VOL. 2, NO. 4, 2017
ISSN 2452-302X

Letter

TO THE EDITOR

Apoptosis, A Double-Edge Sword!

We read with interest the paper by Weil et al. (1), which has also been editorialized by Jaffe (2) and Amgalan et al. (3). In this paper, a single brief episode of 10-min myocardial ischemia and 24-h reperfusion was shown to increase serum cardiac troponin I, with transient regional apoptosis of single dispersed cardiomyocytes being proposed as a potential mechanism. We would like to put the focus on the link between such short periods of ischemia/reperfusion, the apoptotic process, and cardioprotection.

Ischemic pre-conditioning (IPC), whereby transient episodes of ischemia and reperfusion (IR) protect the myocardium from prolonged IR injury, is the most powerful cardioprotective therapy known and has become the paradigm for cardioprotection (4). The IPC infarct size-limiting effect is mediated through the recruitment of pro-survival signaling cascades at the early reperfusion phase, known as the reperfusion injury salvage kinase pathway, which encompasses the activation of 2 parallel kinases: PI3K and ERK. The activation of this pathway has been extrapolated to most cardioprotective interventions, and is hence considered a unifying signaling pattern for cardioprotection.

The reperfusion injury salvage kinase pathway was first described by our group in 2002 while assessing the mechanisms underlying the cardioprotective effect induced by urocortin at reperfusion (5). At that time, pro-apoptotic proteins were the object of study to develop new targets against IR injury after the realization that apoptosis may play an important role in early reperfusion. The interest focused on 2 main areas: 1) reducing cell death through the inhibition of pro-apoptotic caspases (6); and 2) antagonizing the apoptotic process through the activation of pro-survival protein kinases, such as PI3K and ERK (7).

We believe that the results reported by Weil et al. (1) further strengthen our understanding of cell death. The increase in troponin levels following a short protocol of IR injury (IPC-like) has been justified by the increased 6-fold regional apoptosis when compared with the nonischemic tissue. The activation of the apoptotic process should be put alongside the well recognized activation of pro-survival pathways following a short protocol of IR injury. Therefore, it seems that both pro-apoptotic and pro-survival pathways are activated after such a stimulus, maybe as a counter-regulatory process. Despite it seeming contradictory, we would speculate that this is exactly what may happen. If the stimulus is left for longer, apoptosis contributes alongside necrosis to the final infarct size (8), whereas if left only for a shorter period, the IR injury actually leaves a "footprint," i.e., a memory in the form of activated pro-survival pathways to protect the heart when a prolonged injury comes later. Maybe it is time to take apoptotic death more seriously during early reperfusion!

Xavier Rossello, MD
***Derek M. Yellon, DSc**

*The Hatter Cardiovascular Institute
University College London
67 Chenies Mews
London WC1E 6HX
United Kingdom
E-mail: d.yellon@ucl.ac.uk

http://dx.doi.org/10.1016/j.jacbts.2017.07.008

Please note: Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Weil BR, Young RF, Shen X, et al. Brief myocardial ischemia produces cardiac troponin I release and focal myocyte apoptosis in the absence of pathological infarction in swine. J Am Coll Cardiol Basic Trans Science 2017;2:105–14.

2. Jaffe AS. Another unanswerable question. J Am Coll Cardiol Basic Trans Science 2017;2:115–7.

3. Amgalan D, Pekson R, Kitsis RN. Troponin release following brief myocardial ischemia. J Am Coll Cardiol Basic Trans Science 2017;2:118–21.

4. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med 2007;357:1121–35.

5. Schulman D, Latchman DS, Yellon DM. Urocortin protects the heart from reperfusion injury via upregulation of p42/p44 MAPK signaling pathway. Am J Physiol Heart Circ Physiol 2002;283:H1481–8.

6. Mocanu MM, Baxter GF, Yellon DM. Caspase inhibition and limitation of myocardial infarct size: protection against lethal reperfusion injury. Br J Pharmacol 2000;130:197–200.

7. Hausenloy DJ, Yellon DM. New directions for protecting the heart against ischaemia-reperfusion injury: targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. Cardiovasc Res 2004;61:448–60.

8. McCully JD, Wakiyama H, Hsieh Y-J, Jones M, Levitsky S. Differential contribution of necrosis and apoptosis in myocardial ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 2004;286:H1923–35.