Pathogenic role of DNA single-strand break accumulation and DNA damage response in pressure overload-induced heart failure

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Introduction: The DNA damage response (DDR) pathway is a protein kinase cascade which is activated upon DNA damage. In mitotic cells, the DDR plays an essential role in maintaining genomic stability and preventing cancer formation. DNA damage and activation of the DDR are also observed in the post-mitotic cardiomyocytes of patients with end-stage heart failure, however, their roles in the pathogenesis of heart failure remain elusive.

Methods and Results: We performed transverse aortic constriction (TAC) operation to produce the pressure overload-induced heart failure model in mice. Alkaline- and neutral- comet assay revealed that unrepaired DNA single-strand break (SSB), not double-strand break, is accumulated in cardiomyocytes of the failing heart. Mice with cardiomyocyte-specific deletion of XRCC1, a scaffold protein essential for SSB repair, exhibited more severe heart failure and higher mortality after the TAC operation. Knockdown of XRCC1 using siRNA produced SSB accumulation in cardiomyocytes and SSB accumulation-induced persistent DDR through activation of ataxia telangiectasia mutated (ATM) kinase. Activated ATM in turn induced nuclear translocation of NF- κ B and increased the expression of inflammatory cytokines in cardiomyocytes. Activation of the DDR, nuclear translocation of NF- κ B, and cardiac inflammation were also observed in the failing heart and were enhanced in the heart of cardiomyocyte-specific XRCC1 knockout mice. Further heterozygous deletion of ATM ameliorated the level of DDR and rescued the cardiac inflammation and dysfunction in cardiomyocyte-specific XRCC1 knockout mice.

Conclusions: Unrepaired DNA SSB accumulates in post-mitotic cardiomyocytes and plays a pathogenic role in pressure overload-induced heart failure through activating the DDR pathway. Approaches that promote efficient SSB repair or suppress aberrant activation of DDR may become a novel therapeutic strategy against the progression of heart failure.