Targets for Cardioprotection and Neuroprotection

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ABSTRACT: Evidence from our lab and others supports that the permeability transition pore complex (PTP) is the end-effector of protection signaling in the heart and brain (Juhaszova et al. *J. Clin. Invest.* 2004;113(11):1535-49 and online supplement). We have proven that the convergence of a multiplicity of upstream pathways via the inhibition of glycogen synthase kinase-3β (GSK-3β) on the PTP to limit its induction is the general mechanism of cardiomyocyte and neuron protection. Cardiac muscle stretch and loading are important factors in controlling cellular growth and survival, but the underlying mechanisms are not fully established. We have found that cardiomyocyte stretch elicits cardioprotective signaling via the activation of the PI3K-Akt-eNOS-NO-PKG pathways (independently of the mitoK_{ATP} channel) by enhancing PTP resistance to oxidant stress and promoting cell survival. The specific mechanisms of Akt, PKG (a cGMP-dependent protein kinase), and GSK-3β remain to be elucidated. Pursuing the link between GSK-3β and the PTP, we have found that conventionally-defined pro- and anti-apoptotic members of the Bcl-2 family (via BH3 and BH4 domains, respectively) are critical mediators of protection signaling downstream of GSK-3β, regulating susceptibility of the mPTP to oxidant stress.

KEYWORDS: Reactive oxygen species, mitochondrial permeability transition pore, mitochondrial membrane, transport proteins, glycogen synthase kinase 3 beta, signal transduction

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