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Review Article

Circulating MicroRNAs in Atherosclerosis, Biomarkers and Therapeutic Targets

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Abstract

Atherosclerosis, a chronic inflammatory disease of the arterial wall characterized by the accumulation of lipids and the formation of plaques, remains a leading cause of morbidity and mortality worldwide. The pathogenesis of this complex disease involves a multitude of cellular and molecular factors that intricately interact to drive its initiation and progression. Among these factors, microRNAs (miRNAs), small endogenous non-coding RNA molecules, have emerged as critical post-transcriptional regulators of gene expression, playing significant roles in various biological processes, including cardiovascular diseases. The involvement of miRNAs in key processes underlying atherosclerosis, such as endothelial dysfunction, inflammation, lipid metabolism and vascular smooth muscle cell behavior, has garnered increasing attention in recent years.

Introduction

MicroRNAs as crucial molecular biomarkers that participate in the sequential steps of atherosclerosis development. The review emphasized the ability of these short RNA molecules to bind to specific sequences on target messenger RNAs (mRNAs), thereby modulating gene expression after transcription [1]. The critical role of miRNAs in epigenetic regulation and the entire spectrum of atherosclerosis, from the initial risk factors to the eventual plaque formation, progression, and rupture. Furthermore, the review explored the potential of miRNAs as therapeutic candidates for atherosclerosis, along with the application of exosomes for miRNA delivery and their significance in prognosis and diagnosis. Key cellular and molecular processes implicated in miRNA regulation of atherosclerosis, as identified in the review, included endothelial cell function, inflammation, reverse cholesterol transport, cell proliferation, vascular inflammation, and lipid metabolism. By incorporating recent advancements in the field, discussing specific miRNAs, their mechanisms of action, and their potential for diagnosis and therapy in atherosclerosis [2]. The pivotal role of miRNAs in the progression of atherosclerosis and their potential as biomarkers for early detection and management. Studies have consistently shown that aberrant expression of miRNAs is significantly associated with the development of atherosclerosis, further solidifying the notion that circulating miRNAs in the bloodstream hold promise as diagnostic markers. While not explicitly research on specific miRNAs like miR-181b has explored the therapeutic potential of restoring miRNA levels to combat vascular inflammation, a central component of atherosclerosis [3]. This concept aligns with the broader theme of miRNA therapeutics discussed in the earlier review.

These recent reviews corroborate that miRNAs exert their influence on atherosclerosis by modulating a wide array of processes, including the function of endothelial cells and vascular smooth muscle cells, the orchestration of vascular inflammation, and the maintenance of cholesterol homeostasis within the vessel wall [4]. The stability of circulating miRNAs in peripheral blood makes them attractive candidates as non-invasive biomarkers for the diagnosis of atherosclerosis across different arterial territories. Notably, distinct miRNA profiles have been observed in atherosclerosis affecting different vascular beds, such as the coronary, carotid, and lower limb arteries, suggesting that these profiles could provide insights into the specific pathophysiology of the disease in various locations [5]. Furthermore, the potential of miRNAs as novel therapeutic targets for the management of atherosclerosis and other cardiovascular diseases is being increasingly explored. Dysregulation of miRNA expression and function has been consistently linked to various human diseases, including atherosclerosis, highlighting their critical regulatory roles. Specific miRNAs derived from tissues are emerging as promising biomarkers for different stages and subtypes of coronary artery disease. Preclinical studies have demonstrated the beneficial effects of manipulating miRNA expression in the context of atherosclerosis treatment [6]. The involvement of miRNAs in fundamental processes such as endothelial dysfunction, plaque formation and stabilization, and cholesterol metabolism underscores their therapeutic potential. Recent research emphasizes the theranostic capabilities of miRNAs, suggesting their utility in both diagnosis and therapy for atherosclerosis [7].

Impact of miR-221 on Vascular Smooth Muscle Cells

The landscape of miRNA research in atherosclerosis has identified numerous specific miRNAs with diverse roles in the dis-

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ease process. Certain miRNAs exhibit pro-atherogenic effects, contributing to the development and progression of the condition. For instance, miR-155 is frequently upregulated in atherosclerotic conditions and is known to promote inflammation [8]. Similarly, miR-92a is upregulated in endothelial dysfunction, fostering inflammation and potentially hindering angiogenesis. MiR-21 is also found to be elevated in atherosclerosis and participates in various pro-atherogenic mechanisms. Furthermore, miR-221 shows increased levels in atherosclerosis and promotes the proliferation and calcification of vascular smooth muscle cells. The miR-33a/b family is overexpressed in atherosclerosis and plays a crucial role in regulating cholesterol and fatty acid homeostasis, contributing to lipid accumulation. In the context of coronary artery disease, miR-206 is upregulated and inhibits the survival and migration of endothelial progenitor cells, while miR-216a is elevated in older patients with coronary artery disease and is implicated in endothelial aging and dysfunction [9].

