controlling the transcription and translation efficiency of RGS6 and the stability of protein may provide valuable insight into the role of RGS6 in a variety of pathologies, including cancer and cardiomyopathy. Furthermore, the expression pattern of RGS6 observed in mice is very similar to that observed in humans, confirming the feasibility of applying mouse models to further study the role of RGS6 in human diseases [76].

Physiological correlation makes GPCR one of the most popular drug targets [83]. This is why GPCR is the largest family of proteins targeted by approved drugs [84]. RGS proteins are becoming potential therapeutic targets for the treatment of various diseases because they regulate the GPCR signaling pathways in the nervous system in physiological and pathophysiological settings. Inhibition of specific RGS proteins may provide additional spatial or temporal selectivity compared to GPCR-targeted drugs, allowing the use of lower agonist doses or a wider range of treatments, or improving pathological conditions directly caused by imbalance of RGS proteins. Therefore, RGS6 becomes an attractive new drug target. In particular, the ability of RGS6 to affect mood, motor coordination, and cardiac automaticity depends on the GAP activity of RGS6, while tumor inhibition of RGS6 is not related to G protein. Therefore, inhibitors of RGS6G protein regulation may not affect the tumor inhibition of RGS6. Exploring the mechanism of tumor inhibition of RGS6 may be the next hot research topic.

Declarations

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