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INHIBITION OF *MIR-128-3P* BY TONGXINLUO PROTECTS HUMAN CARDIOMYOCYTES FROM ISCHEMIA/REPERFUSION INJURY VIA UPREGULATION OF P70S6K1/P-P70S6K1

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Aims: Tongxinluo (TXL) is a multifunctional Traditional Chinese Medicine that has been widely used to treat cardiovascular diseases. However, no studies have explored whether TXL can protect human cardiomyocytes (HCMs) from ischemia/reperfusion (I/R) injury. Reperfusion Injury Salvage Kinase (RISK) pathway activation was previously demonstrated to protect the hearts against I/R injury and it is generally activated via Akt or Erk 1/2, and their common downstream protein, ribosomal protein S6 kinase (p70S6k). In addition, prior studies proved that TXL treatment of cells promoted secretion of VEGF, which could be stimulated by the increased phosphorylation of one p70S6k subtype, p70S6k1. Consequently, we hypothesized TXL could protect HCMs from I/R injury by activating p70S6k1 and investigated the underlying mechanism.

Methods & Results: HCMs were exposed to hypoxia/reoxygenation (H/R), with or without TXL pretreatment. H/R reduced mitochondrial membrane potential, increased bax/bcl-2 ratios and cytochrome C levels and induced HCM apoptosis. TXL preconditioning reversed these H/R-induced changes in a dose-dependent manner and was most effective at 400 μg/mL. The anti-apoptotic effect of TXL was abrogated by rapamycin, an inhibitor of p70S6k. However, inhibitors of Erk1/2 (U0126) or Akt (LY294002) failed to inhibit the protective effect of TXL. TXL increased p70S6k1 expression and, thus, enhanced its phosphorylation. Furthermore, transfection of cardiomyocytes with siRNA to p70S6k1 abolished TXL's protective effects. Among the micro-RNAs (*miR-145-5p*, *miR-128-3p* and miR-497-5p) previously reported to target p70S6k1, TXL downregulated *miR-128-3p* in HCMs during H/R, but had no effects on *miR-145-5p* and miR-497-5p. An in-vivo study confirmed the role of the p70S6k1 pathway in the infarct-sparing effect of TXL, demonstrating that TXL decreased *miR-128-3p* levels in the rat myocardium during I/R. Transfection of HCMs with a hsa-*miR-128-3p* mimic eliminated the protective effects of TXL.

Conclusions: The *miR-128-3p*/p70S6k1 signaling pathway is involved in protection by TXL against HCM apoptosis during H/R. Overexpression of p70S6k1 is, therefore, a potential new strategy for alleviating myocardial reperfusion injury.

BIOGRAPHY

Guihao Chen has completed his MD from Southern Medical University and currently, he is pursuing his PhD degree in Fuwai Hospital, Peking Union Medical College. His research interests include acute myocardial infarction complicated by cardiogenic shock, and the protective effects of Chinese traditional medicine in myocardial reperfusion injury. So far, he has published more than 10 papers in reputed journals.

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