Low Shear Stress Regulating Autophagy Mediated by the p38 Mitogen Activated Protein Kinase and p53 Pathways in Human Umbilical Vein Endothelial Cells

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To the Editor: Autophagy is reported to play a critical role in low shear stress (LSS)-induced endothelial cell injury and the formation of atherosclerotic plaques.[1] However, the corresponding mechanisms remain unclear.[2-8] This study was to investigate the changes and mechanism of LSS-induced autophagy in human umbilical vein endothelial cells (HUVECs). HUVECs were treated with LSS of 5 dyn/cm^2 for 0, 5, 15, 30, and 60 min in a parallel plate flow chamber system. Light chain (LC) II, LC3 I, and p62, p38 mitogen-activated protein kinase (MAPK) and their protein of phosphorylation of p38 (p-p38) were detected with Western blot analysis. The protein levels of p-p53 (ser15) and their distribution were detected by immunofluorescence (IF). Same conditions and detection were done using p38 MAPK inhibitor SB203580 (10 μmol/L) and p53 inhibitor Pifithrin-α (30 μmol/L). This study found that LSS induced autophagy and reduced autophagy flux in HUVECs. The LC3 II/I ratio was upregulated by LSS as time increased. The autophagy substrate SQSTM1/p62 also increased with the time process under LSS. It was found that LSS-induced phosphorylated p38 expression and LSS-induced autophagy could be inhibited by p38 inhibitor SB203580 in HUVECs. In LSS, the amount of p38 MAPK did not change even when the time was extended from 0 min to 60 min, while p-p38 gradually increased with time. When HUVECs were pretreated with p38 inhibitor SB203580 at 10 μmol/L for 60 min, SB203580 reduced the transformation of LC3 I to LC3 II in the LSS-exposed endothelial cells in 60 min. In contrast, the degradation of p62 was accelerated. P-p53 in nucleus was reduced under LSS, and LSS-induced LC3 II/LC3 I elevation could not be influenced by p53 inhibitor Pifithrin-α, while p62 decreased under the same conditions. IF was used to detect changes of p-p53 in cells exposed to LSS, and thereby determining whether p-p53 significantly located to the nucleus as a transcription factor under LSS treatment. It was found that the expression of p-p53 in the nucleus was significantly reduced at LSS treatment for 60 min. HUVECs were treated with Pifithrin-α or not under LSS treatment for 60 min. Compared to 60-min LSS treatment with Pifithrin-α, there was strong evidence of autophagy under LSS without Pifithrin-α, namely, LC3 II/I increased. However, in the presence of Pifithrin-α, the LC3 II/I level did not change. For further confirmation of the role of p53 in the LSS-treated HUVECs, the Western blot analysis was used to detect changes in p62. The p62 accumulation of HUVECs exposed to LSS was ameliorated when they were treated with the p53 inhibitor Pifithrin-α. In summary, the ratio of LC3 II/LC3 I was elevated under LSS, while the autophagic substrate p62 and p-p38 MAPK was also increased. P-p53 expression in nuclear was decreased in LSS. The ratio of LC3II/I and the p62 were down-regulated when the endothelial cells treated with p38 MAPK inhibitor in LSS, while the ratio of LC3II/I did not change and the p62 were down-regulated when the endothelial cells treated with p53 inhibitor in LSS. Hence, this study concluded that LSS induced autophagy by activating the p38 MAPK signaling pathway and inhibited autophagy flux by the p53 pathway in HUVECs.

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Conflicts of interest

There are no conflicts of interest.

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