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Response to Letter to the Editor Regarding Article, "Protein Phosphatase 2A Regulates Cardiac Na^+ Channels"

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Cardiovascular disease is a leading cause of death and is expected to account for more than 23 million deaths by 2030. Of those deaths, one-half million each year will experience arrhythmia-induced sudden cardiac death.[1] Therefore, research on new strategies to mitigate adrenergic imbalance associated with arrhythmogenesis is essential to public health. In the heart, while the activity of the primary voltage-gated Na_v channel, $Na_v1.5$, is critical for normal cardiac excitability, alteration of the "late" component of I_{Na} ($I_{Na,L}$) is linked with heritable and acquired arrhythmias. Our group and others have identified CaMKII-dependent phosphorylation of $Na_v1.5$ as an important driver of increased pathogenic $I_{Na,L}$ in myocyte, animal models of cardiovascular disease, and human heart.

We recently published new findings that support a critical role for protein phosphatase 2A (PP2A) in the regulation of pathogenic $I_{Na,L}$ in heart.[2] PP2A is a ubiquitously-expressed serine/threonine phosphatase with high expression in the heart. While protein phosphatase 1 is the dominant PP in heart, PP2A activity regulates the activity of key membrane proteins. The PP2A holoenzyme is comprised of three subunits (scaffolding [A], regulatory [B], and catalytic [C]). PP2A A/C subunits are encoded by two genes while thirteen different genes encode PP2A regulatory subunits. Our findings support that mice lacking a specific

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regulatory subunit (B56α) display alteration in $Na_v1.5$ CaMKII-dependent phosphorylation (reduced) and ultimately decreased $I_{Na,L}$ in response to isoproterenol.[2] While the findings support an unanticipated role for B56α in $I_{Na,L}$ regulation, the work raises questions regarding the underlying molecular mechanism. For example, loss of B56α may lead to defects in the expression of $Na_v1.5$ regulatory complex in the myocyte. Further, prior structural work has supported that in the absence of the regulatory subunit, the PP2A A/C holoenzyme while less regulated, displays increased activity.[3] Additionally, alterations in the ratio of regulatory subunit: catalytic subunit may increase PP2A activity.[4] Loss of B56α may impact the activity of other regulatory subunits as well as up- and downstream regulatory molecules. Finally, as our work utilized mice lacking B56α in all tissue, secondary non-cardiac mechanisms may contribute to phenotypes. In summary, the work provides a rationale for future studies to understand the link between PP2A and $I_{Na,L}$, particularly given the arrhythmogenic role for $I_{Na,L}$ in humans.

We appreciate the comments from Cristóbal et al.[5] highlighting the global impact of PP2A regulation (and potential PP2A-based therapies). Relevant to their comments, the occurrence of cardio-oncologic complications secondary to anti-neoplastic agents represent a major challenge to comprehensive care teams. Cardiovascular disease is the number one cause of death in cancer survivors[6, 7], and so it is imperative that we focus on the interaction between cardiovascular function and cancer therapies.

PP2A is a well-established tumor suppressor and the role of PP2A in cancer is illustrated by PP2A inactivation and genetic alteration of PP2A subunits in multiple cancers.[8] As noted by Cristóbal et al. these findings have led to PP2A-activating therapeutic strategies in malignancy.[8] Our findings support the role of PP2A for regulation of arrhythmogenic $I_{Na,L}$ in heart, and so a dual role for PP2A promoting cardiac protection in the face of cancer therapy is intriguing. As with all potential therapeutic pathways, it will be important to define the impact of PP2A regulation at the cell, organ, and animal level. To take these challenges head on, our institution has a multidisciplinary and comprehensive cardio-oncology program comprised of cardiologists, oncologists, basic science researchers, biomedical engineers, pharmacologists, and pharmacists to evaluate the impact of new therapies across the different disease disciplines. In summary, we underscore the necessity to evaluate PP2A-activating agents in conjunction with standard therapeutics to better understand the potential risk of developing cardiac phenotypes in malignancy. Likewise, when designing anti-arrhythmia compounds related to PP2A, it will be critical to understand potential impact on cancer induction.

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