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Atherosclerosis: Multifaceted Lipid Dysregulation Across Systems

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Abstract

Atherosclerosis involves complex lipid metabolic dysregulation at cellular and systemic levels. Macrophage lipid metabolism, contributing to foam cell formation, is critical, alongside the interplay with non-alcoholic fatty liver disease and gut microbiota metabolites. Lipidomic approaches reveal diverse lipid species impacting inflammation and plaque stability. Mitochondrial dysfunction, emerging non-cholesterol lipids, and exosomal lipid cargos further highlight the disease's multifaceted nature. Adipose tissue and dynamic lipid droplets also play active roles in atherogenesis. Understanding these diverse pathways offers promising targets for therapeutic interventions and personalized risk management, moving beyond cholesterol-centric views.

Keywords

Atherosclerosis; Lipid Metabolism; Macrophages; Foam Cells; NAFLD; Lipidomics; Mitochondria; Exosomes; Gut Microbiota; Adipose Tissue

Introduction

Atherosclerosis remains a major global health challenge, characterized by chronic inflammation and lipid accumulation in arterial walls. Our understanding of this complex disease has significantly advanced, moving beyond simple cholesterol accumulation to encompass a wide array of intricate lipid metabolic processes and their systemic interactions. Central to this understanding is the critical role of macrophage lipid metabolism in the initiation and progression of atherosclerosis. Dysregulation in lipid uptake, efflux, and intracellular processing within macrophages directly contributes to the formation of foam cells, a definitive hallmark of atherosclerotic plaques [1].

This dysregulation impacts crucial lipid metabolic pathways, including cholesterol esterification and triglyceride synthesis, and profoundly influences macrophage inflammatory responses. Identifying these specific pathways offers promising therapeutic targets for mitigating atherosclerosis. The intricate relationship between atherosclerosis and non-alcoholic fatty liver disease (NAFLD) further underscores the systemic nature of lipid dysregulation. Shared lipid metabolic derangements in NAFLD, such as hepatic lipid overload, lead to systemic dyslipidemia, altered lipoprotein profiles, and an increase in inflammatory mediators. This intricate cross-talk, involving pathways like VLDL production, reverse cholesterol transport, and fatty acid metabolism, exacerbates atherosclerotic plaque development [2].

Therapeutic strategies are increasingly focusing on these fundamental mechanisms, particularly targeting macrophage lipid metabolism. Various interventions aim to modulate cholesterol uptake, efflux, and intracellular processing in macrophages, preventing foam cell formation and reducing overall plaque burden. Approaches involving LXR agonists, SREBP inhibitors, and mechanisms related to fatty acid oxidation and synthesis are being explored, providing valuable insights for future cardiovascular drug development [3].

New analytical techniques, like lipidomic approaches, are vital for uncovering novel biochemical pathways involved in atherosclerosis pathogenesis. Comprehensive lipid profiling can identify specific lipid species such as oxylipins, sphingolipids, and phospholipids. These lipids play diverse roles in inflammation, plaque stability, and vascular remodeling, and their unique signatures hold potential as biomarkers for risk stratification and as targets for personalized therapeutic interventions [4].

Mitochondrial lipid metabolism presents another critical dimension to atherosclerosis. While essential for energy homeostasis, mitochondrial dysfunction, driven by altered fatty acid oxidation, phospholipid synthesis, and cholesterol transport, contributes significantly to oxidative stress and inflammation in vascular cells and macrophages. This dual nature means that dysregulation in mitochondrial lipid metabolism can accelerate atherogenesis, presenting both challenging and promising therapeutic opportunities [5].

Expanding beyond the traditional focus on cholesterol, researchers are exploring other emerging lipid players that contribute significantly to atherosclerosis. Non-cholesterol lipids, including ceramides, sphingosine-1-phosphate, and oxidized phospholipids, are key modulators of vascular inflammation, endothelial dysfunction, and foam cell formation. Elucidating the biochemical pathways involving these lipids reveals their profound physiological implications for disease progression and therapeutic targeting [6].

The interplay between lipid metabolism and inflammation is also intricately mediated by exosomes. These tiny vesicles, laden with lipids, proteins, and RNA, facilitate intercellular communication within the arterial wall. Exosomes influence foam cell formation, endothelial activation, and immune cell responses, with their lipid cargos acting as crucial propagators of inflammatory signals and dysregulators of lipid homeostasis. This offers new avenues for both diagnostic and therapeutic strategies [7].

The gut microbiota, through its derived metabolites, has a compelling link to atherosclerosis, particularly impacting host lipid metabolism. Metabolites such as trimethylamine N-oxide (TMAO) and short-chain fatty acids influence host lipid synthesis, cholesterol transport, and lipoprotein profiles, contributing to the development and progression of atherosclerotic lesions. Understanding how this gut-vascular axis offers novel insights into managing cardiovascular risk [8].

Adipose tissue lipid metabolism, often underestimated, also plays a pivotal role in atherosclerosis pathogenesis. Moving beyond its function as a simple energy reservoir, adipose tissue actively secretes adipokines and fatty acids that profoundly influence systemic lipid profiles, insulin sensitivity, and vascular inflammation. Dysfunctional adipose tissue lipid handling contributes to dyslipidemia and accelerates atherosclerotic plaque formation [9].

Finally, lipid droplets (LDs) in macrophages and other vascular cells are now recognized as dynamic, active regulators rather than inert storage sites. These organelles are involved in regulating lipid homeostasis, inflammatory signaling, and cellular stress responses. The biochemical pathways governing LD formation, breakdown, and interaction with other organelles reveal them as crucial regulators of atherogenesis and promising therapeutic targets [10].

