Interconnected Biological Processes in Atherosclerosis: A Survey

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Abstract

Atherosclerosis, a complex and systemic disease, involves a network of interconnected biological processes including lipid metabolism, glycolysis, mitochondrial dynamics, vascular remodeling, oxidative stress, and cellular metabolism. This survey paper explores these processes, emphasizing their roles in plaque formation and cardiovascular disease progression. Lipid metabolism, influenced by hormonal and genetic factors, is central to atherosclerotic plaque development, affecting lipid synthesis, breakdown, and transport. Glycolysis supports energy production and inflammatory responses within plaques, while mitochondrial dynamics influence cellular functions and vascular health, with mechanotransduction regulating mitochondrial behavior. Vascular remodeling, involving structural changes in blood vessels, is mediated by inflammatory cells, perivascular adipose tissue, and fibrous cap dynamics, which are crucial for plaque stability. Oxidative stress exacerbates vascular inflammation and plaque progression by impacting lipids, proteins, and DNA, with antioxidant strategies showing potential in mitigating these effects. The integration of metabolic pathways and immune cell metabolism is essential for understanding atherosclerosis. Future research should focus on elucidating mitochondrial dynamics in immune cells and developing therapeutic strategies targeting these pathways. Advanced modeling techniques and multi-dimensional data integration are necessary for a comprehensive understanding of coronary artery disease and the development of precision medicine approaches. Additionally, exploring the roles of microRNAs, lncRNAs, gut microbiota, and sex differences, along with targeting inflammatory pathways such as the NLRP3 inflammasome, may offer promising strategies for improving patient outcomes. This survey underscores the need for a multifaceted approach to address atherosclerosis complexities and enhance cardiovascular health.

1 Introduction

1.1 Significance of Atherosclerosis in Cardiovascular Diseases

Atherosclerosis is a leading cause of morbidity and mortality globally, characterized by plaque formation in arterial walls, which critically affects cardiovascular health [1]. This chronic inflammatory condition is closely associated with cardiovascular diseases, leading to severe events like myocardial infarction and ischemic strokes [2]. The pathophysiology involves lipid-rich plaque accumulation, resulting in arterial narrowing and reduced blood flow, key factors in cardiovascular complications. The rising prevalence of atherosclerosis, particularly among younger populations and women, highlights the urgent need for effective management strategies. Impaired resolution of chronic inflammation plays a crucial role in disease progression, underscoring the complex interplay between inflammation and metabolic dysregulation. Comorbid conditions, such as cancer, further complicate management [3]. The heterogeneity in disease progression, especially in early plaque development, necessitates advanced research methodologies [4]. Carotid atherosclerosis, a significant contributor to ischemic stroke, leads to high mortality and disability rates [5]. Consequently, atherosclerosis remains a critical

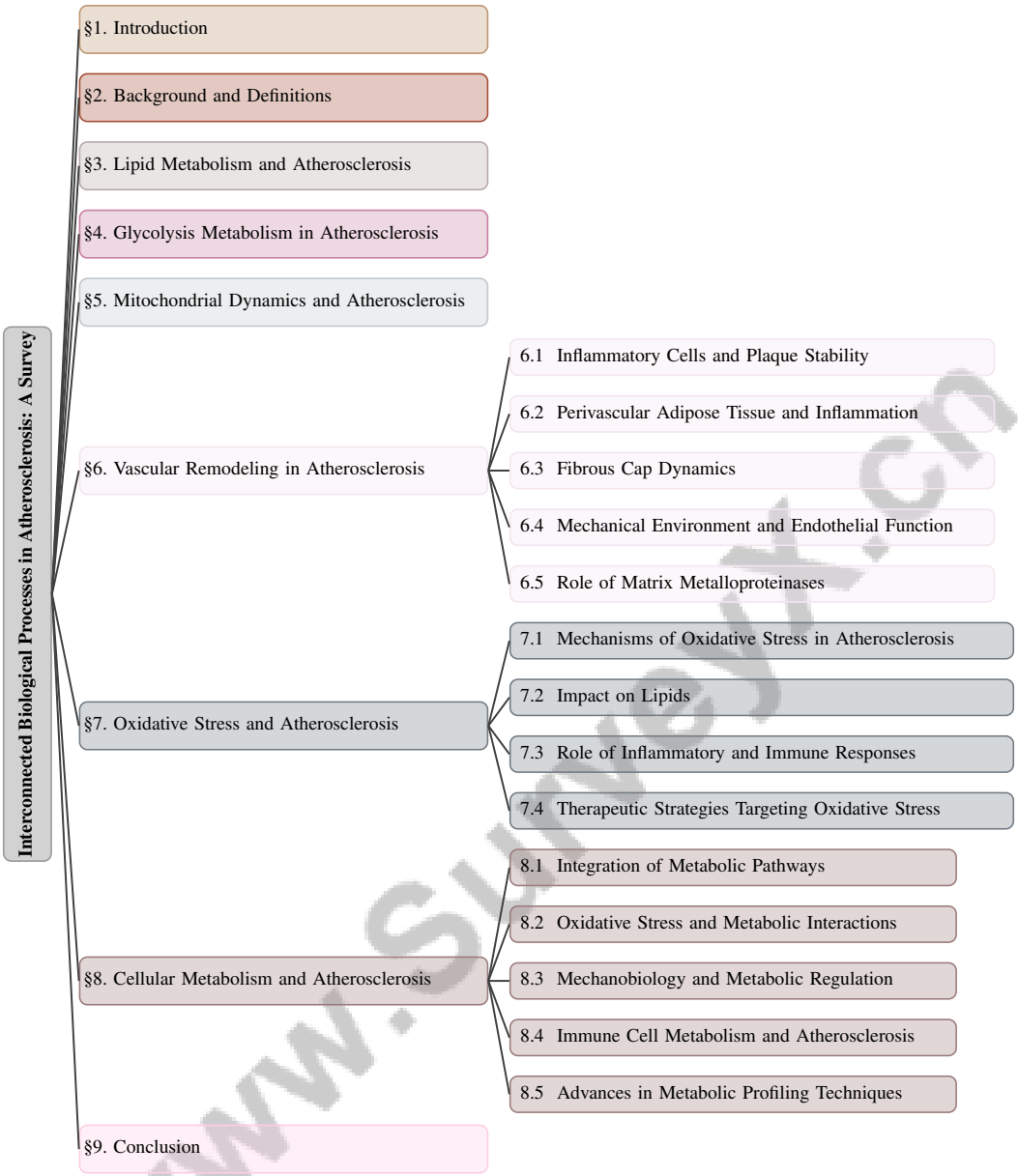

Figure 1: chapter structure

focus in cardiovascular research, demanding innovative approaches for prediction, diagnosis, and therapeutic interventions.

1.2 Interconnected Biological Processes

Atherosclerosis involves a complex network of biological processes that drive plaque development and progression. Central to this network is lipid metabolism, with oxidized low-density lipoprotein (oxLDL) and cytokines playing crucial roles in monocyte recruitment and foam cell formation, which are vital for plaque growth [4]. In addition to lipid factors, inflammation is a significant contributor, with specialized pro-resolving mediators (SPMs) essential for countering chronic inflammatory responses [6].

The disease's pathophysiology encompasses endothelial dysfunction, lipid accumulation, inflammatory processes, and genetic influences, illustrating the intricate interplay of these elements [7]. Key

signaling pathways, including the NLRP3 inflammasome, toll-like receptors, PCSK9, Notch, and Wnt pathways, drive inflammation within the disease context [8].

