Mechanisms of cardiovascular ischemia and therapeutic strategies

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Abstract

Ischemic heart disease (IHD) accounts for >50% of deaths in patients with type 2 diabetes, affecting >20 million people in US, with alarmingly rising prevalence. Diabetes-induced vascular injury exacerbates IHD morbidity. More importantly, it blocks the cardioprotective against MI response to multiple endogenous prosurvival molecules (such as insulin, the most important anti-diabetic molecule) and exogenous interventions (such as ischemic pre-conditioning, the most powerful cardioprotective strategy in the non-diabetic heart), increasing mortality. The molecular mechanisms leading to "universal" impairment of cardioprotective signaling in the diabetic heart remain unclear. Caveolins (Cav) serve as scaffolding regulators of signaling proteins. Many signaling molecules bind to Cav and compartmentalize within caveolae, forming signaling complexes. Altered Cav expression causes "aberrant signaling" involved in numerous physiological regulations, resulting in cellular dysfunction or death. Cav3, the predominant form of Cav in cardiomyocytes, is required for both cardiac insulin signaling and protective preconditioning. We demonstrate that the cardioprotective effect of insulin was significantly blunted as early as four weeks of high fat diet (HFD) feeding (pre-diabetes), a time point where expression levels of insulin signaling molecules remained unchanged. However, Cav3/IRβ complex formation was significantly reduced. Among multiple post-translational modifications altering protein/protein interaction, Cav3 (not IRβ) tyrosine nitration is prominent in the prediabetic heart. Treatment of cardiomyocytes with SIN-1 reduced the signalsome complex and blocked insulin transmembrane signaling. Mass spectrometry identified Tyr73 as the Cav3 nitration site. Phenylalanine substitution of Tyr73 (Cav3Y73F) abolished SIN-1 induced Cav3 nitration, restored Cav3/IRβ complex, and rescued insulin transmembrane signaling. Most importantly, AAV9-mediated cardiomyocyte-specific Cav3Y73F re-expression blocked HFD-induced Cav3 nitration, preserved Cav3 signalsome integrity, restored transmembrane signaling, and rescued insulin protective action against ischemic HF. Finally, diabetic nitrative modification of Cav3 at Tyr73 also reduced Cav3/AdipoR1 complex formation and blocked adiponectin

cardioprotective signaling. These results indicate that nitration of Cav3 at Tyr73 and resultant signal complex dissociation results in cardiac insulin/adiponectin resistance in the prediabetic heart, contributing to ischemic HF progression. Early interventions preserving Cav3-centered signalsome integrity is an effective novel strategy against diabetic exacerbation of ischemic HF.