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Atherosclerosis: Mechanisms, Diagnosis and Therapies

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Introduction

Atherosclerosis is widely recognized as a chronic inflammatory disease, and current research highlights the critical role of immunometabolism in its development. Metabolic reprogramming within immune cells, especially macrophages and T cells, significantly drives the progression of atherosclerotic plaques, offering potential therapeutic targets to modulate these metabolic pathways and mitigate inflammation and disease advancement [1].

Diagnosis and risk stratification for coronary artery disease, a direct consequence of atherosclerosis, heavily rely on non-invasive imaging. Advanced modalities such as CT angiography, PET, and MRI are reviewed for their strengths and limitations, while future directions point towards molecular imaging and Artificial Intelligence-enhanced analysis for improved early detection and patient management [2].

The intricate relationship between lipid metabolism and immune cell function is central to atherosclerosis. Dysregulated lipid profiles, notably oxidized LDL, initiate inflammatory responses and contribute to plaque formation through a complex interplay between various immune cell types and lipid pathways, suggesting new therapeutic avenues beyond traditional lipid-lowering strategies [3].

Emerging evidence points to the gut microbiota as a significant player in the development and progression of atherosclerosis. Microbial dysbiosis and specific microbial metabolites, like TMAO, interact with the host immune system, leading to endothelial dysfunction and plaque instability. This understanding opens doors for novel strategies, including probiotics and fecal microbiota transplantation, for prevention and treatment [4].

Genetic factors profoundly influence individual susceptibility to atherosclerosis. Summaries of current knowledge detail genetic variants linked to increased risk of coronary artery disease, demonstrating how genomic studies have identified novel pathways and targets, paving the way for personalized medicine in prevention and therapy, despite challenges in clinical translation [5].

Vascular calcification is an important, yet often overlooked, component of atherosclerosis, contributing substantially to plaque instability and adverse cardiovascular events. The complex mechanisms underlying this process, involving cellular and molecular pathways, have significant clinical implications for disease progression and are targets for existing and emerging therapeutic strategies aimed at inhibiting or reversing arterial calcification [6].

Beyond specific immune cell metabolism, broader metabolic reprogramming in various cell types, including immune and endothelial cells, is a hallmark of atherosclerosis. Altered cellular metabolism, involving shifts in glucose and lipid utilization, impacts the inflammatory response and plaque development, identifying novel metabolic checkpoints as potential therapeutic targets for interventions beyond conventional lipid-lowering therapies [7].

The field is actively exploring emerging therapeutic strategies for atherosclerosis, transitioning from foundational molecular mechanisms to potential clinical translation. Innovative approaches include gene therapy, RNA interference, and novel immunomodulatory drugs, alongside advancements in traditional pharmacotherapies. Emphasis is placed on understanding disease heterogeneity to develop more personalized and effective treatments for advanced atherosclerotic cardiovascular disease [8].

Epigenetic modifications, encompassing DNA methylation, histone modification, and non-coding Ribonucleic Acids, are critical regulators of gene expression in atherosclerosis. These mechanisms influence key cellular processes such as inflammation, lipid metabolism, and endothelial function, thereby contributing to plaque development and instability. Understanding these regulatory layers offers promising avenues for developing epigenetic therapies to prevent or treat atherosclerotic cardiovascular disease [9].

Finally, hemodynamic forces, particularly disturbed blood flow and shear stress, are pivotal in the initiation and progression of atherosclerosis. Research elucidates the molecular mechanisms through which different patterns of shear stress influence endothelial cell function, inflammation, and plaque formation, discussing how these mechanical forces can be therapeutically targeted, exploring innovations in biomaterials and drug delivery systems to prevent disease development [10].

Description

Atherosclerosis is fundamentally a chronic inflammatory disease, where understanding immunometabolism is crucial. Metabolic reprogramming in immune cells, particularly macrophages and T cells, directly drives the progression of atherosclerotic plaques. This complex process involves altering how these cells utilize glucose and lipids, impacting their inflammatory responses and contributing to plaque development. Such insights are identifying novel metabolic checkpoints as promising therapeutic targets, moving beyond conventional lipid-lowering strategies [1, 7]. Moreover, the intricate relationship between lipid metabolism and immune cell function is pivotal. Dysregulated lipid profiles, specifically oxidized LDL, trigger significant inflammatory responses and contribute to plaque formation. This highlights a complex interplay between various immune cell types and lipid pathways, offering new perspectives for therapeutic interventions [3].

