G Protein–Coupled Receptor Kinase 5
Exploring Its Hype in Cardiac Hypertrophy

Stephen L. Belmonte, Burns C. Blaxall

It is an established dogma that G-protein–coupled receptor kinases (GRKs) classically direct the desensitization and internalization of their eponymous receptors through direct phosphorylation. Yet, it is the noncanonical action of GRKs that has increasingly attracted the interest of groups seeking novel insight into vexing pathophysiological questions. Among the 7 GRK isoforms, several findings suggest that GRK5 may have particular relevance to the development of cardiac hypertrophy and heart failure (HF). Beyond its classical function, GRK5 contains a DNA-binding nuclear localization sequence[1] and has recently been reported to modify myocardial gene transcription through histone deacetylase kinase activity.[2] Furthermore, GRK5 expression is elevated in the ventricles of patients with HF,[3] and transgenic cardiac-specific GRK5 overexpression produced pronounced hypertrophy and accelerated HF progression upon pressure-overload challenge in mice.[2]

Article, see p 1048

To date, the question remains whether endogenous GRK5 is a prerequisite for hypertrophy and HF development in the face of cardiac stress. In this issue of *Circulation Research*, Gold et al[4] have begun to address this issue by using global and cardiac-restricted GRK5 knockout mice. They report that when subjected to transverse aortic constriction, both the global and cardiac-restricted GRK5 null animals show delayed hypertrophy and preserved heart function compared with control mice, as determined by serial left ventricular posterior wall thickness assessment and ejection fraction, respectively. Furthermore, they used semiquantitative polymerase chain reaction to demonstrate that mRNA expression of a host of hypertrophy marker genes was significantly reduced in the hearts of both GRK5 knockout mice. Similar results were obtained after chronic administration of a subpressor dose of phenylephrine in the global GRK5 knockout mice. Overall, the data suggest that GRK5 is integral to maladaptive cardiac hypertrophy.

In evaluating the results presented in the article by Gold et al,[4] it becomes apparent that GRK5 may represent a viable therapeutic target for the treatment of HF, for which new therapies are desperately needed. As with most new and exciting discoveries, there are various facets of GRK5 biology to consider before clinical application. For example, it was previously reported that the global GRK5 knockout mouse exhibits enhanced muscarinic receptor sensitivity but no gross anatomic differences from wild-type littermates.[5] In addition, a recent study found high expression of GRK5 in white adipose tissue, underlying reduced adipogenesis and obesity in GRK5-null animals.[6] Thus, while cardiac functional parameters clearly suggest a protective role of GRK5 in the heart, it would also be valuable to assess ratios of heart weight to tibia length in addition to body weight, as well as to quantify myocyte size. It is interesting to note that both global and cardiac-restricted GRK5 knockout mice demonstrated progressive, mild (possibly compensatory) cardiac hypertrophy after transverse aortic constriction, whereas the wild-type mice followed the more traditional progression of concentric hypertrophy followed by rapidly decompensated, eccentric hypertrophy coupled to ventricular wall thinning. Attenuation of the hypertrophic gene expression profile after myocardial insult in GRK5 knockouts, partially explained by modest but significant alterations in non-nuclear histone deacetylase phosphorylation, further validates an important role for GRK5 in pathological cardiac hypertrophy.

Importantly, GRK5 is expressed in multiple cardiac cell types. In their current article, Gold et al[4] report relatively similar results in both the global and cardiomyocyte-restricted GRK5 mice. Future investigation will be needed to determine the possible functional relevance of GRK5 in the maladaptive hypertrophic response in various nonmyocyte cardiac cells (eg, fibroblasts). Interestingly, prior studies have documented divergent effects of altered GRK5 expression/activity. For example, hybrid transgenic mice overexpressing cardiac GRK5 and a constitutively active α1B-adrenergic receptor mutant demonstrated that GRK5 reduced α1B-adrenergic receptor hypertrophy and partially reduced atrial natriuretic factor mRNA.[7] Although somewhat inconsistent with the current report, the inherent differences in the mechanism of injury induced by an activated mutant receptor, transverse aortic constriction, and persistent agonist stimulation may, in large part, explain the discrepancy. It is known that GRK5 phosphorylates and desensitizes α1B-adrenergic receptor basally but not after agonist stimulation.[8] Furthermore, the α1B-adrenergic receptor is preferentially expressed in cardiac fibroblasts, whereas the α1A subtype predominates in myocytes.[9] It is also likely that GRK5 overexpression confers protection via enhanced desensitization

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of β-adrenergic receptors, as observed previously in mice.[10] This is also the putative explanation for the improved outcomes of patients with HF with a highly active GRK5 polymorphism.[11] Considering that GRK5 exhibits differential receptor subtype specificity and has both nuclear and membrane receptor kinase activity, further work is required to establish a definitive role for GRK5 in maladaptive cardiac hypertrophy in a variety of cardiac cell types.

One final point to address is how GRK5 regulates gene transcription. Hypertrophic gene expression is primarily considered in terms of upregulated genes, but downregulated genes are also clinically relevant to hypertrophy and HF. Indeed, it was recently reported that in mice overexpressing $G\alpha_q$, which produces a pressure-overload cardiac phenotype, enhanced GRK5 expression normalized a subset of downregulated mRNAs responsible for carbohydrate metabolism and energy production.[12] Furthermore, expression of a truncated GRK5 that expresses the regulator of G protein signaling homology domain, which inhibits nuclear factor-κB transcriptional activity, reduced left ventricular hypertrophy in spontaneously hypertensive rats or normotensive rats exposed to chronic phenelyephrine.[13] Taken together, these results suggest that GRK5 expression counteracts at least some types of hypertrophic stimuli.

In summary, GRK5 expression is clearly pertinent to maladaptive cardiac hypertrophy and the development of HF. Further advances in our understanding of the functional role of GRK5 in heart failure, including those reported by Gold et al,[4] may serve to clarify some inconsistencies and take the quest for a new HF therapeutic yet one step closer to reality.

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Disclosures

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