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Mechanisms of Angiogenesis in Atherosclerosis: Implications for Therapeutic Strategies

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Introduction

Atherosclerosis is a progressive disease characterized by the accumulation of fatty deposits, inflammatory cells, and extracellular matrix components within the walls of arteries. This condition leads to the thickening and hardening of the arterial walls, contributing to various cardiovascular diseases, including coronary artery disease, stroke, and peripheral artery disease. As atherosclerotic plaques enlarge, they can become hypoxic due to insufficient blood supply, triggering a response known as angiogenesis the formation of new blood vessels. Although angiogenesis is traditionally seen as a repair mechanism, its role in atherosclerosis is complex and paradoxical. Angiogenesis can stabilize plaques by providing oxygen to ischemic tissue, but it can also promote plaque instability by creating fragile and leaky blood vessels that increase the risk of plaque rupture. Understanding the mechanisms of angiogenesis in atherosclerosis is essential for developing therapeutic strategies to either promote or inhibit angiogenesis, depending on the clinical context [1].

Description

Molecular mechanisms of angiogenesis in atherosclerosis

Angiogenesis is a tightly regulated process in which new blood vessels form from existing ones. In atherosclerosis, angiogenesis is primarily driven by the local hypoxic environment within the plaque. As plaques grow and outstrip their existing blood supply, oxygen levels within the plaque decrease, initiating a cascade of molecular signals that promote the formation of new blood vessels [2].

Hypoxia-inducible factors (HIFs): One of the key mediators of angiogenesis in atherosclerosis is hypoxia-inducible factor (HIF), a transcription factor that is stabilized in low-oxygen conditions. HIF activates the expression of pro-angiogenic molecules, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and angiopoietins. These factors promote the proliferation, migration, and differentiation of endothelial cells, the building blocks of new blood vessels. In atherosclerotic plaques, HIF-driven angiogenesis is critical for attempting to re-establish a blood supply to hypoxic regions.

Vascular endothelial growth factor: VEGF is perhaps the most important angiogenic factor in atherosclerosis. It binds to receptors on endothelial cells and stimulates their proliferation and migration, ultimately leading to the formation of new blood vessels [3]. In addition to promoting angiogenesis, VEGF also enhances vascular permeability, which can contribute to the leakage of inflammatory cells and fluid into the plaque, further exacerbating the inflammatory environment.

Fibroblast growth factors: FGF is another important angiogenic factor that plays a role in atherosclerosis. It promotes endothelial cell proliferation and aids in the stabilization of new blood vessels. Like VEGF, FGF also supports the migration of smooth muscle cells and the remodeling of the extracellular matrix (ECM), which can contribute to both plaque progression and the development of collateral circulation in ischemic tissues [4].

Matrix metalloproteinases: MMPs are enzymes involved in the degradation of the ECM, which is a critical step in both angiogenesis and plaque instability. In atherosclerotic plaques, MMPs facilitate the remodeling of the ECM, making space for new blood vessels. However, excessive MMP activity can lead to the degradation of the fibrous cap that covers the plaque, rendering the plaque more prone to rupture. Thus, the balance between MMP activity and ECM stability is crucial for determining plaque vulnerability.

Role of inflammation in angiogenesis

Atherosclerosis is inherently an inflammatory disease, and the inflammatory microenvironment within atherosclerotic plaques significantly influences angiogenesis. Inflammatory cells such as macrophages, T-cells, and mast cells secrete cytokines and growth factors that contribute to angiogenesis [5]. These cells produce pro-angiogenic factors such as VEGF and FGF, which drive the formation of new blood vessels. Additionally, inflammation promotes the upregulation of adhesion molecules on endothelial cells, which facilitate the recruitment of immune cells to the plaque.

However, the inflammatory environment also complicates the process of angiogenesis. While new blood vessels can provide necessary nutrients to the plaque, the leakiness of these vessels can exacerbate inflammation by allowing immune cells and pro-inflammatory molecules to enter the plaque. This continuous cycle of inflammation and angiogenesis can lead to further plaque growth and instability, increasing the risk of rupture and acute cardiovascular events [6].

Angiogenesis and plaque stability

The formation of new blood vessels within atherosclerotic plaques is a double-edged sword. On the one hand, angiogenesis can stabilize plaques by improving their blood supply, reducing hypoxia, and promoting healing of the fibrous cap [7]. A well-vascularized plaque may have a stronger fibrous cap that helps prevent rupture. On the other hand, the new vessels in atherosclerotic plaques are often disorganized, fragile, and prone to leakage. These characteristics make them more likely to rupture, releasing pro-thrombotic material and triggering thrombosis, which can lead to the sudden occlusion of the artery and acute cardiovascular events [8].

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Conclusion

Angiogenesis in atherosclerosis is a complex process with dual effects on plaque stability. While it can provide necessary blood supply to ischemic tissues and stabilize plaques, it can also contribute to plaque instability and increase the risk of rupture by promoting the formation of fragile, leaky blood vessels. Understanding the molecular mechanisms driving angiogenesis in atherosclerosis and the role of inflammation is essential for developing targeted therapeutic strategies. Whether the goal is to inhibit angiogenesis to stabilize vulnerable plaques or promote angiogenesis to enhance blood flow in ischemic regions, carefully modulating this process holds the potential to improve cardiovascular outcomes and prevent catastrophic events such as heart attacks and strokes.

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Conflict of Interest

None

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