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Review

Endothelial cytoskeleton in mechanotransduction and vascular diseases

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Abstract

The cytoskeleton is an important structural component that regulates various aspects of cell morphology, movement, and intracellular signaling. It plays a pivotal role in the cellular response to biomechanical stimuli, particularly in endothelial cells, which are critical for vascular homeostasis and the pathogenesis of cardiovascular diseases. Mechanical forces, such as shear and tension, activate intracellular signaling cascades that regulate transcription, translation, and cellular behaviors. Despite extensive research into cytoskeletal functions, the precise mechanisms by which the cytoskeleton transduces mechanical signals remain incompletely understood. This review focuses on the role of cytoskeletal components in membrane, cytoplasm, and nucleus in mechanotransduction, with an emphasis on their structure, mechanical and biological behaviors, dynamic interactions, and response to mechanical forces. The collaboration between membrane cytoskeleton, cytoplasmic cytoskeleton, and nucleoskeleton is indispensable for endothelial cells to respond to mechanical stimuli. Understanding their mechanoresponsive mechanisms is essential for advancing therapeutic strategies for cardiovascular diseases.

Introduction

Cells exhibit remarkable capabilities to sense and respond to a broad range of physical stimuli, including mechanical forces. In the cardiovascular system, endothelial cells (ECs) are equipped with specialized mechanosensors that detect mechanical stimuli, such as shear stress, stretch and extracellular matrix (ECM) stiffness, and transduce these signals into intracellular biochemical cascades(Lim and Harraz, 2024). These processes are essential for regulating blood flow dynamics and vascular homeostasis and have important implications for therapeutic outcomes in vascular-related diseases.

The ability of ECs to deform in response to mechanical stress is governed by their viscoelastic cytoskeleton(Bonakdar et al., 2016). This dynamic structure, composed of actin microfilaments, microtubules, and intermediate filaments, is crucial for maintaining cell integrity, supporting intracellular transport, and mediating cellular responses to both intracellular and extracellular mechanical environments(Pradeau-Phelut and Etienne-Manneville, 2024). Mechanical forces are transduced through the cytoskeleton to the nucleus, where they regulate gene expression and activate intracellular signaling pathways(Di et al., 2023). These biochemical changes, in turn, can induce cytoskeletal remodeling, thereby altering the cell mechanical properties and the surrounding microenvironment(Pires et al., 2022).

The cytoskeleton is a fundamental regulator of endothelial cell behaviors and functions. Recent studies explored the role of the spectrin network in mechanotransduction, particularly in sensing and distributing mechanical force at the apical surface of ECs(Mylvaganam et al., 2022). Among them, βIV-spectrin has been identified as a key mediator of angiogenesis(Ahmed et al., 2023). Spectrin beta non-erythrocytic 1 (*sptbn1*) has emerged as a potential regulator of the leaky phenotype observed in atherosclerotic microvessels(Rademakers et al., 2024). In addition, the actin cytoskeleton serves as a structural framework that maintains the integrity of the vascular endothelial barrier(Zhang et al., 2024b). Interestingly, ECs exhibiting F-actin stress fibers demonstrate enhanced efficiency in transendothelial drug delivery, highlighting a functional interplay between cytoskeletal organization and therapeutic outcomes(Meijlink et al., 2024). Furthermore, the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex within the nucleus has been identified as a key component in mechanotransduction, which mediates cell adhesion and facilitates adaptive responses to shear forces and mechanical stretching(Denis et al., 2021).

This review provides a comprehensive understanding of the structure, composition, and mechanoresponsive mechanisms of the cytoskeleton, with a focus on the role of these components in vascular endothelial cell function. Given the central role of ECs in mechanotransduction and vascular homeostasis, understanding their cytoskeletal dynamics is critical for elucidating disease pathogenesis and developing novel therapeutic strategies for cardiovascular diseases.

Section snippets

Overview of cytoskeletal components: structure, composition, and functions

The cytoskeleton components are classified into three primary types based on their location: membrane cytoskeleton, cytoplasmic cytoskeleton, and nucleoskeleton. Each of these types has distinct structures, compositions, and functions. …

Endothelial cytoskeleton in mechanotransduction

The cytoskeleton plays a critical role in mechanotransduction, the process by which ECs respond to mechanical stimuli such as shear stress. Alterations in the mechanical environment, such as those observed in conditions like hypertension or atherosclerosis, can lead to cytoskeletal remodeling and impair endothelial function(Huang et al., 2022, Sun et al., 2024, Zhang et al., 2023). The mechanotransduction pathways mediating these responses involve a variety of signaling molecules, including …

Implications of endothelial cytoskeletal abnormalities in human diseases

The cytoskeleton systems play a crucial role in maintaining the morphology, structural integrity, and barrier function of vascular ECs (Fig. 5). Disruptions in endothelial cytoskeletal architecture can lead to increased permeability, inflammation, and the development of various diseases including diabetes, sepsis, hypertension, atherosclerosis, neurovascular diseases, and cancers. Moreover, dysregulation of endothelial cell function can cause increased vascular stiffness and impaired …

Targeting of the cytoskeleton to mitigate endothelial dysfunction

The intricate relationship between endothelial cytoskeletal dynamics and vascular hemostasis underscores the importance of maintaining cytoskeletal integrity. Therapeutic approaches targeting the regulation of cytoskeletal dynamics have shown promise in restoring vascular integrity and counteracting pathological conditions associated with endothelial dysfunction. …

Conclusions and perspective

The mechanical behaviors of cells, and their response to mechanical loading, are primarily governed by the cytoskeleton. These behaviors are highly sensitive to changes in the cellular environment and are closely linked to both cellular development and disease progression. As the cytoskeletal networks are deformed, their stiffness increases, which may help cells limit excessive deformation when exposed to abnormal stresses. Dysruptions in the cytoskeleton can impair mechanotransduction, leading …

CRediT authorship contribution statement

Linlu Jin: Writing – review & editing, Writing – original draft, Visualization. **Yixue Qin:** Writing – review & editing, Visualization. **Yunran Zhao:** Writing – review & editing, Visualization. **Xintong Zhou:** Writing – review & editing, Visualization. **Ye Zeng:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition, Conceptualization. …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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