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Fluid Shear Stress Regulates the Expression of Lectin-like Oxidized Low Density Lipoprotein Receptor-1 via KLF2-AP-1 Pathway Depending on its Intensity and Pattern in Endothelial Cells

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BACKGROUND AND AIMS:
Vascular endothelial cells (ECs) are exposed to fluid shear stress (FSS), which modulates vascular pathophysiology. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is crucial in endothelial dysfunction and atherosclerosis. We elucidated the mechanism regulating LOX-1 expression in ECs by FSS.

METHODS:
Human umbilical vein endothelial cells were exposed to laminar shear stress (LSS) of indicated intensities using a unidirectional steady flow, or to oscillatory shear stress (OSS) using a bidirectional disturbed flow. In vivo studies were performed in a mouse model of partial carotid ligation and human pulmonary artery sections.

RESULTS:
Within ECs, OSS upregulated LOX-1 expression, while LSS (20 dyne/cm2) downregulated it. We confirmed that OSS-induced LOX-1 expression was suppressed when the mechanotransduction was inhibited by knockdown of the mechanosensory complex. In addition, we demonstrated that Kruppel-like factor 2 (KLF2) has an inhibitory role on OSS-induced LOX-1 expression. Next, we determined that activator protein-1 (AP-1) was the key transcription factor inducing LOX-1 expression by OSS, which was inhibited by KLF2 overexpression. To explore whether the intensity of LSS affects LOX-1 expression, we tested three different intensities (20, 60, and 120 dyne/cm2) of LSS. We observed higher LOX-1 expression with high shear stresses of 120 dyne/cm2 compared to 20 and 60 dyne/cm2, with OSS-like KLF2-AP-1 signaling patterns. Furthermore, ECs within disturbed flow regions showed upregulated LOX-1 expression in vivo.

CONCLUSIONS:
We concluded that LOX-1 expression on ECs is regulated via FSS depending on its intensity as well as pattern. Furthermore, this is mediated through the KLF2-AP1 pathway of mechanotransduction.