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TAK1 is a nodal regulator of programmed necrosis and myocardial remodeling

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We recently identified a novel signaling molecule, TAK1 (TGFβ-activated kinase 1, also known as MAP3K7), as a key regulator of cardiac cell survival/death. Importantly, TAK1 is activated in mouse models of heart failure as well as in diseased human myocardium. Here, we defined a novel role for TAK1 in promoting cardiac cell survival and homeostasis using cardiac-specific gene-targeted mice. Cardiac-specific ablation of TAK1 in mice using a Cre-LoxP system showed enhanced pathological cardiac remodeling and massive cell death, and these mice gradually developed heart failure and spontaneous death. Remarkably, ablation of TNF receptor 1 (TNFR1) largely rescued the pathological phenotype of TAK1-deficient mice, preventing early lethality and cardiac fibrosis, suggesting that TNFR1 signaling is critical in mediating adverse remodeling and heart failure associated with TAK1 deficiency. Genetic or pharmacological inactivation of TAK1 in cardiomyocytes markedly induced programmed necrosis and apoptosis in response to TNFα. Conversely, activation of TAK1 protected cardiomyocytes from TNFα-induced cell death. Mechanistically, inactivation of TAK1 promoted formation of the necroptotic cell death complex consisting of RIP1, RIP3, caspase 8, and FADD. Genetic ablation of RIP1, RIP3, caspase 8, or FADD largely blocked TNFα-induced cell death in TAK1-deficient cells, whereas deletion of Bax/Bak or cyclophilin D showed no effects. Further, IKK/NFκB-mediated cell survival signaling was greatly impaired in TAK1-deficient cardiomyocytes. Taken together, our data indicate that TAK1 functions as a critical "molecular switch" in TNFα-induced programmed necrosis in cardiomyocytes, by interacting with the RIP1/3-caspase 8-FADD cell death pathway as well as the IKK-NFκB cell survival pathway.

Biography

Qinghang Liu received his Ph.D. in physiology from the University of Tennessee Health Science Center. He performed his postdoctoral studies in the Division of Molecular Cardiovascular Biology at Cincinnati Children's Hospital Medical Center. He is currently an Assistant Professor in the Department of Physiology and Biophysics at the University of Washington. His current research focuses on defining novel signaling and transcriptional regulatory mechanisms of cardiac hypertrophy and heart failure, using innovative molecular, genetic, and functional approaches.

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