

## Oscillatory Shear Stress Induces Endothelial Dysfunction through the Activation of P2Y12

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**Abstract:** Endothelial cell injured or dysfunction, which results lipid deposition and inflammation, is the key point to exacerbate the process of atherosclerosis [1, 2]. Meanwhile oscillatory shear stress is a key factor that results cell dysfunction in vascular disease [3, 4]. Previous research reported that P2Y12 plays a critical role in the development of atherosclerotic lesion through promoting smooth muscle cells migration [5]. As well P2Y12 stimulated the internalization and transendothelial transport of high density lipid. However, whether the P2Y12 induce atherosclerosis through endothelial cell remain elusive. In this study we firstly found P2Y12 were expressed in endothelial cells of atheroprone areas with western diet in APOE<sup>-/-</sup> mice. Meanwhile, the expression of P2Y12 was down-regulated in smooth muscle cells, compared to the up-regulated in endothelial cells in the left carotid artery with partial ligation to establish oscillatory shear stress in APOE<sup>-/-</sup> mice [6]. The endothelial cells are normal in P2Y12 global deficiently (P2Y12<sup>-/-</sup>) and apoE double knockout mice under oscillatory shear stress, compared with the endothelial cells disruption and intimal hyperplasia in apoE knockout mice. Meanwhile we also found that ADP promotes endothelial cells migration and F-actin disassembly. On the contrast, clopidogrel alone inhibited endothelial cells migration, suggesting that P2Y12 may dynamically regulate rearrangement of F-actin to control endothelial cells function. We further proved the expression of VE-cadherin in endothelial cells was increased under the P2Y12 stimulated. Furthermore, we also performed that P2Y12 stimulated also up-regulate Gi and PI3K class1, which are important in endothelial permeability [7]. Our data discovered that P2Y12 may participate in endothelial cells mechanotransduction and atherogenic signaling showing a potential therapeutic strategy to deal with endothelial permeability in vascular disorder.

**Keywords:** Hemodynamics; oscillatory shear stress; atherosclerosis; P2Y12; VE-cadherin

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