Mitochondrial dynamics and oxidative stress are integral to cellular metabolism and vascular remodeling, influencing plaque stability and progression [9]. Understanding these metabolic pathways is essential for a comprehensive view of atherosclerosis as a systemic disease. Advances in omics technologies, such as metabolomics and genomics, facilitate holistic studies of these biological systems, relying on integrative data analysis to elucidate cellular processes and molecular mechanisms.

The relationship between pulse wave velocity (PWV) and various forms of atherosclerosis, including coronary, cerebral, and carotid, underscores the systemic impact of these interconnected processes [10]. The complexity of risk prediction is further compounded by patient distribution imbalances, challenging the understanding of carotid atherosclerosis [5]. Stress-induced remodeling of cellular networks, observed in various biological contexts, highlights the significance of cellular adaptation to environmental stressors [11].

Integrating machine learning and explainable AI in analyzing multi-modal biological data presents significant potential for enhancing our understanding of atherosclerosis. This approach can improve predictive models and therapeutic strategies by utilizing interpretable deep learning methods, such as convolutional neural networks, to analyze carotid ultrasound images for patient stratification, and network-based multi-omics analyses to identify critical biological features. Furthermore, applying deep learning techniques to large-scale cardiac MRI datasets, like those from the Multi-Ethnic Study of Atherosclerosis (MESA), enables automated extraction of detailed anatomical information, enriching our comprehension of cardiovascular disease mechanisms and informing effective clinical interventions [5, 12, 13]. These interconnected processes emphasize the multifaceted nature of atherosclerosis, necessitating comprehensive approaches to study its pathophysiology and develop effective management strategies.

1.3 Structure of the Survey

This survey is structured to provide a thorough examination of the interconnected biological processes involved in atherosclerosis. The paper begins with an **Introduction**, establishing the significance of atherosclerosis in cardiovascular diseases, followed by a discussion on interconnected biological processes and an overview of the survey's organization. The **Background and Definitions** section explains core concepts such as atherosclerosis, lipid metabolism, glycolysis, mitochondrial dynamics, vascular remodeling, oxidative stress, and cellular metabolism, highlighting their roles and interactions in the context of atherosclerosis.

Subsequent sections delve into specific biological processes: **Lipid Metabolism and Atherosclerosis** explores lipid synthesis, breakdown, and transport in plaque formation and stability, alongside hormonal, genetic, and inflammatory influences. **Glycolysis Metabolism in Atherosclerosis** examines altered glucose metabolism and its effects on energy production, vascular inflammation, and plaque development. **Mitochondrial Dynamics and Atherosclerosis** analyzes the impact of mitochondrial changes on cellular functions, oxidative stress, and vascular health.

Further, the section on **Vascular Remodeling in Atherosclerosis** discusses structural changes in blood vessels, focusing on plaque stability, the role of inflammatory cells, and the influence of perivascular adipose tissue. The section on **Oxidative Stress and Atherosclerosis** investigates oxidative damage's contribution to vascular inflammation and plaque progression, including potential therapeutic strategies targeting oxidative stress.

Finally, the paper addresses **Cellular Metabolism and Atherosclerosis**, exploring the integration of metabolic pathways and their interactions with oxidative stress, mechanobiology, and immune cell metabolism, along with advances in metabolic profiling techniques. The survey culminates in a comprehensive conclusion that synthesizes key findings, highlights the interconnectedness of various biological processes, outlines potential future research directions, and proposes therapeutic interventions, emphasizing the importance of multi-omics integration and network-based approaches in understanding complex health and disease mechanisms [14, 12, 15, 16, 17].The following sections are organized as shown in Figure 1.

AI-generated, for reference only.

2 Background and Definitions

2.1 Atherosclerosis as a Chronic Inflammatory Disease

Atherosclerosis is fundamentally a chronic inflammatory condition, initiated by endothelial dysfunction that triggers inflammatory responses leading to plaque formation [7]. This disease results from a complex interplay of genetic and environmental factors that non-linearly affect coronary artery disease (CAD) and myocardial infarction (MI) development [18]. Inflammation is pivotal in both the progression and potential regression of atherosclerotic plaques, with macrophage-mediated NLRP3 inflammasome activation contributing to the chronic inflammatory milieu.

The pathogenesis involves a multifaceted immune response, with immune cells and cytokines driving arterial wall inflammation [19]. Oxidized low-density lipoprotein (oxLDL) exacerbates inflammation by inducing macrophage and foam cell toxicity, leading to apoptosis and affecting plaque stability [20]. Vascular smooth muscle cells (VSMCs) contribute significantly to plaque stability through fibrous cap formation, though traditional markers may underestimate their role in plaque pathology [1].

The complexity of atherosclerosis is highlighted by the challenges of integrating multi-omics data to identify causal mediators in cardiovascular disease, necessitating comprehensive analyses of biological interactions [17]. Regulatory mechanisms involving microRNAs further complicate the inflammatory landscape by influencing glucose and lipid metabolism [21].

Addressing atherosclerosis as a chronic inflammatory disease requires innovative approaches, including advanced computational models and systems biology, to enhance understanding of its systemic nature and develop effective therapeutic interventions [22]. Integrating these methodologies is crucial for overcoming challenges in targeting inflammatory processes without adverse effects, thereby advancing cardiovascular research [2].

In recent years, understanding the intricate relationship between lipid metabolism and atherosclerosis has become increasingly crucial. The complexity of lipid metabolism encompasses various processes, including lipid synthesis, transport, and the influence of hormonal and genetic factors, as well as inflammatory responses. These components are not only significant in the context of atherosclerosis but also present potential therapeutic targets and methodologies for intervention. Figure 2 illustrates this hierarchical structure, providing a visual representation that enhances our comprehension of these interrelated processes. By examining this figure, we can better appreciate the multifaceted nature of lipid metabolism and its implications for cardiovascular health.

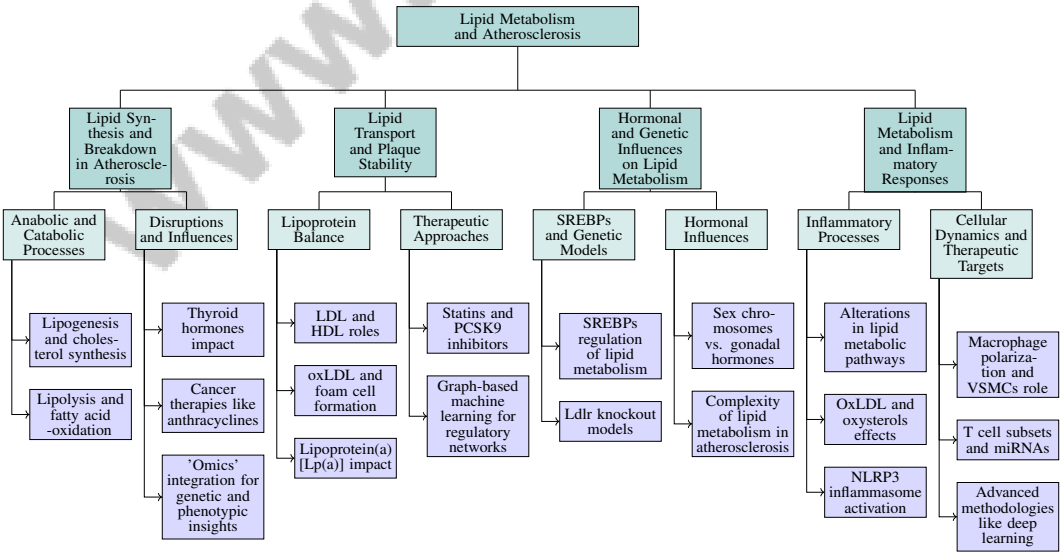

Figure 2: This figure illustrates the hierarchical structure of lipid metabolism and its relationship with atherosclerosis, highlighting key processes such as lipid synthesis, transport, hormonal and genetic influences, and inflammatory responses, along with potential therapeutic targets and methodologies.

