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Remodeling of vascular endothelial cells exposed to fluid shear stress: experimental and numerical approach

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Abstract

Vascular endothelial cells are an interface between blood vessel walls and blood flow, and play important roles in physiological functions. Since endothelial cell responses to fluid shear stress have been implicated in the localization of atherosclerosis, the effect of shear stress on endothelial cell morphology and functions has been exclusively studied. After applying fluid shear stress, cultured endothelial cells show marked elongation and orientation in the flow direction. In addition, thick stress fibers of actin filaments appear and align along the cell long axis. Thus, the endothelial cell morphology is closely related to the cytoskeletal structure. The purpose of this review is to summarize endothelial cell responses to fluid flow which have been studied, focusing on the changes in cell shape and cytoskeletal structure. Numerical studies to simulate local flow field at the cellular level and the resulting intracellular stresses are also reviewed.

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1. Introduction

Vascular endothelial cells form a monolayer lining the luminal surface of blood vessel walls and play important roles in physiology and pathology of blood vessel walls. Endothelial cells are exposed to complex mechanical forces mainly due to blood flow. These mechanical forces are important factors

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of remodeling in endothelial cell morphology (Nerem, 1993). Morphological changes induced by mechanical stresses are known to influence several aspects of endothelial cell biology that are critical to normal endothelium functions (Davies, 1995). In *p*, endothelial cell responses to fluid shear stress have been implicated in the localization of atherosclerosis. Atherosclerosis is generally characterized by the formation of atheroma on the intima, which occurs primarily at bends, branching, and bifurcations of the arterial walls, where would experience complex blood flow. Therefore the effects of fluid shear stress on endothelial cell remodeling, including morphology and cytoskeletal structure, have been exclusively studied over the last 30 years.

A lot of efforts have been done to study the correlation between pattern of blood flow and morphology of endothelial cells relating to the development of atherosclerosis. In the in vivo experiments, Flaherty et al. (1972) studied the relationship between orientation of endothelial cell nuclei and blood flow pattern using a canine artery. In straight regions, the nuclei were elongated and oriented parallel to the axis of the blood vessels, while, in entrance regions, less ordered nuclei orientation and elongation were found. Nerem et al . (1981) demonstrated the quantitative study of size and shape of endothelial cells using a vascular cast of rabbit aorta. They suggested that endothelial cell morphology and orientation around a branch vessel might be an indicator of the detailed features of blood flow. These results indicated that there are correlations between the endothelial cell morphology and atherogenesis. On the other hand, the in vitro experiments have been performed under controlled flow conditions by many researchers. For example, Dewey et al. (1981) demonstrated the bovine endothelial cell alignment by applying unidirectional shear stress in steady flow. Levesque and Nerem (1985) reported that elongation and orientation of bovine endothelial cells to flow direction were dependent on flow exposure time and magnitude of shear stress. Furthermore, Ookawa et al. (1992) showed that the changes in distribution of actin filaments, one of the major cytoskeletons, occurred in porcine endothelial cells exposed to shear stress before morphological changes in cells.

In addition to morphological responses, it has been revealed that endothelial cells have many flow-induced functional changes, including gene expression of adhesion molecule and cell permeability. For example, Nagel et al. (1994) studied the effect of shear stress on expression of adhesion molecules on human umbilical vein endothelial cells. The expression of intercellular adhesion molecule-1 was increased by shear stress, where as the expression of E-selectin and vascular adhesion molecule-1 was not affected. The alternation of permeability was addressed by Jo et al. (1991). Permeability of bovine endothelial cells increased during exposure to temporary shear stress and then returned to preshear value after removal of shear stress. Furthermore, distribution of vascular endothelial cadherin, which forms the endothelial adherence junction, was reorganized under shear conditions (Haselton and Heimark, 1997; Noria et al., 1999). Thus fluid shear stress changes endothelial cell shape and cytoskeletal structure, and also regulates many physiologically important functions.

One may wonder that which is the major factor to the endothelial cell responses, shear stress or shear rate. Ando et al. (1993) studied quantitative changes in the cytoplasmic Ca^{2+} concentration in bovine aortic endothelial cells to identify the relative importance of shear stress or shear rate, following the perfusion of two buffers with different viscosities. The fluorescence study showed that an increase in the shear rate and higher viscosity enhanced Ca^{2+} responses, but the responses were virtually identical at the same shear stress, suggesting that shear stress rather than shear rate would be a major factor to regulate endothelial cell responses to flow.

Another research interest is how we simulate the remodeling of endothelial cells to fluid flow. To achieve this, at the early stage, computational fluid dynamics for analyzing the local flow field at the