Conversely, several miRNAs have been identified as exhibiting anti-atherogenic properties, potentially protecting against the development of the disease. MiR-126, for example, regulates endothelial function, promotes endothelial cell proliferation, limits atherosclerosis progression, and inhibits endothelial permeability and apoptosis. MiR-146a suppresses inflammatory responses in both endothelial cells and macrophages, and it reduces lipid uptake by macrophages. MiR-10a inhibits the expression of pro-inflammatory genes in endothelial cells. MiR-181b has been shown to inhibit NF-κB signaling and reduce vascular inflammation. The miR-143/145 cluster is involved in regulating vascular smooth muscle cell function and contributes to plaque stability. The let-7 family of miRNAs plays a critical role in maintaining the integrity of endothelial cells and reduces inflammation and monocyte adhesion [10].

Roles of miRNAs in Endothelial Dysfunction

The diverse roles of these miRNAs in atherosclerosis are mediated through various mechanisms that affect key cellular processes. In the context of endothelial dysfunction, miR-10a inhibits pro-inflammatory genes such as VCAM-1 and E-selectin by targeting the NF-κB signaling pathway. MiR-181b directly targets KPNA4, thereby inhibiting the nuclear translocation of NF-κB and reducing vascular inflammation. MiR-126, miR-31, and miR-17-3p regulate vascular inflammation by controlling the expression of adhesion molecules like VCAM-1, ICAM-1, and E-SEL. Endothelial cell activation is also influenced by shear stress through miRNAs; atheroprotective laminar flow downregulates miR-92a, leading to increased expression of KLF2 and KLF4. MiR-216a contributes to endothelial aging and dysfunction by targeting Smad3, resulting in enhanced monocyte adhesion [11].

Inflammation, a central feature of atherosclerosis, is significantly modulated by miRNAs. MiR-155 exhibits a well-established pro-inflammatory function and is upregulated in atherosclerosis. Conversely, miR-146a expression can be reduced in response to oxidized low-density lipoprotein (ox-LDL), impacting the release of inflammatory factors. However, miR-146a can also suppress the inflammatory response of endothelial cells. MiR-130a-3p has been shown to inhibit endothelial inflammation by regulating MAPK8 in endothelial cells. Notably, miR-92a, induced by ox-LDL and low shear stress, enhances pro-inflammatory markers through a STAT3-dependent mechanism [12].

Regulation of Lipid Metabolism in Atherosclerosis

Lipid metabolism, another critical process in atherosclerosis, is also under the control of miRNAs. MiR-33a and miR-33b are key regulators of cholesterol and fatty acid homeostasis. MiR-148a influences hepatic LDLR and ABCA1 expression, thereby affecting the levels of LDL-C and HDL-C. MiR-122 plays a role in regulating plasma triglyceride and cholesterol levels. Furthermore, miRNAs can target cholesterol uptake into the liver by inhibiting SR-BI and LDLR, and they also impact cholesterol efflux from atherosclerotic plaques. The proliferation and migration of smooth muscle cells, crucial events in plaque development, are also regulated by miRNAs. MiR-143 and miR-145 are involved in controlling these processes in vascular smooth muscle cells and may exert an anti-atherogenic effect. In contrast, miR-21 enhances both the migration and proliferation of vascular smooth muscle cells and miR-221 promotes their proliferation [13].

Diagnostic Potential of Circulating miRNAs in Atherosclerosis

The potential of miRNAs as therapeutic tools in atherosclerosis is significant, encompassing both diagnostic and therapeutic applications [14]. Circulating miRNAs in peripheral blood hold promise as non-invasive biomarkers for the diagnosis of atherosclerosis and for predicting future cardiovascular events. Studies have shown that dysregulated levels of these miRNAs can effectively distinguish patients with arterial disease from healthy individuals. Specific miRNAs, such as miR-223-3p and serum miR-122-5p, are being investigated as potential biomarkers for coronary artery disease and plaque instability. MiR-423-3p has shown promise as a prognostic biomarker for CAD [15]. Moreover, a specific pattern of miRNA expression, characterized by the upregulation of miR-100, miR-133a/b, and miR-127, may be indicative of vulnerable atherosclerotic plaques. The observation of distinct miRNA signatures associated with atherosclerosis in different arterial territories suggests their potential in elucidating the underlying pathophysiology in specific vascular beds. Beyond diagnostics, miRNAs are considered promising therapeutic candidates for atherosclerosis. Therapeutic strategies involve the use of miRNA inhibitors (antagomirs) to suppress the activity of pro-atherogenic miRNAs and miRNA mimics to enhance the effects of anti-atherogenic miRNAs [16]. Preclinical studies have demonstrated the benefits of modulating miRNA expression in the treatment of atherosclerosis. For instance, viral vectors have been employed for miRNA deliveryand the specific overexpression of miR-145 in vascular smooth muscle cells has been shown to reduce plaque burden and inflammation in animal models. The inhibition of miR-33a/b is being explored as a therapeutic approach to improve cholesterol efflux and restoring miR-181b levels is considered a potential strategy for anti-inflammatory therapy. However, challenges such as target specificity, safety, delivery, and the overall efficiency of miRNA-based therapeutics need to be addressed.

