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 downregulation 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 demen-

REFERENCES


