Heart failure involves changes in cardiac structure, myocardial composition, myocyte deformation, and multiple biochemical and molecular alterations that impact heart function, collectively referred to as adverse cardiac remodeling. Left ventricular remodeling is a complex process involving cardiac myocyte growth and death, vascular rarefaction, cardiac fibrosis, inflammation, alterations in cardiac energetics, and electrophysiological remodeling. Recently, several endogenous negative regulators of cardiac hypertrophy have been discovered, which are basally inactive and become activated in response to a pathological stimulus. Understanding the mechanisms of activation of these endogenous negative regulators and their target positive regulators will allow the development of novel therapeutic strategies.

Regulators of G protein signaling (RGS) family proteins are such negative regulators which primarily fine-tune G protein–coupled receptor (GPCR)–induced signaling by regulating its magnitude and duration through direct interaction with the alpha subunits of heterotrimeric G proteins. Miao et al studied the novel role of RGS10 in heart failure by using 2 mutant murine models, RGS10 overexpression and knockout (KO), and showed RGS10-mediated regulation of Gαq/11 plays a crucial role in the maintenance of heart function. Signal transduction through the activation of GPCRs is a dominant mechanism for the regulation of cardiovascular physiology, including the regulation of heart rate, myocardial hypertrophy, and contractility, and vascular tone. The success of pharmaceuticals that inhibit β-adrenergic receptors and AT1 receptors, which represent stereotypical GPCRs, also demonstrate the importance of these signaling pathways in disease pathogenesis. Ligand-induced activation of GPCR results into the exchange of guanosine diphosphate and guanosine triphosphate on the alpha subunit, which then dissociates from the βγ-subunit and, in turn, activates the respective downstream targets, leading to cellular responses. The activity of the GPCR is terminated when alpha subunit’s intrinsic guanosine triphosphatase activity hydrolyses the guanosine triphosphate to guanosine diphosphate, and the resultant inactive Gα reassociates with Gβγ subunit and can enter a new activation cycle. RGS family proteins are the activators of guanosine triphosphatase and hence the regulators of the GPCR signaling.

Various isoforms of the RGS are expressed in the human heart. RGS4 and RGS6 are well-studied RGS isoforms, which are found in sinoatrial node and atrial myocytes. Activation of β1 and β2 receptors in the sinoatrial node causes Gαs to activate adenylyl cyclase to produce cAMP, which in turn activates PKA and regulates cardiac automaticity (Figure). Muscarinic M2 receptors couple through Gtxi to inhibit cAMP production and activation of PKA. Activation of M2 receptors also can directly induce G protein–coupled inwardly rectifying potassium channel current (I KACD), resulting in membrane hyperpolarization and inhibition of cell firing (Figure). Extreme parasympathetic stimulation can lead to atrioventricular block, and dysregulation of parasympathetic influence can result in sinoatrial node dysfunction and cardiac arrhythmia, and therefore, a tight regulation of parasympathetic influence is a crucial necessity. RGS4 and RGS6 are found to regulate the M2 receptor activation–mediated I KACD. In addition to M2 receptors, atrial cardiomyocytes also express M3R, and its activation may play a key role in initiation and perpetuation of atrial fibrillation. Therefore, RGS2, a putative regulator of the M3R receptor, may be a target for therapeutic importance. RGS2 negatively regulates signaling through Gαq and Gαi and has shown promising anti-hypertrophic and anti-fibrotic effects, where the anti-hypertrophic effect of phosphodiesterase type 5 inhibition is also mediated via RGS2 (Figure). Thus, RGS2, primarily via regulation of GPCR signaling in cardiomyocytes and noncardiomyocytes, could have therapeutic effects against pathological remodeling and heart disease.

