Letter by Karlstaedt and Taegtmeyer
Regarding Article, “Loss of Adult Cardiac Myocyte GSK-3 Leads to Mitotic Catastrophe Resulting in Fatal Dilated Cardiomyopathy”

To The Editor:

We have read with interest the article by Zhou et al.1 The authors demonstrated that in cardiomyocytes, conditional deletion of glycogen synthase kinase-3 (GSK-3) isoforms A and B leads to development of severe dilated cardiomyopathy. Zhou et al1 also report that GSK-3 suppresses cell cycle induction and that the subsequent loss of cardiac myocytes leads to impaired contractile function, development of dilated cardiomyopathy, and death. These are exciting findings, which are in agreement with previous studies investigating the effect of GSK-3 inhibition in cancer. However, we suggest that there are aspects deserving further consideration to elucidate the mechanism linking the loss of GSK-3A and B with structural remodeling in the heart.

The current study shows that loss of GSK-3A and B induces mitotic catastrophe, leading to cardiomyocyte polyplody and cell death. However, GSK-3 is also involved in the regulation of various other cellular processes, particularly nutrient and energy homeostasis. What are the metabolic consequences of GSK-3A and B knockout? Patel et al2 showed that GSK-3B knockout improves glucose tolerance in skeletal muscle and enhances glycogen synthesis and deposition by insulin. A double knockout of GSK-3 isoforms most likely disrupts myocardial glycogen turnover and shifts the balance toward glycogen synthesis through hyperactivation of glycogen synthase. Here, analysis of glycogen synthase activity and measurements of glycolytic flux may help to unravel whether a GSK-3 double knockout affects cardiac glucose metabolism. Recent studies have shown that alteration of glucose metabolism by GSK-3 inhibition causes dissociation of hexokinase II from the outer mitochondrial membrane. This, in turn, promotes mitochondrial destabilization and apoptosis.3 These findings suggest that downregulation of GSK-3 in heart failure is part of a more complex regulatory response system and underline the importance of understanding alterations of enzyme activities on a systems level.

What are the clinical implications of the findings presented by Zhou et al?1 The pharmacological suppression of GSK-3 in cardiac myocytes could be relevant for reducing infarct size in the ischemic heart by targeting GSK-3A. However, the current findings from Zhou et al1 indicate that isoform-specific inhibition of GSK-3 may have the greatest promise in providing cardiac protection.

Disclosures

None.

Anja Karlstaedt
Heinrich Taegtmeyer
Department of Internal Medicine
Division of Cardiology
McGovern Medical School
The University of Texas Health Science Center at Houston
Houston, TX

References

Letter by Karlstaedt and Taegtmeyer Regarding Article, "Loss of Adult Cardiac Myocyte GSK-3 Leads to Mitotic Catastrophe Resulting in Fatal Dilated Cardiomyopathy"

Anja Karlstaedt and Heinrich Taegtmeyer

_Circ Res._ 2016;119:e28
doi: 10.1161/CIRCRESAHA.116.309055

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2016 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/119/2/e28

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/