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LAMINAR SHEAR STRESS-INDUCED ACTIVATION OF RAF/MEK/ERK1/2 SIGNALING PATHWAY CONTRIBUTES TO UPREGULATION OF T-PA EXPRESSION IN HUMAN ENDOTHELIAL PROGENITOR CELLS

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Background Shear stress has been proved to enhance the expression of tissue-type plasminogen activator (t-PA) in endothelial progenitor cells (EPCs), which may contribute to maintenance of vascular homeostasis. However, the underlying mechanism is not clear. Here, we investigated the possible role of mitogen-activated protein kinases (MAPK) and nuclear factor (NF- κ B) signaling in shear stress-mediated upregulation of t-PA expression in endothelial progenitor cells (EPCs).

Methods The peripheral blood mononuclear cells of healthy subjects were induced into EPCs. The human EPCs were treated with four levels of laminar shear stress including stationary condition, low (5 dyn/cm²), media (15 dyn/cm²) and high (25 dyn/cm²) laminar shear stress. The protein expression of MAPK, NF- κ B and t-PA of human EPCs were evaluated by western blot analysis.

Results Shear stress, in a dose-dependent manner, increased t-PA secretion and protein expression of human EPCs. When exposed to 15 dyn/cm² laminar shear stress, the phosphorylation of extracellular signal-related kinase (ERK)1/2 and c-Jun N-terminal protein kinase (JNK) of human EPCs were activated from 12 to 24 h. In parallel, 15 dyn/cm² laminar shear stress increased the phosphorylation of p38 and NF- κ B of human

EPCs from 6 to 24 h. However, 5 dyn/cm² laminar shear stress had no effect on the phosphorylation of ERK1/2, JNK, p38 and NF- κ B of human EPCs. After ERK1/2 and Raf inhibition, the effects of laminar shear stress on the protein and gene expression of t-PA in human EPCs were inhibited.

Conclusions The present findings demonstrate for the first time that shear stress-induced activation of Raf/MEK/ERK1/2 signaling pathway contributes to upregulation of t-PA expression in human EPCs, providing a novel insight into the potential mechanisms of shear stress-exhibited beneficial effects on vascular homeostasis.