Miao et al showed that RGS10 is expressed in human and murine hearts, and RGS10 protein levels were decreased in failing human myocardial tissue, as well as in pressure-overloaded murine ventricles. They used transgenic mice with RGS10 overexpression in cardiomyocytes and RGS10KO to elucidate the role of RGS10 in pressure-overload heart failure using the surgical aortic banded model. Generation of RGS10KO mice by Miao et al was accomplished by CRISPR-Cas9 technology, a precise and efficient genome editing tool that identifies any DNA sequence by a programmable single guide RNA, which has become a popular approach in genetic engineering. As used in this study, this technology created a basic germline knockout of RGS10, meaning that RGS10...
was absent in all tissues through development and adulthood. This technology may increase the feasibility of making new gene knockouts, but it has the limitation of being a germline knockout, so RGS10 is absent in all tissues at all times, creating the potential for confounding developmental and baseline physiological effects. Importantly, RGS10KO mice did not show any baseline cardiac abnormalities but showed greater hypertrophy and cardiac dysfunction in response to pressure overload, whereas RGS10 overexpression largely preserved heart morphology and function in the aortic banded model. Knockdown of RGS10 also exacerbated angiotensin (Ang) II–induced hypertrophy in cultured neonatal rat cardiomyocytes. However, this study could be further extended to study adult cardiomyocytes because the signaling mechanisms in neonatal cardiomyocytes may not simulate the physiological responses of the adult heart.

Similar to most other RGS isoforms, RGS10 seems to be dispensable in the otherwise normal heart, but becomes important in disease models for limiting pathological GPCR signaling; unfortunately, it is in these disease models that RGS10 is reduced. Therefore, understanding the mechanism for RGS10 reduction in disease models may lead to a therapeutic target for intervention and is an important question raised by this study.4 Tumor necrosis factor-α downregulates RGS10 mRNA and protein levels in neuronal cells; overexpression of RGS10 activated the cyclic adenosine monophosphate (cAMP) response element–binding protein and protected the cells from tumor necrosis factor-α–induced damage.13 RGS10 negatively correlated with extracellular signal-regulated kinases (ERK) activation; the importance of this connection was demonstrated when direct inhibition of mitogen-activated protein kinase kinase, the kinase for ERK, rescued the negative phenotype seen in RGS10KO mice (Figure). GPCR-mediated activation of ERK is well-known, but the precise mechanism connecting RGS10 with blocked ERK activation is still unclear. GPCR-activated ERK becomes localized to the nucleus,14 and RGS10 can also by trafficking between the cytosol and the nucleus;15 future studies should examine the subcellular localization and coimmunoprecipitation binding partners of RGS10 and ERK in human heart failure samples, as well as mouse models of heart disease. Altered cellular localization can also play a role in protein turnover rates; localization of RGS10 may also influence the rate of protein degradation and partially account for the reduced RGS10 protein levels seen in the diseased hearts.

This study is an important first look at RGS10 function in the heart and will hopefully lead to follow-up studies that will expand on this topic. RGS10KO mice showed markedly increased pressure overload–induced cardiac fibrosis, and considering that Ang II has profound effects on the cardiac fibroblasts, role of RGS10 in the regulation of Gq/11 in the cardiac fibroblasts should be studied. An in vivo chronic Ang II administration model would be relevant to perform in the RGS10KO and overexpressing mice. Ang II can activate ERK through both GPCR, as well as β-arrestin, pathways,16 so it would be of interest to see whether increased RGS10 can fully attenuate ERK activation by Ang II in a chronic in vivo model. Would RGS10 have beneficial effects on blood pressure, cAMP overproduction, and other features of Ang II–driven pathophysiology and does it limit Ang II–mediated hypertrophy and fibrosis as expected from this current study? If Ang II–induced hypertension was not altered by RGS10,
but pathological remodeling of heart was reduced, it would uncouple the humoral driving factors of pathological hypertrophy from the effects of increased ventricular wall stress resulting from hypertension. In summary, Miao et al have clearly demonstrated a critical role of RGS10 in heart disease, and pharmacological approaches aimed at enhancing RGS10 action may show salutary therapeutic effects.

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None.

References
Regulators of G-Protein Signaling 10 and Heart Failure: The Importance of Negative Regulators of Heart Disease

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