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Glycogen synthase kinase-3β controls autophagy during myocardial ischemia and reperfusion

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Autophagy is a catabolic process that degrades long-lived proteins, pathogens and damaged organelles. Autophagy is active in the heart at baseline and is further stimulated by stresses, such as nutrient starvation, ischemia/reperfusion (I/R) and heart failure. Baseline autophagy plays an adaptive role in the heart, and contributes to the maintenance of cardiac structure and function and the inhibition of age-associated abnormalities, by achieving quality control of proteins and organelles. Activation of autophagy during ischemia is beneficial because it improves cell survival and cardiac function. However, excessive autophagy with robust upregulation of BECN1 during reperfusion appears to enhance cell death, which is detrimental to the heart. We have shown recently that autophagy during prolonged ischemia and I/R is critically regulated by glycogen synthase kinase-3β (GSK-3β), a ubiquitously expressed serine/threonine kinase, in a phase-dependent manner. Here we discuss the role of GSK-3β in mediating autophagy in the heart.

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Many biological responses relevant to autophagy, including deprivation of nutrients, a decrease in ATP, endoplasmic reticulum (ER) stress and an increase in reactive oxygen species, are elicited during ischemia and reperfusion in the heart. The signaling pathways through which these stressors induce autophagy have not been fully worked out. GSK-3β is dephosphorylated at serine 9 (Ser9) during ischemia, whereas it is phosphorylated at Ser9 during reperfusion. Since the activity of GSK-3β is negatively regulated by Ser9 phosphorylation, GSK-3β is activated during ischemia, whereas it is inhibited during reperfusion. Our results suggest that activation of GSK-3β during ischemia stimulates autophagy, whereas inactivation of GSK-3β inhibits autophagy during reperfusion. Such phase-dependent regulation of endogenous GSK-3β appears to be adaptive, since inhibition of endogenous GSK-3β during ischemia and activation of GSK-3β during reperfusion are both detrimental to the heart.

We have shown previously that AMP-activated protein kinase (AMPK) is activated and plays an important role in mediating autophagy during myocardial ischemia. Thus, AMPK and GSK-3β act as dual sensors for myocardial ischemia where AMPK is activated by an increase in AMP, whereas GSK-3β is activated by a decrease in Ser9 phosphorylation. Although AMPK and GSK-3β could act independently, there may be an interaction between the two molecules as well. One of the major kinases that phosphorylate GSK-3β at Ser9 is AKT, which is phosphorylated/activated by mTORC2. AMPK inhibits mTOR through activation of tuberous sclerosis complex 2 (TSC2). Thus, starvation-induced inactivation of mTOR leads to inactivation of AKT, which in turn decreases Ser9 phosphorylation on GSK-3β. On the other hand, GSK-3β, together with AMPK, inhibits mTOR through TSC2-dependent mechanisms. Thus, AMPK may initiate, whereas GSK-3β may act as a component of, a positive feedback loop, which mediates mTOR suppression and autophagy during ischemia. This may explain in part why suppression of either AMPK or GSK-3β achieves significant influence upon autophagy during

ischemia. It would be interesting to test whether suppression of AMPK abolishes the initiation of the feedback mechanism, including GSK-3β dephosphorylation.

Since GSK-3β inhibits mTOR through a TSC2-dependent mechanism, we speculate that activation of GSK-3β during prolonged ischemia induces autophagy through inhibition of mTOR. However, GSK-3β may stimulate autophagy through mTOR-independent mechanisms as well. An important precedent is the fact that AMPK stimulates autophagy not only through suppression of mTOR via activation of TSC2, but also through direct phosphorylation of mTORC1 or ULK1. Interestingly, Presenilin-1 (PS1), an Alzheimer disease-related protein, plays an important role in mediating autolysosome acidification and cathepsin activation through targeting of the V-ATPase V_0 a1 subunit to lysosomes. GSK-3β phosphorylates PS1, thereby reducing binding of PS1 to N-cadherin, its cell-surface expression and substrate cleavage. Whether GSK-3β affects PS-1's ability to regulate the V-ATPase V_0 a1 subunit remains to be elucidated.

Modulation of autophagy is critical in mediating the adaptive roles of GSK-3β activation during prolonged myocardial ischemia and GSK-3β inhibition during reperfusion. However, autophagy may not be the only mechanism mediating the effects of GSK-3β during prolonged ischemia and I/R. For example, GSK-3β phosphorylates glycogen synthase and inhibits glycogen synthesis. Glycogen is an efficient source of energy during early ischemia. The temporary halt of glycogen synthesis by GSK-3β activation, together with activation of glycogen phosphorylase, could make more glucose available for glycolysis during acute ischemia. Second, GSK-3β phosphorylates MCL-1 and leads to proteasomal degradation of this protein. MCL-1, a member of the BCL-2-related protein family, is a critical mediator of cell survival. Inhibition of GSK-3β during reperfusion stabilizes MCL-1, thereby inhibiting apoptosis. Third, during I/R, phosphorylation of GSK-3β inhibits mitochondrial permeability transition pore (mPTP) opening through multiple mechanisms, including maintaining hexokinase II in the mPTP complex, hindering the interaction of cyclophilin-D with adenine nucleotide translocase, inhibiting the activation of p53, and inhibition of ATP hydrolysis. mPTP opening plays a critical role in cell death during reperfusion. The relative contribution by autophagy, and each of these functions of GSK-3β, to prolonged ischemic injury and I/R injury remains to be elucidated.

Although autophagy activated during transient ischemia, ischemic preconditioning, and myocardial hibernation appears to be beneficial, whether autophagy induced during reperfusion is protective or harmful to the heart has been controversial. While some studies suggest that upregulation of autophagy during I/R is cardioprotective and promotes cell survival, others demonstrate that stimulation of autophagy during I/R promotes cell death. Our study shows that reperfusion-induced autophagy is attenuated by GSK-3β inhibition and that the inhibition of autophagy is protective against reperfusion injury. Molecular mechanisms responsible for the detrimental effects of autophagy during reperfusion have not been elucidated. It is speculated that excessive autophagy, due to its relatively nonspecific nature in degradation, may digest organelles and molecules that are protective against cell death during reperfusion. Interestingly, although chronic suppression of autophagy alleviates reperfusion injury, the protection is reduced if the duration of ischemia before reperfusion is prolonged. Thus, the overall effects of autophagy suppression upon reperfusion injury may be determined by the balance of its effects upon ischemia and reperfusion. In order to improve the outcome of the treatment for I/R injury, a strategy should be developed to stimulate autophagy during ischemia but inhibit it during reperfusion. One possibility is to enhance the action of endogenous GSK-3β, which controls autophagy in a phase-dependent manner. Further investigation is required to elucidate how the activity of endogenous GSK-3β is regulated during I/R. Judging from the paucity of effective medical treatment for I/R injury, however, the phase-specific modulation of autophagy through modulation of GSK-3β appears to be a promising treatment for patients with ischemic heart disease.

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