Shear stress increases differentiation of circulating endothelial progenitor cells via the VEGF-R2/PI3K/Akt/mTOR signaling

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Abstract—Shear stress increases adhesion, proliferation, tube formation, and differentiation of floating-circulating endothelial progenitor cells by activating the VEGF-R2/PI3K/Akt/mTOR signal transduction pathway.

I. INTRODUCTION

Endothelial progenitor cells (EPCs) are demonstrated to play an important role in vascular regeneration (1). EPCs are mobilized from bone marrow to peripheral blood, attach to existing endothelial cells in nearby hypoxic lesions, transmigrate into tissue, proliferate, differentiate, and induce neovascularization. In the process EPCs are exposed to shear stress generated by blood flow or tissue flow. We have previously demonstrated that shear stress induces differentiation of adhesive phenotype EPCs (2, 3). Here, we investigated whether shear stress influences biological floating-circulating EPCs in a suspension culture. Furthermore we investigated the signal transduction pathway in response to shear stress (Fig. 1).

II. MATERIAL AND METHODS

Culture of EPCs. Human CD133-positive cells were prepared from freshly obtained human umbilical cord blood samples, expanded for a week, and used for EPCs as in (4).

Shear stress loading experiments. EPCs were exposed to laminar shear stress with a rotating-disk-type flow-loading device for 1 or 2 days followed by all the other assays.


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III. RESULTS

When floating-circulating EPCs were exposed to a laminar shear stress of 2.5 dynes/cm² for 24 hours, the bioactivities of adhesion, proliferation, and tube formation increased. The surface protein expression rate of the endothelial markers VEGF-R1, VEGF-R2, VE-cadherin, and Tie2 increased in shear-stressed EPCs. Those protein increases were dependent on the magnitude of shear stress. The PI3K Inhibitor and the mTOR inhibitor decreased the bioactivities of adhesion, proliferation, and tube formation. Moreover they decreased the expression level of every endothelial marker protein (Fig. 2). It is reported that VEGF-R2 activates the PI3K/Akt signal pathway. Western blotting analysis showed that shear stress increased the phosphorylation of VEGF-R2.

Figure 1. EPCs are exposed to shear stress in circulation.

Figure 2. Effect of the PI3K and mTOR signals on the protein expression. N=3-5, *p < 0.05 vs. static control.

IV. CONCLUSION

Shear stress increases bioactivities of adhesion, proliferation, and tube formation and induces differentiation of floating-circulating EPCs. The mechanism of flow response is the activation of VEGF-R2/PI3K/Akt/mTOR signal transduction pathway.

V. REFERENCES