Collectively, these studies highlight the multifaceted nature of lipid metabolism in atherosclerosis, from cellular processes within macrophages and mitochondria to systemic interactions with the liver, gut, and adipose tissue, offering diverse avenues for intervention.

Description

Atherosclerosis, a leading cause of cardiovascular morbidity and mortality, is intricately linked to dysfunctions in lipid metabolism at various physiological levels. The disease process often begins with the critical involvement of macrophage lipid metabolism, where the precise control of lipid uptake, efflux, and intracellular processing is paramount. When this balance is disturbed, macrophages accumulate lipids, transforming into foam cells that are characteristic features of atherosclerotic plaques [1]. These cellular events are not isolated; they involve complex metabolic pathways such as cholesterol esterification and triglyceride synthesis, which directly influence inflammatory responses within the arterial wall. Understanding these mechanisms is key to developing new therapeutic strategies aimed at preventing foam cell formation and mitigating plaque burden. For example, interventions targeting macrophage lipid handling, including LXR agonists and SREBP inhibitors, are promising avenues for future drug development [3].

Beyond individual cell types, systemic lipid dysregulation plays a significant role. A prime example is the compelling connection between atherosclerosis and non-alcoholic fatty liver disease (NAFLD). NAFLD, characterized by hepatic lipid overload, contributes to systemic dyslipidemia, unfavorable lipoprotein profiles, and an increase in pro-inflammatory mediators. This creates a vicious cycle that exacerbates atherosclerotic plaque development through shared pathways like very-low-density lipoprotein (VLDL) production and altered reverse cholesterol transport [2]. Furthermore, the profound influence of the gut microbiota on host lipid metabolism highlights a crucial gut-vascular axis. Metabolites produced by gut bacteria, such as trimethylamine N-oxide (TMAO) and short-chain fatty acids, can significantly impact host lipid synthesis, cholesterol transport, and lipoprotein profiles, thus contributing to atherosclerotic lesion progression [8].

The landscape of lipid research in atherosclerosis is also expanding to encompass a broader range of lipid species and cellular structures. Lipidomic approaches allow for comprehensive profiling, uncovering novel biochemical pathways and identifying specific lipid species beyond traditional cholesterol, such as oxylipins, sphingolipids, and phospholipids. These molecules are not merely bystanders; they actively participate in inflammation, plaque stability, and vascular remodeling, offering potential as biomarkers and targets for personalized interventions [4]. Similarly, the often-underestimated role of adipose tissue lipid metabolism is gaining recognition. Adipose tissue is not just an energy storage site; it actively secretes adipokines and fatty acids that profoundly influence systemic lipid profiles, insulin sensitivity, and vascular inflammation. Dysfunctional lipid handling in adipose tissue directly contributes to dyslipidemia and accelerates plaque formation [9].

Intracellular organelles and communication mechanisms further complicate the picture. Mitochondrial lipid metabolism, while critical for energy, can become a double-edged sword. Its dysfunction, stemming from altered fatty acid oxidation, phospholipid synthesis, and cholesterol transport, generates oxidative stress and inflammation in vascular cells and macrophages, thereby accelerating atherogenesis [5]. Adding to this complexity are lipid droplets (LDs), now understood as dynamic, active regulators of lipid homeostasis, inflammatory signaling, and cellular stress responses within macrophages and other vascular cells, rather than inert storage sites [10]. The cross-talk between lipid metabolism and inflammation is also profoundly influenced by exosomes. These extracellular vesicles, laden with a variety of cargos including lipids, proteins, and RNA, mediate crucial intercellular communication within the arterial wall. Exosomal lipid cargos are particularly important in propagating inflammatory signals and disrupting lipid homeostasis, opening new diagnostic and therapeutic avenues [7]. Even non-cholesterol lipids like ceramides, sphingosine-1-phosphate, and oxidized phospholipids are emerging as critical modulators of vascular inflammation, endothelial dysfunction, and foam cell formation, moving the focus beyond solely cholesterol-centric views [6].

In summary, the progression of atherosclerosis is a highly integrated process involving a multitude of lipid metabolic pathways and cellular interactions. From macrophage foam cell formation to systemic metabolic conditions like NAFLD, and the influence of the gut microbiome, to the nuanced roles of various lipid species and organelles, each element contributes to the disease's pathogenesis. A holistic understanding of these diverse mechanisms is essential for developing effective strategies to prevent and treat this pervasive cardiovascular disease.

Conclusion

Atherosclerosis is fundamentally linked to dysregulated lipid metabolism across various biological systems. Macrophage lipid metabolism is crucial, with altered uptake, efflux, and processing leading to foam cell formation and influencing inflammatory responses, offering therapeutic targets. There is a significant link between atherosclerosis and non-alcoholic fatty liver disease (NAFLD), where shared lipid derangements contribute to systemic dyslipidemia and plaque development. Lipidomic approaches identify specific lipid species like oxylipins and sphingolipids involved in inflammation and plaque stability. Mitochondrial lipid metabolism, when dysfunctional, can accelerate atherogenesis by increasing oxidative stress. Beyond cholesterol, emerging lipids such as ceramides and oxidized phospholipids modulate vascular inflammation. Exosomes mediate communication by carrying lipid cargos that propagate inflammatory signals. The gut microbiota, through metabolites like TMAO, influences host lipid synthesis and lipoprotein profiles, linking the gut-vascular axis to cardiovascular risk. Adipose tissue also actively secretes factors that impact systemic lipid profiles and inflammation. Finally, lipid droplets in vascular cells are dynamic regulators of lipid homeostasis and inflammatory signaling, presenting further therapeutic avenues.

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