3 Lipid Metabolism and Atherosclerosis

3.1 Lipid Synthesis and Breakdown in Atherosclerosis

Lipid metabolism plays a pivotal role in atherosclerosis, with lipid synthesis and degradation being crucial to plaque development. The equilibrium between anabolic processes like lipogenesis and cholesterol synthesis, and catabolic processes such as lipolysis and fatty acid -oxidation, is vital for vascular health [23]. Disruptions in these pathways, often affected by thyroid hormones, contribute to lipid accumulation in arterial walls, promoting plaque formation and instability, notably during metabolic transitions like menopause [24, 25]. Cancer therapies, particularly anthracyclines, can induce dyslipidemia, exacerbating atherosclerosis [3]. 'Omics' integration offers insights into genetic and phenotypic variations in lipid metabolism, while both invasive and non-invasive diagnostic tools enhance our understanding of its role in atherosclerosis [26, 27].

3.2 Lipid Transport and Plaque Stability

Lipid transport mechanisms are critical for atherosclerotic plaque stability. The balance between LDL and HDL significantly impacts cholesterol accumulation in arterial walls. Elevated oxLDL levels promote inflammation and foam cell formation, while HDL facilitates cholesterol efflux, mitigating plaque progression [28, 29, 30]. The interplay between these mechanisms is essential for preventing adverse outcomes like myocardial infarction and ischemic stroke. Lipoprotein(a) [Lp(a)] complicates this balance by impairing fibrinolysis and enhancing plaque thrombogenicity. Graph-based machine learning techniques allow exploration of lipid transport mechanisms, identifying regulatory networks that could serve as therapeutic targets [26]. Targeting lipid transport pathways with agents like statins and PCSK9 inhibitors offers promising strategies for stabilizing plaques and reducing cardiovascular events [14, 31, 7, 23, 4].

3.3 Hormonal and Genetic Influences on Lipid Metabolism

Hormonal and genetic factors significantly influence lipid metabolism and atherosclerosis pathogenesis. SREBPs regulate lipid metabolism by controlling genes involved in cholesterol and fatty acid synthesis, modulated by insulin signaling and lipid feedback mechanisms [32]. Disruptions in SREBP activity can lead to dyslipidemia, exacerbating atherosclerotic plaque development. Ldlr knockout models have elucidated cholesterol metabolism mechanisms, revealing genetic predispositions to atherosclerosis [33]. The challenge of distinguishing the effects of sex chromosomes from gonadal hormones complicates understanding hormonal influences on lipid metabolism, as variations can significantly alter lipid profiles and atherosclerotic risk [34].

To illustrate these complex interactions, Figure 3 presents a figure that depicts the hierarchical structure of hormonal and genetic influences on lipid metabolism. This visual representation highlights key regulatory pathways and genetic models, emphasizing the role of hormonal factors in lipid metabolic processes. The interplay between hormonal signals and genetic factors underscores the complexity of lipid metabolism in atherosclerosis, characterized by lipid accumulation and endothelial dysfunction, influenced by immune responses and genetic variations [34, 7, 35, 19, 18]. Continued research is essential for identifying novel therapeutic targets to manage lipid-related cardiovascular diseases.

3.4 Lipid Metabolism and Inflammatory Responses

The relationship between lipid metabolism and inflammatory responses is critical in atherosclerosis pathogenesis. Alterations in lipid metabolic pathways enhance inflammatory processes, contributing to plaque initiation and progression. Lipid metabolic reprogramming affects cellular dynamics under stress, influencing plaque development [3]. OxLDL induces cytotoxic effects in macrophages, leading to apoptosis and altering early plaque morphology [36]. Oxysterols exacerbate this effect by promoting cellular stress and inflammation, facilitating plaque growth [20]. The activation of the NLRP3 inflammasome links lipid metabolism and inflammation, leading to pro-inflammatory cytokine secretion [37]. Macrophage polarization, influenced by lipid metabolic signals, can either promote or mitigate inflammation, affecting plaque stability [38]. The imbalance between pro-inflammatory mediators and specialized pro-resolving mediators (SPMs) complicates inflammation resolution, contributing to plaque instability [6]. VSMCs actively participate in plaque dynamics, exhibiting phenotypic plasticity that influences their role in atherosclerosis [1]. T cell subsets impact

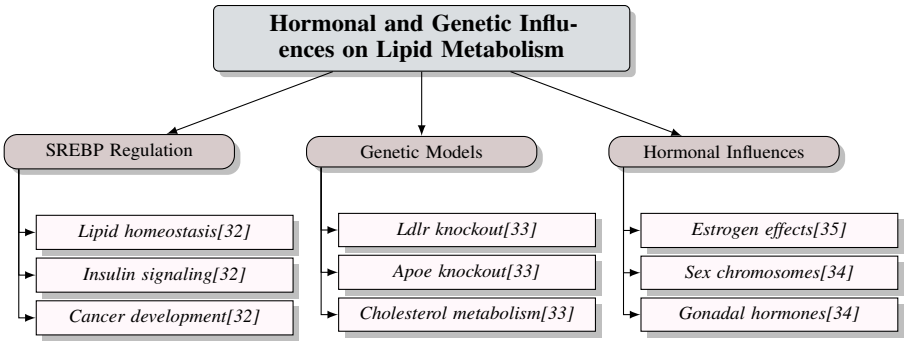

Figure 3: This figure illustrates the hierarchical structure of hormonal and genetic influences on lipid metabolism, highlighting key regulatory pathways and genetic models, as well as the role of hormonal factors in lipid metabolic processes.

the inflammatory landscape, with their effects dependent on the context and microenvironment. The modulation of lipid metabolism can affect T cell function, intertwining metabolic and immune responses in atherosclerosis progression [39]. MicroRNAs (miRNAs) have emerged as crucial regulators of metabolic pathways, representing potential therapeutic targets for metabolic disorders [21]. Advanced methodologies, such as deep learning and atlas-based analysis, enhance our understanding of lipid metabolism and inflammatory responses in atherosclerosis [13]. These approaches facilitate the exploration of specific pathways and the development of targeted therapies addressing both metabolic and inflammatory aspects of atherosclerosis, essential for stabilizing plaques and reducing cardiovascular risk.

4 Glycolysis Metabolism in Atherosclerosis

Glycolysis is integral to atherosclerosis, influencing energy production and inflammatory processes within plaques. It provides energy for cells in the hypoxic environment of atherosclerotic lesions, supporting cellular functions essential for plaque development.

4.1 Role of Glycolysis in Energy Production

Glycolysis, converting glucose to pyruvate and generating ATP via substrate-level phosphorylation, is crucial for endothelial cells, macrophages, and VSMCs in plaques, especially under hypoxia [40]. This pathway not only meets immediate energy needs but also supports cell proliferation and survival. In macrophages, glycolysis enhances ATP production and provides intermediates for pro-inflammatory cytokine synthesis, highlighting its role in inflammation and lipid metabolism during macrophage activation [41, 38, 40, 42]. Regulated by HIFs, glycolysis adapts inflammatory cells to hypoxic plaque environments, sustaining inflammation and contributing to plaque destabilization [36, 6]. Understanding glycolysis in plaques offers insights into metabolic adaptations, identifying therapeutic targets for atherosclerosis and cardiovascular complications [2, 43, 40].