To facilitate a comparative understanding of the roles of different miRNAs in atherosclerosis, a summary table is provided below. This table highlights key microRNAs, their primary cellular targets or processes affected in atherosclerosis, their overall impact on the disease, and their potential as biomarkers or therapeutic targets (Table1).

The field of miRNA research in atherosclerosis continues to evolve, and several challenges and future directions warrant consideration. Further investigations are essential to fully elucidate the potential of miRNAs as both prognostic and diagnostic biomarkers, as well as to overcome the limitations associated with their therapeutic application. These limitations include issues related to target specificity, safety, efficient delivery, and overall efficacy. Future studies should focus on validating cur-

rent findings in larger clinical cohorts and exploring the possibility of combination therapies involving miRNAs. Understanding the role of miRNAs in different stages of atherosclerosis progression and in diverse patient populations, considering factors such as age, sex, and comorbidities, is also crucial. The intricate interplay between miRNAs and other non-coding RNAs, such as long non-coding RNAs (lncRNAs), in the pathogenesis of atherosclerosis represents another important area for future research. Finally, the development of more effective and targeted delivery systems for miRNA-based therapeutics remains a key priority for translating these promising findings into clinical practice [17].

Discussion

The exploration of microRNAs (miRNAs) in the context of atherosclerosis presents a compelling convergence of molecular biology, epigenetics, and cardiovascular research. These small, non-coding RNA molecules have garnered attention as crucial regulators of gene expression and as promising biomarkers and therapeutic targets for atherosclerosis. Their ability to bind to specific sequences on messenger RNAs (mRNAs) allows them to modulate post-transcriptional gene expression, influencing multiple cellular pathways relevant to atherosclerosis development.Numerous studies and reviews have highlighted that miRNAs orchestrate key processes such as endothelial dysfunction, lipid metabolism, inflammation, cell proliferation, and reverse cholesterol transport. For instance, miRNAs like miR-33 regulate cholesterol homeostasis, while miR-145 influences vascular smooth muscle cell phenotype, thereby affecting plaque stability. Moreover, miR-181b has shown potential in mitigating vascular inflammation—a central component of atherosclerosis-suggesting its therapeutic value.

One of the most appealing features of miRNAs is their presence and stability in peripheral blood. This stability allows them to serve as non-invasive biomarkers, enabling early detection of atherosclerotic changes even before clinical symptoms arise. Circulating miRNA profiles differ significantly between patients with atherosclerosis and healthy individuals and may vary depending on the arterial territory affected—such as the coronary, carotid, or peripheral arteries—thus offering a location-specific diagnostic advantage.

Furthermore, the development of miRNA-based therapeutics is an expanding frontier. Strategies such as using miRNA mimics to restore downregulated protective miRNAs or antagomirs to inhibit harmful ones are being investigated in preclinical models. These approaches have shown promising results in reducing plaque burden, improving endothelial function, and modulating inflammation.

The use of exosomes as delivery vehicles further enhances the translational potential of miRNA-based therapies, offering targeted and biocompatible options for gene regulation. As research continues to uncover the complexities of miRNA expression and function in atherosclerosis, the concept of "theranostics"—the integration of diagnostic and therapeutic capabilitiesbecomes increasingly feasible.

In summary, miRNAs play a pivotal role in the pathophysiology of atherosclerosis and represent a promising class of molecules for both diagnosis and treatment. Future clinical applications will depend on further validation of specific miRNAs, optimization of delivery systems, and understanding patient-specific miRNA signatures to pave the way for personalized cardiovascular medicine.

Conclusion

MicroRNAs play significant and multifaceted roles in the pathogenesis of atherosclerosis, influencing a wide range of cellular and molecular processes. The continued research in this field has not only expanded our understanding of the disease but has also highlighted the potential of miRNAs as valuable diagnostic and therapeutic tools. While challenges remain, the ongoing efforts to unravel the complexities of miRNA regulation in atherosclerosis hold considerable promise for the development of novel strategies to combat this prevalent and life-threatening disease.

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