Modulating Phenotypic Expression of the PRKAG2 Cardiac Syndrome

Michael H. Gollob, MD

The PRKAG2 cardiac syndrome is a rare, autosomal-dominant genetic disease of the heart. Genetic defects in the Prkag2 gene, encoding the regulatory subunit of AMP-activated protein kinase (AMPK), lead to a diverse cardiac phenotype of variable clinical expressivity. Typically, affected patients present in late adolescence with frequent paroxysms of supraventricular arrhythmias, demonstrate ventricular preexcitation on 12-lead ECG, and commonly progress to high-grade conduction system disease requiring a permanent pacemaker by their fourth or fifth decade of life. A significant proportion of patients develop mild to severe cardiac hypertrophy with progression to dilated cardiomyopathy. Phenotypic variability within a family is common, suggesting an influence of genetic modifiers. In addition, specific mutations of the Prkag2 gene may predict clinical expression. Mutations giving rise to atrial fibrillation and conduction disease only, severe neonatal cardiomyopathy of variable clinical expressivity. Typically, affected patients present in late adolescence with frequent paroxysms of supraventricular arrhythmias, demonstrate ventricular preexcitation on 12-lead ECG, and commonly progress to high-grade conduction system disease requiring a permanent pacemaker by their fourth or fifth decade of life. A significant proportion of patients develop mild to severe cardiac hypertrophy with progression to dilated cardiomyopathy. Phenotypic variability within a family is common, suggesting an influence of genetic modifiers. In addition, specific mutations of the Prkag2 gene may predict clinical expression. Mutations giving rise to atrial fibrillation and conduction disease only, severe neonatal cardiomyopathy with death, or skeletal myopathy with a cardiac phenotype have all been described.

Most intriguing, the arrhythmogenic nature and cardiomyopathic process of this disease are not caused by primary genetic defects in cardiac ion channels or structural proteins. Rather, the PRKAG2 cardiac syndrome is a disease of cardiac metabolism. AMPK enzymatic activity serves a critical role in regulating cellular glucose and fatty acid metabolic pathways. In situations of increased cellular energy demand in muscle, AMPK activation promotes ATP repletion by facilitating cellular glucose uptake and oxidative metabolism. A perturbation in the exquisite regulation of these metabolic pathways, as caused by mutations in the regulatory subunit of AMPK, leads to a derangement in cardiac metabolism, giving rise to the profound cardiac phenotypes described. Controversy has existed regarding whether this genetic disease enhances or impairs AMPK activity. Compelling evidence now exists that Prkag2 mutations cause a “gain of function” in basal AMPK activity, at least in the early stages of disease progression, leading to excessive cellular glucose uptake and pathological glycogen storage in the heart. The end result is a potentially fatal cardiac phenotype.

In this issue of Circulation, Wolf and colleagues provide evidence that the severe manifestations of this metabolic disease may be attenuated or significantly reversed by the direct modulation of AMPK-mediated cardiac metabolism. This finding introduces a landmark paradigm, suggesting that the appropriate pharmacological targeting of AMPK or its downstream effectors may improve the phenotypic expression of the disease. Their finding has implications not only for the PRKAG2 cardiac syndrome but for the numerous other single gene defects responsible for metabolic cardiomyopathies of childhood.

To address their hypothesis, the investigators developed transgenic mice expressing a human N488I Prkag2 mutant protein under transcripational control of a tetracycline-repressible α-myosin heavy chain promoter. Oral administration of tetracycline results in suppression of mutant protein expression, leaving only normal, endogenous mouse AMPK activity. With the use of this model, their data demonstrate that on tetracycline-induced suppression of mutant AMPK activity, all phenotypic manifestations of the syndrome may be reversed or partially resolved, including established cardiac hypertrophy and myocardial dysfunction in adult mice. Development of ECG evidence for ventricular preexcitation was prevented by suppressing mutant protein during early postnatal life. Importantly, resolution of all phenotypic characteristics was due to the same biochemical phenomena: a significant reduction in cellular glycogen content. What may be learned about disease pathogenesis by this observation?

Ideally, the diverse clinical features of the PRKAG2 cardiac syndrome should be explained by a single dominant cellular abnormality resulting from altered AMPK activity. The findings of Wolf et al provide strong evidence that excessive cellular glycogen content alone is a unifying mechanism of disease pathogenesis for the variable phenotypes manifested in affected patients. The degree of cardiac hypertrophy observed on imaging will be dependent on the extent of myocyte enlargement secondary to glycogen accumulation. Why some patients demonstrate extraordinary hypertrophy while members of the same family may not remains an enigma but likely reflects a role of functional polymorphisms of other genes influencing cellular glucose metabolism. The presence of ventricular preexcitation is also the result of cellular enlargement due to excessive glycogen content, resulting in the disruption of the normal development of the annulus fibrosus, as observed by Wolf et al. The end result is ECG evidence for ventricular preexcitation and, in the context of frequent supraventricular arrhythmias, features consistent with the Wolff-Parkinson-White syndrome. How-
ever, the molecular etiology of Wolff-Parkinson-White syndrome not associated with this genetic syndrome is likely quite different. Perhaps the most common feature of the PRKAG2 cardiac syndrome is paroxysmal and persistent atrial fibrillation, even in the absence of gross structural disease as detected by imaging modalities. Although an effect of AMPK in the regulation of ion channel gating is plausible, the decrease in cellular pH due to excessive glycogen content may affect the kinetics of numerous ion channels, making the atria more prone to fibrillation. Progression to conduction system disease may reflect a proapoptotic effect of altered AMPK activity or prolonged exposure to glycogen excess.

The discovery that genetic defects leading to altered AMPK activity give rise to a metabolic cardiomyopathy has implications far beyond this rare condition. Most importantly, this genetic disease has confirmed a critical role for AMPK in regulating cardiac and muscle metabolism. As a major determinant of energy substrate utilization, AMPK-mediated energy metabolism may be considered a key molecular pathway in more common metabolic diseases, such as type 2 diabetes mellitus and obesity. Indeed, drugs such as metformin and rosiglitazone, mainstays in the treatment of type 2 diabetes mellitus and obesity, both exert an AMPK-activating effect and presumably result in enhanced cellular glucose uptake through this mechanism. The role of AMPK during myocardial ischemia is also being studied extensively, and it is suggested that AMPK activation may serve a protective role to the heart under these conditions.

Thus, AMPK as a therapeutic target in modulating common metabolic disorders is an appealing concept. However, in light of lessons learned from this rare genetic disease, potent pharmacological manipulation of AMPK activity should be approached with cautious optimism.

Disclosures
None.

References

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