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Review

Regulating the regulators: Epigenetic, transcriptional, and post-translational regulation of RGS proteins

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ABSTRACT

Regulators of G protein signaling (RGS) are a family of proteins classically known to accelerate the intrinsic GTPase activity of G proteins, which results in accelerated inactivation of heterotrimeric G proteins and inhibition of G protein coupled receptor signaling. RGS proteins play major roles in essential cellular processes, and dysregulation of RGS protein expression is implicated in multiple diseases, including cancer, cardiovascular and neurodegenerative diseases. The expression of RGS proteins is highly dynamic and is regulated by epigenetic, transcriptional and post-translational mechanisms. This review summarizes studies that report dysregulation of RGS protein expression in disease states, and presents examples of drugs that regulate RGS protein expression. Additionally, this review discusses, in detail, the transcriptional and post-transcriptional mechanisms regulating RGS protein expression, and further assesses the therapeutic potential of targeting these mechanisms. Understanding the molecular mechanisms controlling the expression of RGS proteins is essential for the development of therapeutics that indirectly modulate G protein signaling by regulating expression of RGS proteins.

1. Introduction

Regulator of G protein signaling (RGS) proteins control signaling through heterotrimeric G proteins by accelerating the intrinsic GTPase activity of Gα subunits, typically resulting in an inhibition of downstream G protein signaling pathways [1,2]. Due to the critical role of G protein signaling pathways in diverse cellular functions, it is unsurprising that RGS proteins are also essential in maintaining normal physiological processes and that dysregulation of RGS proteins is implicated in many pathologies. Like the more extensively studied G protein coupled receptors (GPCRs), which activate heterotrimeric G proteins, RGS proteins have emerged as attractive therapeutic targets [3]. However, RGS protein activity is typically regulated by control of expression, stability and localization rather than ligand binding, so RGS proteins are not as amenable to direct small molecule regulation as GPCRs. Therefore, to exploit RGS protein regulation of G protein pathways as a therapeutic target, a comprehensive understanding of the mechanisms that regulate the expression of RGS proteins is critical. In this review, we discuss the molecular mechanisms governing the expression and stability of RGS proteins, and evaluate the therapeutic potential of targeting these mechanisms.

2. RGS proteins in pathophysiology

The established role of G proteins and GPCRs in the central nervous system, cardiovascular system, and in cancer biology naturally led to exploration of the physiologic role of RGS proteins in these systems. In this section, we will briefly discuss evidence demonstrating the roles and the regulation of RGS proteins in normal physiology and disease states in these systems. Also, it should be mentioned that in addition to their roles in the central nervous system, cancer and cardiovascular system, RGS proteins have important roles in multiple other systems, such as the immune system [4].

2.1. RGS proteins in the central nervous system

RGS proteins participate in multiple processes in the central nervous system, including synaptic plasticity [5], memory [6], and vision [7]. Therefore, predictably, dysregulation of RGS protein expression is evident and implicated in several CNS disorders [8,9]. For example, RGS9 is a critical component of the phototransduction machinery of retinal neurons, and loss of RGS9 results in a visual disorder in which patients cannot adapt to changes in light [10,11]; RGS7 and RGS9 critically regulate responses to dopamine [12] and opiate receptors [13] and are implicated in the development of tolerance and addiction [14]; and RGS14 has recently been identified as a critical control point for long-

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term potentiation and memory [6]. In many cases, multiple RGS proteins contribute to the same CNS-related pathology, as is the case in Parkinson's Disease (PD). RGS4 knockout animals display reduced motor symptoms in PD animal models [15], and inhibition of RGS4 improves symptoms of PD [16,17] suggesting that RGS4 contributes to the pathology of this disease. On the contrary, RGS2 [18], RGS6 [19], and RGS10 [20] protect dopaminergic neurons and delay Parkinson's progression. These opposing roles in PD do not simply correlate with distinct G protein selectivity of GAP function or the activity of domains outside of the RGS domain, since RGS4 and RGS10 are both small Gi/o selective GAPs. This suggests that each RGS protein is finely tuned to a specific response, and subtle differences in regulation are critical in determining the physiologic role of RGS proteins. In addition to acting as classic GAPs, some RGS proteins modulate the pathogenesis of these diseases by GAP-independent mechanisms. For example, RGS2 protects neurons by directly binding and inhibiting LRRK2 in a mechanism that does not require RGS2 binding to G proteins [18]. This indicates that targeting GAP-independent functions of RGS proteins can be a beneficial approach in the treatment of some CNS diseases.

A common mechanism for regulation of G protein pathways is the modulation of RGS expression by upstream receptor agonists, and this regulation can result in feedback inhibition or feedforward activation. The expression of many RGS encoding genes and protein levels is highly sensitive to CNS-targeted drugs, with distinct mechanisms and time courses. For example, examination of human tissues revealed that RGS4 protein level is increased in the prefrontal cortex of long-term opiate abusers with no change in short-term users, while RGS10 protein level is decreased in short-term opioid abuse but shows no change in long-term users [21]. The increase in RGS4 expression is recapitulated in a rat model following chronic exposure to morphine [21]. Both RGS4 and RGS10 proteins have been shown to modulate μOR signaling, suggesting that μOR-induced regulation of RGS protein levels may mediate, at least partially, some tolerance to opioid agonists. Similarly, complex regulation of RGS expression occurs in psychosis and anti-psychotic treatment. RGS4 transcript levels are decreased in the prefrontal cortex of individuals with schizophrenia [22], and RGS4 immunoreactivity is higher in subjects treated anti-psychotics [23]. The antipsychotic drug olanzapine, which primarily targets 5-HT2A serotonin receptors, has been shown to increase RGS7 protein levels, and this effect is mediated by a Jak/Stat dependent pathway [24]. Therefore, changes in RGS protein expression levels are associated with both the pathology and therapeutic responses in several CNS diseases.

