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

Disclosures

None.

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References

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