Beyond cellular mechanisms, systemic factors play a substantial role. The gut microbiota, for instance, has emerged as a significant player in atherosclerosis

development and progression. Microbial dysbiosis, along with specific microbial metabolites like TMAO, interact with the host immune system, contributing to endothelial dysfunction and plaque instability. This understanding inspires novel strategies such as probiotics and fecal microbiota transplantation for prevention and treatment [4]. Concurrently, genetic factors profoundly influence individual susceptibility to atherosclerosis. Genomic studies have summarized current understanding of genetic variants associated with increased risk, identifying novel pathways and targets, which are now paving the way for personalized medicine approaches in both prevention and therapy, though challenges remain in translating these findings clinically [5].

Structural and physical aspects also significantly shape the disease. Vascular calcification, often overlooked, is a critical component of atherosclerosis that contributes to plaque instability and adverse cardiovascular events. Detailed research has elucidated the complex mechanisms underlying this process, including cellular and molecular pathways. Examining its clinical implications in disease progression is leading to discussions on existing and emerging therapeutic strategies aimed at inhibiting or reversing arterial calcification, providing hope for improved patient outcomes [6]. Equally important are hemodynamic forces, especially disturbed blood flow and shear stress, which are pivotal in the initiation and progression of atherosclerosis. The molecular mechanisms by which different patterns of shear stress influence endothelial cell function, inflammation, and plaque formation are well-documented. Targeting these mechanical forces therapeutically, through innovations in biomaterials and drug delivery systems that leverage flow dynamics, shows potential to prevent disease development [10].

For effective management, non-invasive imaging plays a crucial role in the diagnosis and risk stratification of coronary artery disease. This area reviews current advanced imaging modalities, including CT angiography, PET, and MRI, detailing their strengths and limitations. Future directions for imaging technology include molecular imaging and Artificial Intelligence-enhanced analysis, aiming to improve early detection and patient management significantly [2].

The landscape of atherosclerosis treatment is continually evolving with emerging therapeutic strategies. These range from foundational molecular mechanisms to potential clinical translation, exploring innovative approaches like gene therapy, RNA interference, and novel immunomodulatory drugs. Advancements in traditional pharmacotherapies are also ongoing. A key emphasis is placed on understanding disease heterogeneity to develop more personalized and effective treatments for advanced atherosclerotic cardiovascular disease [8]. Furthermore, epigenetic modifications, encompassing DNA methylation, histone modification, and non-coding Ribonucleic Acids, are recognized as critical regulators of gene expression in atherosclerosis. These mechanisms influence key cellular processes such as inflammation, lipid metabolism, and endothelial function, contributing to plaque development and instability. Understanding these regulatory layers offers promising avenues for developing epigenetic therapies to prevent or treat atherosclerotic cardiovascular disease [9].

Conclusion

Atherosclerosis is a multifaceted chronic inflammatory disease driven by diverse factors and mechanisms. Research highlights the critical role of immunometabolism and metabolic reprogramming in immune cells, particularly macrophages and T cells, which drives atherosclerotic plaque progression and offers potential therapeutic targets. Advanced non-invasive imaging, including CT angiography, PET, and MRI, is crucial for diagnosis and risk stratification, with future directions emphasizing molecular imaging and Artificial Intelligence-enhanced analysis for improved early detection. Dysregulated lipid metabolism, especially oxidized LDL, is a key instigator of inflammatory responses and contributes significantly to plaque formation through intricate interactions with various immune cell types. The gut microbiota emerges as a significant player, where microbial dysbiosis and specific metabolites contribute to endothelial dysfunction and plaque instability, prompting novel strategies involving microbiota modulation. Genetic factors profoundly influence individual susceptibility, with genomic studies identifying new pathways for personalized medicine. Vascular calcification, a crucial yet often overlooked component, contributes to plaque instability, and understanding its mechanisms is vital for developing inhibitory or reversal strategies. Emerging therapeutic strategies encompass gene therapy, RNA interference, and novel immunomodulatory drugs, alongside advancements in traditional pharmacotherapies, all emphasizing personalized approaches based on disease heterogeneity. Epigenetic modifications, including DNA methylation and histone changes, are critical regulators of gene expression, influencing inflammation, lipid metabolism, and endothelial function, thus offering promising avenues for epigenetic therapies. Finally, hemodynamic forces, particularly disturbed blood flow and shear stress, are pivotal in the initiation and progression of atherosclerosis, impacting endothelial cell function and inflammation. These mechanical forces represent therapeutic targets for preventing disease development through innovations in biomaterials and drug delivery.

Acknowledgement

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Conflict of Interest

None.

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