2.2. RGS proteins in cancer

In the past two decades, the role of GPCRs and heterotrimeric G proteins in cancer initiation and progression has been established [25], which has led to great interest in the regulatory role of RGS proteins in cancers [26]. Studies have provided an abundance of evidence implicating RGS proteins in multiple cancers, where they may either promote or inhibit cancer progression, depending on the type of cancer and RGS protein involved. For example, RGS2 [27], RGS4 [28], RGS6 [29], and RGS16 [30] suppress various aspects of breast cancer progression, whereas RGS20 promotes breast cancer carcinogenesis [31]. Even the same RGS protein can have opposing effects on cancers derived from different tissue. RGS17 is associated with inhibited cell growth and improved responses to chemotherapeutic drugs in ovarian cancer cells [32–34], while RGS17 has been shown to promote lung and prostate cancer growth [35]. Given the diversity of effects on different cancer types, it is unsurprising that not all RGS proteins mediate their effects through a simple G protein GAP activity. For example, while RGS4 actions in breast cancer are mediated by classic GAP activity, RGS6 and RGS16 inhibit breast cancer via GAP-independent mechanisms [36]. The fact that RGS proteins employ different mechanisms has therapeutic implications. For example, targeting the RGS-G protein interaction would selectively inhibit the GAP-dependent effects of RGS4 in breast cancer cells, while strategies targeting expression would impact both GAP-dependent and -independent functions of RGS4, RGS6 and RGS16.

Aberrant expression of RGS transcripts and proteins is also commonly observed in cancers. In breast cancer cells, RGS2, RGS4, and RGS6–which suppress growth–are down-regulated compared to normal cells [27–29], while RGS20–which promotes growth–is up-regulated in cancer [31]. Thus, in both cases, the changes in RGS expression may contribute to progression of disease. This is also observed in prostate cancer cells, where RGS2–which suppresses prostate cancer cell growth–is reduced [33], while expression of RGS17–which promotes prostate cancer cells growth–is elevated [37,38]. Finally, RGS protein expression is also modulated by chemotherapeutic drugs [32,39,40], suggesting that RGS regulation of cancer cell growth continues to be modified through disease progression and therapy. Together, these observations demonstrate that RGS proteins are important regulators of cancer cell growth and survival, and dysregulation of RGS protein expression in cancer cells can modify disease progression.

2.3. RGS proteins in cardiovascular disease

Both GPCRs and G proteins are essential mediators of critical cardiovascular functions, and GPCRs are primary targets for many cardiovascular drugs [41]. RGS proteins also regulate multiple essential cardiac processes, and abnormal changes in their expression often results in cardiovascular system dysfunctions. For instance, loss of RGS2 amplifies angiotensin II (AngII) type 1 (AT_1) receptor signaling, which leads to hypertension [42], and cardiac remodeling is regulated by RGS2 [43] and RGS14 [44]. RGS proteins also play important functions in heart failure and drug-induced cardiac injury, among other conditions (reviewed [45,46]).

Changes in RGS expression levels have been reported in cardiovascular disease, suggesting that abnormal expression of RGS proteins may contribute to pathogenesis. In particular, it appears that RGS proteins and GPCRs participate in bi-directional regulatory mechanisms, in which RGS proteins regulate GPCR activity and GPCR activation in turn alters the expression of RGS proteins. For example, the AT1 receptor regulates the expression of RGS2 [47], RGS10 [48] and RGS14 [44], which regulate AT1 receptor-induced effects. Similarly, the β1 and β2 adrenoceptor agonist isoproterenol induces RGS5 expression [49], and RGS2 and RGS16 expression is regulated by lysophospholipid Sphingosine 1-phosphate (S1P) receptor activation in vascular smooth muscle cells [50].

Based on these diverse studies that have defined the role of RGS proteins in various pathophysiologies and the dynamic regulation of RGS expression during disease progression and treatment, several common observations can be made. First, it is evident that RGS proteins are critically important regulators of physiology and disease in these systems. Second, expression of RGS proteins is often dysregulated in disease states. Third, several drugs used in treatment of these diseases also alter the expression of RGS genes or protein levels. These observations suggest that changes in RGS expression may contribute directly to disease initiation, disease progression, treatment efficacy, tolerance, and unwanted side effects. Therefore, approaches targeted to manipulate the expression of RGS proteins can potentially be utilized for treating diseases in different systems, and also enhance the effectiveness or lower the toxicity of a number of drugs. To this end, understanding the molecular mechanisms that regulate the expression of RGS proteins will lay the groundwork for future development of effective and safe RGS-targeted therapies.

3. Mechanisms regulating RGS levels

RGS proteins are primarily regulated by mechanisms that control local concentration of the protein at the site of signaling, either by regulating subcellular localization, protein stability, transcriptional