Regulation and role of myocyte cyclic GMP-dependent protein kinase-1

We were intrigued with the study by Lukowski et al. (1), which investigated mice lacking cGMP-activated kinase (cGK1 α and cGK1 β) in all cells except those with smooth muscle (sm22) promoter activity (cGK1 β -rescue) and concluded that cardiomyocyte cGK1 does not modify hypertrophic responses to β -adrenergic or pressure stress. As this study appears to counter prior work suggesting cGK1 suppresses myocyte hypertrophy, we felt it was important to point out some alternative interpretations to the readers. For example, their conclusions presume that cGK1 activity rose sufficiently in wild-type controls with their stress models, but this was not confirmed. Basal myocyte cGK1 activity is low, yet it may confer potent brake-like effects if sufficiently activated. The authors did not test if antihypertrophic effects of nitric oxide, natriuretic peptides, or other methods to stimulate cGMP levels are myocyte cGK1-independent, which is unlikely. Antihypertrophic action also requires that relevant cGK1 targets (e.g., calcineurin and G α q cascades) be stimulated, which depends on the mode and extent of stress. Sildenafil [phosphodiesterase type 5 (PDE5) inhibitor] augments cGK1 activity similarly in moderate and severe pressure overload but suppresses hypertrophy more in severe overload where cGK1-targeted signaling is activated (2). In Lukowski et al. (1), isoproterenol and pressure overload yielded modest 20–40% increases in left ventricular mass (figures showed higher values because of an unexplained decline in body weight), suggesting that cGK1-targeted cascades may not have been activated. Last, cardiac characteristics of the genetic model were not fully described, although it displays time-dependent increased mortality by 1 year. This is especially relevant, because the rescue model is created in mice harboring a complete cGK1 deletion that cannot be bred because of early mortality and the mice are rescued in the vasculature only.

The authors (1) also question the role of PDE5, suggesting that antiremodeling effects of sildenafil are caused by non-selective targeting of PDE1C in myocytes or inhibition of

PDE5 in fibroblasts and are independent of cGK1. However, multiple groups have reported myocyte PDE5 expression, and the specificity of these analyses was tested and confirmed by gene-silencing studies (3). Sildenafil suppresses myocyte hypertrophy similar to PDE5 gene silencing in a cGK1-dependent manner, with no further impact from the combination, supporting PDE5 targeting by sildenafil at the applied dose (3). Sildenafil does not blunt exacerbated pressure-overload hypertrophy in mice lacking RGS2, a binding and phosphorylation target of cGK1. Depression of calcineurin/nuclear factor of activated T-cell stimulation or adrenergic-enhanced sarcomere shortening by sildenafil is mediated by cGK1-dependent phosphorylation of transient receptor potential canonical channel type-6 (4) or troponin-I, respectively. The contention that prior work used “very high and non-selective” sildenafil doses is inconsistent with reported free plasma concentrations that are unlikely to inhibit PDE1 (1). Studies have also used tadalafil, which is more selective for PDE5. Last, whereas PDE1 inhibition seems to be antihypertrophic, this effect is cGK1-dependent and separable from a PDE5 inhibitory effect (i.e., they were additive) (5).

We fully agree with the authors that better targeted and conditional deletion models are needed but contend that their study does not refute the role of myocyte cGK1 or PDE5 based on prior reported findings and the issues highlighted above.

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The authors declare no conflict of interest.

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