4.2 Regulation of Glycolytic Pathway

The glycolytic pathway is finely regulated by metabolites and hormones to balance energy and biosynthetic demands [40]. In atherosclerosis, this regulation is crucial for metabolic reprogramming in endothelial cells, macrophages, and VSMCs. Key enzymes like hexokinase and phosphofructokinase are modulated by allosteric effectors, adjusting glycolytic flux based on energy status and conditions. Insulin and glucagon significantly influence glycolysis, with insulin promoting glucose uptake and glucagon favoring gluconeogenesis [20, 21, 40]. HIFs enhance glycolytic activity in hypoxic lesions, modulating inflammatory and proliferative responses [36, 6, 4].

As illustrated in Figure 4, the regulation of the glycolytic pathway is depicted, highlighting key enzymes, hormonal influences, and potential therapeutic targets specifically in the context of atherosclerosis. Understanding glycolysis regulation in atherosclerosis reveals therapeutic targets; modulating

glycolytic pathways may reduce inflammation and enhance plaque stability, mitigating cardiovascular risks [2, 14, 6, 8, 4].

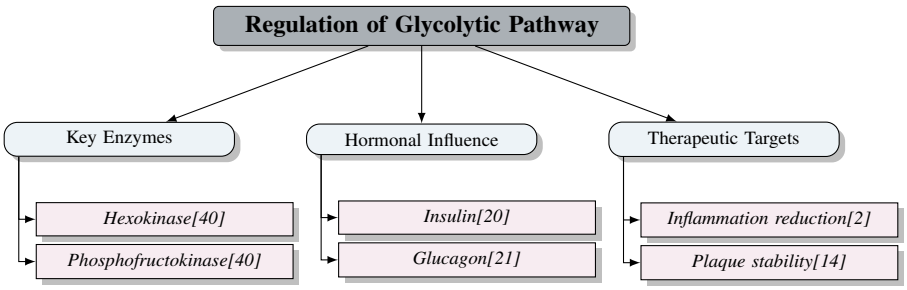

Figure 4: This figure illustrates the regulation of the glycolytic pathway, highlighting key enzymes, hormonal influences, and potential therapeutic targets in the context of atherosclerosis.

4.3 Altered Glucose Metabolism and Atherosclerosis

Altered glucose metabolism contributes to atherosclerosis by dysregulating glycolytic pathways affecting energy balance and inflammation. Glycolysis is vital for ATP production and biosynthetic precursor generation [40]. In atherosclerosis, macrophages adapt to hypoxic, inflammatory environments, exhibiting metabolic plasticity beyond traditional M1/M2 classifications [38]. miRNAs modulate glucose metabolism by regulating insulin signaling, highlighting potential targets for reducing atherosclerotic risk [21]. Alterations in glucose metabolism are linked to disease progression, with glycolytic reprogramming and miRNA regulation as critical nodes. These insights inform strategies to restore metabolic balance and alleviate inflammation in plaques, addressing atherosclerosis as a chronic inflammatory condition [2, 36].

4.4 Glycolysis and Inflammatory Responses

Glycolysis modulates inflammatory responses in plaques, affecting macrophages, endothelial cells, and VSMCs. This metabolic reprogramming resembles the Warburg effect, supporting energy demands of proliferative and inflammatory processes [40]. Glycolysis produces ROS, contributing to oxidative stress and inflammation; enzymes influence ROS levels, with excessive ROS exacerbating inflammation and destabilizing plaques. Mechanisms like Yca1-mediated hydrolysis of oxidized proteins mitigate oxidative stress through glycolytic pathways [44]. Macrophages exhibit metabolic plasticity, adapting to hypoxic, inflammatory plaque environments, with glycolysis sustaining inflammation via cytokine and ROS production [41, 45, 46, 40]. Understanding glycolysis-inflammation links reveals therapeutic targets; modulating glycolytic pathways may reduce inflammation, decreasing plaque rupture risks. This aligns with evidence that targeting inflammatory pathways can mitigate atherosclerosis progression, complementing traditional interventions [8, 14, 2, 4]. Continued research into glycolytic regulation promises novel interventions to reduce inflammation and improve cardiovascular outcomes.

5 Mitochondrial Dynamics and Atherosclerosis

5.1 Overview of Mitochondrial Dynamics

Mitochondrial dynamics, encompassing fusion, fission, mitophagy, and biogenesis, are vital for cellular health and function [47]. The balance between fission and fusion maintains the mitochondrial network's structural and functional integrity, enabling adaptation to metabolic demands and environmental stressors [48, 41]. Fusion ensures mitochondrial DNA integrity and functionality, while fission facilitates mitophagy, removing damaged mitochondria [49, 50]. This dynamic remodeling supports efficient energy production and cellular homeostasis [42].

In atherosclerosis, these dynamics regulate vascular smooth muscle cell (VSMC) behavior and vascular remodeling [47]. Dysregulation can increase oxidative stress and inflammation, exacerbating plaque formation and progression. Understanding the molecular mechanisms of mitochondrial

dynamics can reveal new therapeutic strategies to mitigate atherosclerosis's effects, characterized by oxidative stress and inflammation [51, 43, 52]. Continued research into mitochondrial behavior integration into cellular and vascular health frameworks presents promising avenues for future exploration.

5.2 Mechanotransduction and Mitochondrial Function

Mechanotransduction, the conversion of mechanical stimuli into biochemical signals, significantly impacts mitochondrial function in vascular cells. The interaction between mitochondria and the cytoskeleton underscores the relationship between cellular mechanics and mitochondrial dynamics [53]. Fusion and fission, regulated by proteins like Mfn1, Mfn2, Opa1, and Drp1, are critical for adapting to metabolic demands and environmental stressors, ensuring mitochondrial network integrity [48, 54].

Interactions with external factors such as the endoplasmic reticulum and cytoskeleton further influence mitochondrial dynamics [55]. Mitochondrial reactive oxygen species (mROS) and transient openings of mitochondrial permeability transition pores (mPTP) are key players in mitochondrial fragmentation and recovery, modulated by mechanical stimuli [56]. Targeting mechanotransductive pathways presents potential therapeutic strategies for cardiovascular diseases characterized by mitochondrial dysfunction, offering promising avenues for improving disease outcomes [52, 51].

5.3 Mitochondrial Dynamics and Vascular Health

Mitochondrial dynamics, involving fusion and fission, are crucial for cellular and vascular health, significantly influencing atherosclerosis pathogenesis. Proteins such as Mfn1, Mfn2, and Drp1 regulate these dynamics, which are sensitive to cellular stress and mechanical stimuli [48]. The balance between fusion and fission maintains mitochondrial network integrity and functional efficiency, essential for energy production, cellular viability, and tissue regeneration [48].

Mitochondria, as mechanosensitive organelles in vascular cells, respond to mechanical forces like shear stress, crucial for endothelial cell and VSMC function. Disruptions in mitochondrial dynamics can elevate oxidative stress and inflammation, critical factors in atherosclerosis progression. Excessive ROS production due to mitochondrial dysfunction leads to cellular damage and activates inflammatory pathways, central to atherosclerotic plaque formation and associated cardiovascular diseases [43, 36, 52]. Dysregulation contributes to endothelial dysfunction and VSMC proliferation, key events in plaque formation and vascular remodeling.

