Defining the Complexity of the Junctional Membrane Complex

Barry London

Each heart beat in every cardiac myocyte begins with the surface membrane depolarization during an action potential that opens L-type Ca\(^{2+}\) channels and allows the influx of a small amount of extracellular Ca\(^{2+}\) that triggers a larger release of Ca\(^{2+}\) from the intracellular store, the sarcoplasmic reticulum (SR), through ryanodine receptors (RyR2).\(^1,2\) This process, known as Ca\(^{2+}\)-induced Ca\(^{2+}\)-release, is the primary mechanism underlying excitation–contraction coupling in the heart. Cardiac myocytes are relatively large cells, and efficient cardiac function requires not only the rapid sequential activation of contraction between cells but also the simultaneous activation of the contractile apparatus within each cell. To accomplish this, adult cardiac myocytes localize L-type Ca\(^{2+}\) channels in deep membrane invaginations known as transverse tubules (T-tubules), located along the Z-lines adjacent to the SR Ca\(^{2+}\) release channels in highly ordered structures known as dyads. The potential importance of these organized junctional membrane complexes has been defined during the last decade using in situ imaging techniques that show their loss in pathological conditions, including myocardial infarction and heart failure.\(^3\)

Additional proteins essential for the structure and function of the junctional membrane complex have been identified. Junctophilin-2 (JPH2) connects the T-tubular and SR membranes and is downregulated in many models of heart failure.\(^4–6\) Of greater note, JPH2 disruption leads to heart failure (as opposed to an indirect effect through phosphorylation of another target)? Does phosphorylation of JPH2 predispose to heart failure? What (if any) are the specific roles of the SPEG-\(\alpha\) and SPEG-\(\beta\) isoforms? Which residue(s) of JPH2 is (are) phosphorylated and is the decrease in JPH2 phosphorylation a marked decrease in JPH2 phosphorylation. Taken together, these studies provide strong evidence that SPEG plays a critical role in both the structure and function of cardiac T-tubules and the RyR2-mediated Ca\(^{2+}\) release that they direct. This well-conceived and elegant study is important for several reasons. First, it identifies a novel and important role for SPEG in the junctional membrane complex and suggests a previously unknown functional role for JPH2 phosphorylation. Second, the work provides further evidence that T-tubular disarray can causally contribute to the pathogenesis of heart failure. Finally, it provides insight into Ca\(^{2+}\)-dependent mechanisms leading to heart failure that are independent of changes in SERCA2a expression and function, and that may not be amenable to therapies aimed at raising SERCA2a such as AAV (adeno-associated virus)-SERCA2a gene delivery to the heart.\(^11\)

As would be expected, the identification of SPEG in the junctional membrane complex raises as many questions as it answers. What (if any) are the specific roles of the SPEG-\(\alpha\) and SPEG-\(\beta\) isoforms? Which residue(s) of JPH2 is (are) phosphorylated and is the decrease in JPH2 phosphorylation causally related to the development of T-tubular disarray and heart failure (as opposed to an indirect effect through phosphorylation of another target)? Does phosphorylation of JPH2 alter its proteolytic cleavage? Does SPEG interact with BIN1, and does myotubulin play a role in the junctional membrane complex?\(^7,9\) Do polymorphisms in SPEG predispose to heart failure?\(^10\) The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Division of Cardiovascular Medicine, University of Iowa, Iowa City.
Correspondence to Barry London, MD, PhD, Division of Cardiovascular Medicine, University of Iowa Carver College of Medicine, E315-GH, 200 Hawkins Dr, Iowa City, IA 52242. E-mail barry-london@uiowa.edu

*Circ Res* 2017;120:11-12.

DOI: 10.1161/CIRCRESAHA.116.310214.) © 2017 American Heart Association, Inc.

*Circulation Research* is available at http://circres.ahajournals.org

DOI: 10.1161/CIRCRESAHA.116.310214
failure and arrhythmias? Do mutations in SPEG cause inherited forms of sudden death? 

Although SPEG was the only new protein identified by the MS/MS screen using JPH2 and RyR2, it is likely that other unidentified proteins are playing a role in the junctional membrane complex. These proteins may bind to either JPH2 or RyR2. Alternately, future studies could now use SPEG as bait to identify other members of the protein complex. During the past several years, our understanding of the junctional membrane complex has increased. The article of Quick et al13 has contributed to our improved understanding. That said, we do not yet know just how complex the junctional membrane will turn out to be.

Sources of Funding
This work was supported in part by NIH grant R01 HL 115955.

Disclosures
None.

References

Key Words: Editorials ■ excitation contraction coupling ■ heart failure ■ sarcoplasmic reticulum
Defining the Complexity of the Junctional Membrane Complex
Barry London

Circ Res. 2017;120:11-12
doi: 10.1161/CIRCRESAHA.116.310214

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/120/1/11

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/