·专题报告摘要·

[文章编号] 1007-3949(2007)15-07-0522-01

A20, a Multifunction Protein in Cardiovascular Diseases

Dei-Pei LIU

(*National Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences & Peking Union Medical College Beijing* 100005, *China*)

[**KEY WORDS**] A20; Multifunction Protein; Acute Myocardial Infarction; Apoptosis

A20 was originally characterized as a TNF-inducible gene in human umbilical vein endothelial cells. As an inhibitor of NF-kappaB signaling, A20 could protect apoptosis, inflammatory and cardiac hypertrophy. We investigated the role of A20 on acute myocardial infarction (MI), ox-LDL-induced apoptosis in macrophage, and vascular remodeling. (1) We investigated the role of constitutive human A20 expression in acute MI using a transgenic model. Transgenic mice containing the human A20 gene under the control of the α-myosin heavy chain promoter were constructed. MI was produced by coronary ligation in A20 transgenic mice and control animals. Extent of infarction was then quantitated by two-dimensional and M-mode echocardiography as well as by molecular and pathologic analysis of heart samples in infarct and remote heart regions after 7 days MI. Constitutive overexpression of A20 in the murine heart resulted in attenuated infarct size and improved cardiac function 7 days after myocardial infarction. Significantly, we found a decrease in NF-κB signaling and apoptosis as well as proinflammatory response, cardiac remodeling and interstitial fibrosis in non-infarct regions in the hearts of constitutive A20-expressing animals compared to control animals. Thus cardiac-specific overexpression of A20 improves cardiac function and inhibits cardiac remodeling, apoptosis, inflammation and fibrosis after acute MI. (2) Macrophages apoptosis plays important role in atherogenesis and plaque destabilization. We investigate whether A20 can protect ox-LDL-mediated macrophage apoptosis and elucidate the related molecular mechanisms. Our results showed that A20 expression rescues RAW264.7 cells from ox-LDL-induced apoptosis. The protective effect of A20 on ox-LDL-mediated apoptosis in macrophages may be related to disruption Fas/FasL-dependent activation of caspases-8 and mitochondria pathway. Our studies further indicate that the protective effect of A20 may be also related to modulation of cell cycle progression through coordinating effects on the protein of cell cycle. (3) We examined the effects of A20 on neointimal formation after balloon injury and TNF-alpha-induced vascular smooth muscle cells (VSMCs) proliferation and migration, as well as related molecular mechanisms in vitro and in vivo. We introduced adenovirus expressing A20 or GFP into rat carotid arterial segments after balloon injury. We found that A20 attenuates neointimal formation after arterial injury as well as cell proliferation and migration in response to TNF-alpha in VSMCs through blocking PI3K/Akt/GSKbeta-dependent activation of CREB.

(此文编辑 胡必利)