HIF-1α and paradoxical phenomena in cardioprotection

EXPERT’S PERSPECTIVE

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This editorial refers to an article by Z. Cai et al.,12 published in Cardiovascular Research in 2008. It is accompanied by a retrospective editorial by one of the authors of that original article, G.L. Semenza, pp. 216–219, this issue, as part of this Spotlight on Landmark Papers in Cardiovascular Research.

Ischaemic preconditioning, i.e. one or several brief cycles of myocardial ischaemia/reperfusion preceding a more sustained period of myocardial ischaemia with subsequent reperfusion, does not increase the resulting size of myocardial infarction but paradoxically decreases it.1 Over the past 25 years, ischaemic preconditioning has become the key paradigm of endogenous cardioprotection, and numerous studies have addressed its underlying signal transduction.2,3 In principle, ischaemic preconditioning’s protection is also operative in humans, although—apart from the controlled situation of surgical coronary revascularization—it is difficult to apply therapeutically due to the unpredictable nature of acute myocardial infarction.4

The role of reactive oxygen species (ROS) in the signalling of cardioprotection is as paradoxical as the role of myocardial ischaemia per se; a little ischaemia protects from the consequences of sustained ischaemia, and some ROS are required to trigger protection from damage by excessive ROS formation. Mitochondria and their respiratory chain are not only obvious sources of ROS but also decisive subcellular structures for cardiomyocyte death or survival, and the putative mitochondrial permeability transition pore (MPTP) appears to be a critical element.5 Again, MPTP opening serves a paradoxical function, in that some MPTP opening protects,6 whereas massive MPTP opening initiates cell death.5,7 The inhibition of MPTP opening was therefore proposed as a key target of cardioprotection.7 The release of triggering ROS from mitochondria is apparently closely related to KATP channel activation,8,9 which are—in turn—closely connected to other signalling elements of cardioprotection, such as protein kinase C, glycogen synthase kinase 3β, and connexin 43.10,11

In their landmark paper, Cai et al.12 demonstrated that even heterozygous deficiency for hypoxia-inducible factor 1α (HIF-1α), the master regulator of cellular oxygen homeostasis,13 abrogates protection by ischaemic preconditioning in an isolated, saline-perfused mouse heart preparation. Heterozygous HIF-1α deficiency abrogated protection with the endpoints infarct size, apoptosis, and left ventricular function. HIF-1α deficiency also abrogated the mitochondrial formation of ROS, and it prevented the oxidation of the phosphatase and tensin homologue deleted on chromosome 10 (PTEN) and the increased phosphorylation of protein kinase B/Akt with ischaemic preconditioning. In contrast to ischaemic preconditioning, exogenous adenosine also protected the hearts of heterozygous HIF-1α mice, in line with prior data showing that protection by adenosine does not rely on ROS formation.14 Cai et al. proposed a hierarchy of signalling events, with HIF-1α upstream of mitochondrial ROS formation upstream of PTEN oxidation upstream of Akt phosphorylation, which is intriguing but was not experimentally tested. Is mitochondrial ROS formation really upstream or downstream of Akt activation, or possibly both? In any event, HIF-1α is put into a paradoxical signalling position: As these eminent authors have shown before, HIF-1α regulates the enzyme composition of the mitochondrial respiratory chain to attenuate ROS formation during hypoxia; now HIF-1α is a pre-requisite for the mitochondrial ROS formation to initiate the protection by ischaemic preconditioning.12 The exact nature of this ambivalent function of HIF-1α is not clear; it may relate to the transcriptional activation of proteins critical to ischaemic preconditioning but also to a non-transcriptional function of HIF-1α. Of note in this context, the fact that even heterozygous HIF-1α deficiency abrogated ROS formation and protection completely points to a threshold phenomenon in protection by ischaemic preconditioning. Such a threshold phenomenon appears to be not specific for HIF-1α but is rather genuine to ischaemic preconditioning and its redundant signal transduction, e.g. it was also seen with heterozygous connexin 43 deficiency.15 The interaction of HIF-1α with adenosine signalling in cardioprotection remains somewhat unclear: Why does the formation of endogenous adenosine not initiate protection in the absence of mitochondrial ROS formation with heterozygous HIF-1α deficiency? Is the release of endogenous adenosine quantitatively
insufficient in the absence of HIF-1α. Studies in mice in situ indicate that HIF-1α signalling in cardioprotection requires adenosine 2B receptors; apart from the release of adenosine in HIF-1α-deficient mice and the reliance of HIF-1α signalling on adenosine receptors, exogenous adenosine also protects in heterozygous HIF-1α-deficient mouse hearts.

The above paradoxical phenomena and questions are still stimulating but also contribute to difficulties in our understanding of the signal transduction of cardioprotection and its translation to the clinic, apart from species differences and other confounders, such as age, co-morbidities, and co-medications.

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References