The intricate structure of mitochondrial networks, arising from fission and fusion, enables mitochondria to adapt their architecture and function in response to cellular stresses, influencing energy production, metabolic regulation, and cell signaling pathways critical for proliferation, differentiation, and apoptosis [57, 49, 58]. This dynamic remodeling allows VSMCs and endothelial cells to respond effectively to environmental cues, promoting vascular health and preventing atherosclerotic plaque development.

Genetic studies show that mutations in genes regulating mitochondrial dynamics can disrupt their balance, linking dysregulation to conditions such as neurodegenerative disorders, metabolic diseases, and cancer [57, 49, 51, 52]. In atherosclerosis, alterations exacerbate the disease by promoting endothelial dysfunction and VSMC proliferation, facilitating plaque development. Advanced techniques like photostimulation enable high-resolution studies of mitochondrial dynamics, offering insights into their role in vascular health without substantial damage. Investigating these dynamics is crucial for understanding their role in maintaining vascular health and atherosclerosis pathogenesis, potentially identifying novel therapeutic strategies to mitigate diseases linked to mitochondrial dysfunction, ultimately enhancing cardiovascular health and preventing atherosclerotic progression [49, 47, 51, 52, 43].

6 Vascular Remodeling in Atherosclerosis

6.1 Inflammatory Cells and Plaque Stability

Inflammatory cells are crucial in determining atherosclerotic plaque stability, significantly impacting vascular remodeling. This survey categorizes these cells based on their roles in atherosclerosis,

elucidating their interactions and contributions to disease progression [29]. The interplay between cellular mechanisms and various stimuli complicates understanding atherosclerosis pathogenesis [59]. Inflammatory responses are intricately linked to mechanical and hemodynamic factors, contributing to maladaptive arterial changes, especially in central arteries under hypertension [60]. This remodeling involves inflammatory cell infiltration and activation, releasing cytokines and proteolytic enzymes that degrade the extracellular matrix, compromising plaque stability and increasing rupture risk.

Adult stem cells also contribute to vascular remodeling and cardiovascular disease pathogenesis, including atherosclerosis, by differentiating into cell types involved in inflammatory responses and tissue repair [61]. Integrating morphometric and hemodynamic data enhances understanding of how vascular remodeling affects blood flow and pressure, elucidating inflammatory cells' roles in plaque stability [62]. Moreover, neutrophil-derived extracellular traps (NETs) adversely affect vascular remodeling and recovery post-ischemia, illustrating the complexity of inflammatory cell interactions in atherosclerosis [63]. Identifying specific structural alterations in vascular remodeling correlating with disease severity underscores the potential for targeted therapies modulating inflammatory responses [64].

The intricate interactions between mechanical forces and cellular pathways, particularly involving monocytes, macrophages, and other immune cells, significantly influence plaque stability during vascular remodeling. These interactions affect atheromatous plaques' structural integrity and the overall pathophysiology of cardiovascular diseases, emphasizing the necessity of targeting inflammatory mechanisms for therapeutic interventions [29, 36]. Continued research into these processes is vital for developing effective strategies to improve cardiovascular outcomes in atherosclerosis.

6.2 Perivascular Adipose Tissue and Inflammation

Perivascular adipose tissue (PVAT) significantly influences inflammation and vascular remodeling in atherosclerosis. Beyond being a passive structural component, PVAT actively participates in vascular homeostasis and pathology by secreting bioactive molecules, including adipokines, cytokines, and chemokines, which exert paracrine effects on the vascular wall, influencing endothelial function and smooth muscle cell behavior [65]. PVAT's influence on vascular remodeling is complex, mediated by its phenotypic changes, such as beiging, altering its metabolic activity and inflammatory profile. This phenotypic plasticity contributes to the dynamic process of vascular remodeling, influenced by inflammation, oxidative stress, and the renin-angiotensin system [59]. The interaction between PVAT and these factors underscores the multifaceted nature of vascular remodeling in atherosclerosis, where PVAT-derived signals can exacerbate or mitigate inflammatory responses and structural changes in the vascular wall.

Furthermore, arterial remodeling's classification as adaptive or maladaptive is influenced by mechanical stimuli and inflammatory responses modulated by PVAT. PVAT can promote maladaptive remodeling by initiating inflammatory pathways that lead to adverse structural changes, such as increased stiffness and reduced elasticity [60]. This highlights PVAT's critical role in atherosclerosis pathophysiology, where its influence on inflammation and vascular remodeling significantly impacts disease progression and plaque stability.

Understanding PVAT's role in inflammation and vascular remodeling offers therapeutic avenues for targeting inflammatory processes associated with atherosclerosis. Modulating PVAT's activity and secretory profile, particularly through inducing its beiging process, may influence vascular remodeling outcomes. Such modulation could reduce inflammation and pathological blood vessel changes, enhancing cardiovascular health and lowering atherosclerotic complications risk. PVAT beiging is linked to macrophage accumulation and neuregulin 4 (Nrg4) secretion, promoting alternative macrophage activation and aiding in resolving vascular inflammation, contributing to healthier vascular architecture [66, 65, 47].

6.3 Fibrous Cap Dynamics

Fibrous cap dynamics are central to atherosclerotic plaque stability, influencing vulnerability to rupture. Composed primarily of extracellular matrix proteins, the fibrous cap is formed through the proliferation and migration of vascular smooth muscle cells (SMCs), acting as a barrier that protects the lipid-rich plaque core from bloodstream exposure [67]. This protective function is essential

in preventing plaque rupture, which can lead to acute cardiovascular events such as myocardial infarction and stroke.

Growth factors play a crucial role in regulating SMC behavior during fibrous cap formation, promoting their proliferation and matrix production [67]. The interaction between growth factors and SMCs highlights the complex regulatory mechanisms governing cap dynamics and plaque stability. However, these processes are not uniform across different vascular regions, as mechanical and inflammatory environments can vary, resulting in heterogeneity in fibrous cap development and stability [60].

Extracellular matrix (ECM) remodeling is another critical aspect of fibrous cap dynamics, influencing the cap's mechanical properties and its ability to withstand hemodynamic forces [59]. Continuous ECM remodeling, driven by both adaptive and maladaptive responses to mechanical and inflammatory stimuli, is essential for maintaining cap integrity; however, excessive ECM degradation can weaken the cap, increasing rupture risk.

Inflammatory cells, including neutrophils and their extracellular traps (NETs), adversely affect fibrous cap stability by promoting ECM degradation and impairing SMC reparative functions [63]. This underscores the importance of understanding the interplay between inflammation and fibrous cap dynamics in atherosclerosis.

The dynamics of fibrous cap formation involve a complex interplay of factors, including the regulation of SMC behavior by growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-, ECM remodeling mediated by matrix metalloproteinases (MMPs), and inflammatory responses driving vascular remodeling, all contributing to fibrous cap stability and vulnerability over the fatty plaque core [66, 60, 67]. A comprehensive understanding of these processes is essential for developing therapeutic strategies aimed at enhancing plaque stability and reducing cardiovascular event risks associated with atherosclerosis.

6.4 Mechanical Environment and Endothelial Function

The mechanical environment is crucial in regulating endothelial function and vascular remodeling, processes integral to atherosclerosis pathogenesis. Endothelial cells, which line blood vessels, are highly sensitive to mechanical stimuli such as shear stress and cyclic strain, significantly affecting their functionality and structural integrity. These cells are vital in various physiological processes, including blood flow regulation and vascular homeostasis. Disruptions in their response to mechanical forces can lead to pathological conditions, including atherosclerosis and hypertension, where altered hemodynamics and inflammatory responses contribute to vascular remodeling and disease progression. Understanding these mechanobiological interactions is essential for developing therapeutic strategies to address vascular diseases and improve patient outcomes [68, 7, 69, 60, 70]. These mechanical forces are vital for maintaining endothelial homeostasis and vascular health, as they regulate the expression of genes involved in inflammation, coagulation, and vascular tone.

