The role of peroxiredoxins in ischemia-reperfusion-induced cardiac damage

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MYOCARDIAL ISCHEMIA related to infarction is a disease of multiple pathways with variable outcomes. Both ischemia and reperfusion contribute to cell and tissue damage after cardiac infarction. Myocardial ischemia-reperfusion initiates misdistribution of ions and various signaling mechanisms, leading to oxidative injury and inflammatory responses that include liberation of cytokines (16) and free radicals (14), up- and down-regulation of various genes and their proteins (1, 5, 20), and cell death by apoptosis (13) and/or necrosis (11). The treatment of myocardial infarction is currently mostly directed at restoration of blood flow to the previously ischemic area and reduction of oxygen demand of the heart. However, during reperfusion of cardiac tissue, depending on the duration of the previous ischemic event, the heart undergoes additional damage due to the activation of various pathways, functional and physiological impairments, leading to cell death.

Probably the two most important consequences of ischemia-reperfusion-induced cardiac injury are 1) heart failure and 2) ventricular fibrillation leading to sudden cardiac death. Sudden cardiac death occurs in 1,200,000 cases each year in the industrialized countries of North America and the European Union (2, 6, 18). Thus interventions for the salvage of the myocardium following myocardial ischemia are essential for minimizing the myocardial damage that leads to left ventricular dysfunction and the subsequent risk for heart failure and sudden cardiac death.

Peroxiredoxins (Prdx), the antioxidant components of the thioredoxin superfamily (9, 21), have gained recognition as important redox regulating molecules relevant to the mechanisms underlying ischemia-reperfusion injury. There are currently six known Prdx enzymes that protect cells and tissues from damage caused by reactive oxygen species in mammals (7, 9, 19). Peroxiredoxin 6 (Prdx6) is the only peroxiredoxin of which is glutathione rather than thioredoxins. It is mostly cytosolic and has the longest chain and a unique COOH-terminal domain for dimerization (4) and nuclear targeting (9, 19). All peroxiredoxins have two cysteine residues, but Prdx6 has only one at position 47, changed in mutant C47S by lacking peroxidase activity (10). In addition, Prdx6 is bifunctional because besides its peroxidase activity, protecting cells from oxidative damage, it also has Ca-independent phospholipase A2 activity, and this latter activity is localized to residue 32, identified by mutant S32A (3).

Changes in Prdx are associated with the development of Pick disease, dementia in Lewy body disease, in sporadic Creutzfeldt-Jacob morbidity, and in atherogenesis (12, 17, 23). Prdx6 is elevated in connection with Pick disease, a neurodegenerative illness related to nuclear palsy and temporal demenia in the central nervous system in relation with saitohin Q allele of human tau gene (22). Overexpression of Prdx6 was shown to protect the lung against hyperoxia-induced injury in mice (24). Conversely, Prdx6-null mice were shown to be hypersensitive to hyperoxia, providing evidence that Prdx6 is an important antioxidant enzyme under in vivo conditions.

The results presented by Nagy et al. (15) in the current issue of the American Journal of Physiology-Heart and Circulatory Physiology show for the first time that hearts obtained from Prdx6−/− homozygous knockout mice are more susceptible to ischemia-reperfusion-induced injury, as evidenced by reduced postischemic recovery, increased infarct size, and apoptotic cell death compared with those in the hearts obtained from their wild-type (+/+) littermates. The hearts from Prdx6−/− mice also showed increased levels of tissue malondialdehyde after ischemia and reperfusion.

Because significant amounts of glutathione peroxidase (GSHPx) and catalase are present in the myocardium under in vivo and in vitro conditions, these enzymes may contribute to the attenuation of H2O2-induced damage during cardiac reperfusion. However, in the study of Nagy et al. (15), the absence of Prdx6 in the myocardium of Prdx6 knockout mice was not made up by either catalase or GSHPx's that were present. Thus their studies indicate a nonredundant protective role of Prdx6. Furthermore, Prdx6 could reduce phospholipid hydroperoxides, while GSHPx does not have this ability (8). Nagy et al. (15) hypothesize that a reduction in peroxidized membrane phospholipids by Prdx6 accounts for its unique antioxidant effect. The extrapolation of the findings of Nagy et al. (15) obtained in isolated mouse hearts to an actual clinical situation, however, should be viewed with some caution due to the absence of blood and its elements and the nervous system in their model. Nevertheless, these results clearly demonstrate an important role of Prdx6 in the heart, and perhaps further studies will reveal its clinical significance as a target for the treatment of ischemic heart diseases.

REFERENCES