The interplay between mechanical forces and endothelial function underscores the need to control smooth muscle phenotype and inflammation, particularly concerning maladaptive remodeling associated with hypertension [60]. The mechanical environment can either promote or inhibit endothelial dysfunction, depending on the nature and magnitude of the forces involved. For instance, laminar shear stress is known to exert a protective effect on endothelial cells by promoting anti-inflammatory and anti-thrombotic gene expression, whereas disturbed flow patterns can induce endothelial activation and contribute to atherogenesis.

Quantifying hemodynamic changes and understanding their relationship with vascular remodeling are essential for elucidating the mechanisms underlying endothelial dysfunction [62]. Hemodynamic parameters, such as blood pressure and flow velocity, directly influence the mechanical environment of the endothelium, thereby affecting its function and vascular structure remodeling.

Moreover, mitochondrial dynamics within vascular smooth muscle cells (VSMCs) are influenced by mechanical stimuli, highlighting the systemic implications of mitochondrial dysfunction in vascular remodeling [47]. The integration of mechanical and mitochondrial signals is crucial for maintaining cellular energetics and vascular health, as disruptions in these processes can exacerbate endothelial dysfunction and promote atherosclerotic plaque development.

The role of oxidative stress and lipid metabolism in endothelial function is further emphasized by research on ferroptosis, which provides insights into how these elements interact to influence vascular

health [39]. Targeting neutrophil activity and the formation of NETs presents a potential therapeutic approach to enhance vascular remodeling and improve recovery outcomes, particularly following ischemic events [63].

6.5 Role of Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are critical enzymes in vascular biology, playing a key role in remodeling vascular structures, particularly in atherosclerosis [66]. These enzymes facilitate the degradation of extracellular matrix (ECM) components, a fundamental process in both physiological and pathological vascular remodeling. MMP activity is tightly regulated; excessive ECM degradation can lead to plaque instability, increasing rupture risk and subsequent cardiovascular events.

In atherosclerosis, MMPs are predominantly produced by inflammatory cells such as macrophages and vascular smooth muscle cells (SMCs), activated in response to various stimuli, including cytokines and growth factors. The interaction between SMCs and the ECM, mediated by MMPs, is essential for maintaining fibrous cap integrity. The balance between ECM synthesis and degradation determines whether the fibrous cap remains stable or becomes prone to rupture [67].

The regulatory mechanisms governing MMP activity are intricate, involving various endogenous inhibitors, particularly tissue inhibitors of metalloproteinases (TIMPs), which modulate MMP activity. This regulation is vital to prevent excessive ECM degradation, as imbalances in the MMP/TIMP ratio can lead to pathological conditions such as hypertension, atherosclerosis, and other vascular diseases. MMPs, which are zinc-dependent endopeptidases secreted by various cell types, including fibroblasts and SMCs, are activated from their latent forms through propeptide sequence removal, highlighting the complexity of their regulation and the importance of maintaining ECM integrity during vascular remodeling and tissue repair [66, 67, 59]. However, in atherosclerotic lesions, the balance between MMPs and TIMPs is often disrupted, leading to increased proteolytic activity and plaque destabilization.

Research into the mechanobiological and immunobiological mechanisms underlying arterial remodeling underscores the significance of MMPs in these processes [60]. MMPs contribute to structural changes in the intima, media, and adventitia of arteries, with implications for disease severity and treatment approaches [64]. Understanding MMPs' precise role in vascular remodeling is critical for developing therapeutic strategies aimed at modulating their activity to enhance plaque stability and reduce the risk of adverse cardiovascular events.

Targeting the regulatory pathways of MMPs, including their interaction with PVAT and its secretory profile, presents a potential therapeutic approach for mitigating inflammation and promoting vascular health in atherosclerosis [65]. By modulating MMP activity, it may be possible to influence vascular structure remodeling, thereby improving cardiovascular outcomes.

7 Oxidative Stress and Atherosclerosis

7.1 Mechanisms of Oxidative Stress in Atherosclerosis

Oxidative stress, a pivotal factor in atherosclerosis, arises from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, leading to cellular injury and accelerated atherogenesis [71]. The NLRP3 inflammasome activation links oxidative stress to vascular inflammation by promoting pro-inflammatory cytokine release, exacerbating plaque development [37]. Oxidative stress also contributes to endothelial dysfunction through reduced nitric oxide (NO) bioavailability, increased vasoconstriction, and inflammation, marking early atherosclerosis events. Mitochondrial dysfunction, a significant ROS source, affects mitochondrial dynamics and vascular health, impacting plaque stability. This dual role of oxidative stress—where oxidative eustress is essential for cellular signaling, while oxidative distress drives disease progression—highlights the necessity of maintaining redox balance to mitigate adverse effects in atherosclerosis [72]. Furthermore, oxidative stress interacts with the NFB signaling pathway, amplifying inflammatory responses that promote vascular damage and plaque formation. Oxidative modifications of lipids, proteins, and DNA within the vascular wall are critical in atherosclerosis pathogenesis, particularly the oxidation of low-density lipoproteins (LDL), leading to proatherogenic oxidized LDL and oxysterols that induce cellular oxidative stress, inflammation, and cytotoxicity. These processes disrupt endothelial integrity, promote smooth muscle cell proliferation, and facilitate immune cell recruitment and

activation, ultimately resulting in plaque formation and instability, pivotal in cardiovascular disease progression [7, 43, 36, 30]. Antioxidant interventions show promise in alleviating oxidative stress, enhancing the body's defenses, and reducing ROS levels. This strategy addresses underlying atherogenic mechanisms, including endothelial dysfunction, inflammation, and cellular apoptosis, opening therapeutic avenues for managing cardiovascular diseases linked to elevated oxidative stress, such as type 2 diabetes and metabolic syndrome [43, 46, 30]. Understanding oxidative stress mechanisms in atherosclerosis is vital for developing effective therapeutic strategies.

7.2 Impact on Lipids, Proteins, and DNA

Oxidative stress crucially influences atherosclerosis by modifying lipids, proteins, and DNA, contributing to vascular inflammation and plaque instability. The oxidative modification of low-density lipoproteins (LDL) leads to oxidized LDL (oxLDL) formation, a key factor in foam cell development and plaque progression, enhancing LDL's atherogenic potential and triggering inflammatory responses [71]. Proteins in the vascular wall are vulnerable to oxidative damage, resulting in functional impairments and structural changes. Modifications such as carbonylation, nitration, and cross-linking of amino acid residues disrupt cellular signaling pathways and enzymatic activities, significantly impacting the NFB pathway that influences inflammation and endothelial dysfunction [73]. DNA damage from oxidative stress is another critical aspect of atherosclerosis. ROS can induce base modifications, strand breaks, and cross-linking, leading to genomic instability and altered gene expression. Overwhelmed repair mechanisms may result in apoptosis or senescence of vascular cells, further contributing to plaque instability and atherosclerosis progression [74]. Identifying biomarkers for oxidative stress is essential for understanding its impact on macromolecules and developing targeted therapeutic strategies. Recent research has advanced the identification of these biomarkers, crucial for assessing oxidative damage in various diseases, including atherosclerosis [46]. Compounds like catechins have shown potential in reducing oxidative stress, highlighting their role in disease prevention and improved health outcomes [75]. The profound impact of oxidative stress on lipids, proteins, and DNA underscores its pivotal role in atherosclerosis pathophysiology, contributing to endothelial dysfunction, inflammation, and cellular injury, thereby accelerating atherogenesis through mechanisms such as LDL oxidation and the formation of atherogenic oxysterols [76, 43, 46, 30]. A comprehensive understanding of these interactions is vital for developing effective interventions to mitigate oxidative damage and enhance cardiovascular health.

7.3 Role of Inflammatory and Immune Responses

Oxidative stress significantly interacts with inflammatory and immune responses in atherosclerosis pathogenesis. Characterized by an imbalance between ROS production and antioxidant defenses, oxidative stress mediates atherosclerosis development by influencing inflammatory and immune pathways [43]. This interaction is complex, with ROS exerting bidirectional effects on NFB signaling, either activating or suppressing it depending on exposure context and duration [73]. Such modulation of NFB is crucial, as it regulates pro-inflammatory cytokine and adhesion molecule expression, contributing to endothelial dysfunction and plaque formation. Inflammatory cells, including macrophages, lymphocytes, and neutrophils, are central to atherosclerosis progression. Macrophages, in particular, are pivotal in plaque development by engulfing oxLDL and transforming into foam cells, characteristic of early atherosclerotic lesions [29]. Lymphocytes and neutrophils also exacerbate disease progression through cytokine release and the formation of neutrophil extracellular traps (NETs), contributing to vascular inflammation and plaque instability. The interplay between oxidative stress and immune responses is further elucidated in theoretical models of their interactions, as observed in other diseases such as HIV, where oxidative stress influences immune cell function and disease dynamics [77]. In atherosclerosis, oxidative stress not only activates inflammatory pathways but also affects the immune system, creating a chronic inflammatory state that fosters plaque development [71]. Moreover, oxidative stress impacts extend to cognitive and emotional deficits in the central nervous system (CNS), suggesting potential therapeutic targets for treatment [74]. Identifying and measuring oxidative stress biomarkers is critical for understanding its role in atherosclerosis, with studies emphasizing the importance of context in their application [46]. The intricate relationship between oxidative stress and inflammatory/immune responses is crucial in atherosclerosis pathogenesis, as both factors significantly influence disease progression through endothelial dysfunction, lipid accumulation, and immune cell recruitment and activation, ultimately leading to plaque formation and cardiovascular complications [7, 29, 36, 19, 43]. A comprehensive

understanding of these interactions is essential for developing targeted therapies aimed at mitigating oxidative stress and modulating immune responses to enhance cardiovascular health.

7.4 Therapeutic Strategies Targeting Oxidative Stress

Therapeutic strategies targeting oxidative stress in atherosclerosis aim to rectify the imbalance between ROS production and antioxidant defenses, a critical aspect of the disease's pathogenesis. Antioxidant therapies show promise in preventing and treating atherosclerosis by reducing oxidative damage and associated inflammation. However, the relationship between antioxidant capacity and oxidative damage is complex and varies significantly based on individual and environmental factors, underscoring the need for personalized therapeutic approaches [72]. Recent advances in nanotechnology have led to innovative therapeutic strategies, particularly with cerium oxide nanoparticles (CNPs), which exhibit significant antioxidant properties and biocompatibility. CNPs effectively reduce oxidative stress, a key contributor to neuronal and endothelial cell damage in conditions such as ischemic stroke, without cytotoxic effects. In vitro studies demonstrate that CNPs can mitigate intracellular ROS production in cerebral endothelial cells, while in vivo assessments confirm their safety in animal models. This research highlights the potential of CNPs as a novel intervention for oxidative stress-related pathologies, offering enhanced stability and reduced toxicity compared to traditional antioxidant therapies [74, 78, 79]. These nanoparticles act as catalytic antioxidants, effectively scavenging ROS and protecting vascular cells from oxidative damage, thereby improving plaque stability and reducing cardiovascular event risk. This underscores the potential of nanotechnology in developing novel antioxidant therapies for atherosclerosis. Matrix metalloproteinases (MMPs) are significant in tissue remodeling and serve as potential therapeutic targets for cardiovascular diseases. Modulating MMP activity, involved in extracellular matrix protein degradation, can substantially impact vascular structure remodeling. This modulation can enhance atherosclerotic plaque stability by promoting a balanced MMP/tissue inhibitors of metalloproteinases (TIMP) ratio, reducing the risk of adverse cardiovascular events such as hypertension and aneurysm formation [66, 59]. This highlights the importance of targeting MMP regulatory pathways to mitigate inflammation and promote vascular health. The interplay between oxidative stress and inflammatory responses is crucial in therapeutic strategies. Modulating inflammation can significantly reduce cardiovascular events, but careful consideration of potential adverse effects is necessary [2]. Mathematical modeling of oxidative stress and inflammation interactions can provide insights into atherosclerosis dynamics, guiding targeted intervention development. Future research should focus on identifying effective biomarkers for oxidative stress, informing therapeutic strategies aimed at mitigating oxidative stress in atherosclerosis [71]. A comprehensive approach to targeting oxidative stress in atherosclerosis involves integrating antioxidant therapies, nanotechnology, and systems biology to develop effective strategies that reduce oxidative damage and improve cardiovascular outcomes.

8 Cellular Metabolism and Atherosclerosis

Category	Feature	Method
Oxidative Stress and Metabolic Interactions	Oxidative Stress Mechanisms Antioxidant Interventions	EPR-MD[78] CNPs@Polymer[79]
Immune Cell Metabolism and Atherosclerosis	Metabolic Processes	BRCA2endo[80]
Advances in Metabolic Profiling Techniques	Probability Distribution Analysis	EP[81]

Table 1: This table provides a summary of methodologies employed in studying various metabolic interactions and profiling techniques relevant to atherosclerosis. It categorizes the methods into oxidative stress and metabolic interactions, immune cell metabolism, and advances in metabolic profiling, highlighting specific features and corresponding methodological approaches. The references cited offer further insights into the application and effectiveness of these methods in the context of cellular metabolism and disease progression.

The intricate relationship between cellular metabolism and atherosclerosis is crucial for understanding the disease's onset and progression. This section delves into the integration of metabolic pathways, illuminating the biochemical interactions driving atherosclerosis. By examining these synergies, we can identify mechanisms contributing to disease progression and potential therapeutic targets. Table 1 presents a comprehensive overview of the methods used to investigate metabolic interactions and

profiling techniques essential for understanding the complexities of atherosclerosis. The following subsection focuses on specific metabolic pathway integrations and their roles in cellular functions and responses in atherosclerosis.

8.1 Integration of Metabolic Pathways

The pathogenesis of atherosclerosis is underpinned by the integration of metabolic pathways, reflecting complex biochemical processes driving disease progression. Advanced computational approaches, such as Bayesian inference strategies like Expectation Propagation (EP), enhance our understanding of metabolic flux dynamics within large-scale cellular systems [81]. Lipid metabolism significantly influences macrophage polarization and function, with modulation of these pathways being vital for interventions in metabolic diseases due to their regulation of immune cell responses and inflammation [38]. Thyroid hormones further illustrate this integration by influencing hepatic lipid metabolism through transcriptional and non-genomic signaling pathways [24].

Mitochondrial metabolism is pivotal in integrating metabolic pathways, playing roles in energy production and redox balance. Mitochondrial dynamics are crucial for integrating metabolic signals and immune functions, emphasizing the need to study organelle interactions in immune responses [42]. Future research should focus on identifying mitochondrial transporters and understanding mitochondrial metabolite dynamics, as these factors significantly influence health and disease [41].

Theoretical perspectives on cellular metabolism highlight the role of autophagy and its interaction with lipid metabolic pathways, emphasizing the need to explore how these interactions impact cellular homeostasis and disease progression [31]. Integrating cellular responses to stress at the network level provides insights into the adaptive mechanisms cells employ to maintain metabolic balance under adverse conditions [11]. Establishing a quantitative relationship between energy expenditure in futile cycles and stoichiometric sensitivity modulation in metabolic pathways offers a novel perspective on metabolic regulation's energetic aspects [45].

The integration of metabolic pathways in atherosclerosis reflects a complex network of interactions contributing to the disease's intricacy. A comprehensive understanding of lipid accumulation, inflammatory pathways, and immune responses is crucial for developing targeted therapies aimed at mitigating the metabolic dysregulation associated with atherosclerosis. Addressing these underlying mechanisms may enhance cardiovascular outcomes and reduce the risk of complications such as heart attacks and strokes, major contributors to global mortality [2, 7, 6, 8, 18].

8.2 Oxidative Stress and Metabolic Interactions

Oxidative stress and cellular metabolism interplay significantly in atherosclerosis pathogenesis. Characterized by an imbalance between ROS production and antioxidant defenses, oxidative stress critically impacts cellular metabolic processes, influencing atherosclerotic progression. The generation of mechanoradicals from collagen under mechanical stress highlights a novel ROS source, contributing to oxidative stress and exacerbating vascular damage [78]. Understanding ROS sources and impacts is essential in vascular biology.

Mitochondrial dynamics are central to regulating cellular metabolism and redox balance. Alterations in mitochondrial function, often seen in cancer cells, can lead to metabolic reprogramming and resistance to cell death, phenomena also relevant in atherosclerosis [57]. Mitochondrial dysfunction can exacerbate oxidative stress, further influencing metabolic pathways and contributing to the inflammatory environment within atherosclerotic plaques.

Despite advances in proteomics, significant gaps remain in detecting specific oxidative modifications and analyzing the proteome comprehensively, limiting our understanding of oxidative stress's full impact on cellular metabolism [76]. Addressing these gaps is crucial for elucidating the complex interactions between oxidative stress and metabolic pathways in atherosclerosis.

Antioxidant therapies have shown promise in reducing oxidative stress and its detrimental effects on cellular metabolism. Coated cerium oxide nanoparticles have demonstrated efficacy in maintaining antioxidant activity and interacting with cellular metabolism to potentially mitigate atherosclerosis progression [79]. Similarly, alpha-tocopherol's ability to stabilize oxidized lipid bilayers and prevent pore formation represents a significant advancement over traditional antioxidant strategies [82].

Future research should prioritize developing targeted antioxidant therapies and exploring molecular pathways involved in oxidative stress to enhance therapeutic outcomes in atherosclerosis [74]. Integrating insights into the long-term effects of oxidative stress on NFB signaling could provide valuable information on the chronic inflammatory processes driving atherosclerotic disease [73]. As the field progresses, combining these insights with advanced metabolomic techniques will be essential for unraveling the complex interactions between oxidative stress and cellular metabolism, ultimately informing novel therapeutic strategies.

8.3 Mechanobiology and Metabolic Regulation

Mechanobiology explores how mechanical forces influence cellular behavior and metabolism, particularly in atherosclerosis. The mechanical environment, including shear stress and cyclic strain, is pivotal in regulating cellular metabolism and vascular health. These mechanical stimuli affect endothelial cells and vascular smooth muscle cells (VSMCs), influencing their metabolic pathways and contributing to atherosclerosis pathogenesis. The interplay between mechanotransduction pathways and mitochondrial dynamics is crucial for maintaining cellular homeostasis and adapting to environmental changes [55].

Mitochondrial dynamics, encompassing fusion, fission, and mitophagy, are integral to cellular metabolism. These dynamics enable mitochondria to respond to mechanical cues, influencing energy production and redox balance. Understanding how mechanical forces impact mitochondrial dynamics in VSMCs is essential for exploring novel therapeutic strategies targeting these processes and considering personalized approaches based on individual mitochondrial profiles [47].

The complexity of mitochondrial networks, shaped by the balance between fusion and fission, supports the hypothesis that they operate near a critical phase transition, essential for maintaining cellular homeostasis. This dynamic remodeling allows cells to respond effectively to mechanical and metabolic cues, contributing to vascular health and preventing atherosclerotic plaque development [58]. Current research highlights significant advancements in understanding mitochondrial dynamics, particularly their roles in apoptosis and cellular signaling, contributing to biomedical research progress [49].

Integrating mechanobiology and metabolic regulation is crucial for developing effective therapeutic strategies for atherosclerosis, a complex inflammatory disease characterized by lipid accumulation and plaque formation in arteries, leading to cardiovascular disease and associated mortality. Understanding the interplay between these biological processes can enhance our ability to address atherosclerosis's multifaceted nature and improve treatment outcomes [83, 7]. By elucidating the mechanistic links between mechanical forces, mitochondrial dynamics, and cellular metabolism, researchers can identify potential intervention targets to improve cardiovascular outcomes and reduce the burden of atherosclerotic disease.

8.4 Immune Cell Metabolism and Atherosclerosis

Metabolic processes within immune cells are pivotal in atherosclerosis pathogenesis, influencing disease initiation and progression. Immune cells, including macrophages, T cells, and endothelial cells, undergo metabolic reprogramming in response to the inflammatory milieu characteristic of atherosclerotic plaques. This metabolic reprogramming is essential for meeting increased energy demands and functional requirements as immune cells engage in plaque development and stability, involving shifts in mitochondrial dynamics and lipid metabolism to support their diverse roles in inflammation and tissue repair [57, 38, 42].

Macrophages, key players in atherosclerosis, exhibit metabolic plasticity, allowing adaptation to the dynamic plaque environment. Regulating Sterol Regulatory Element-Binding Proteins (SREBPs) is significant, as these proteins orchestrate lipid metabolism and influence macrophage polarization [32]. Modulating SREBP activity impacts macrophage inflammatory phenotype, thereby affecting plaque stability and progression.

T cells also play a crucial role in atherosclerosis, with their metabolic activity influencing function and disease contribution. The specificity of T cell antigens and developing novel therapeutic approaches targeting T cell responses are active research areas, offering potential strategies for modulating immune responses in atherosclerosis [84]. The metabolic demands of T cells are closely linked to

activation and proliferation, underscoring the importance of understanding immune cell metabolism in this context.

Endothelial cells, forming the inner lining of blood vessels, are affected by metabolic changes in atherosclerosis. The protective role of endothelial BRCA2 against atherosclerosis under hypercholesterolemic stress highlights the potential for targeting endothelial cell metabolism as a therapeutic strategy [80]. This underscores the interplay between endothelial cell metabolism and the broader immune response in atherosclerosis progression.

The role of oxysterols in vascular cells further illustrates the complexity of immune cell metabolism in atherosclerosis. Oxysterols can modulate immune cell function and contribute to the inflammatory environment within plaques, suggesting that targeting oxysterol pathways could offer therapeutic benefits [30]. This aligns with ongoing research exploring the therapeutic potential of metabolic modulation in atherosclerosis.

Understanding metabolic processes in immune cells is integral to atherosclerosis pathophysiology. Insights from these processes can inform potential therapeutic targets and strategies for modulating immune responses to improve cardiovascular outcomes. Future research should delve deeper into the complex interplay between immune cell metabolism and atherosclerosis, employing cutting-edge metabolic profiling techniques and innovative therapeutic strategies. This exploration is crucial, given atherosclerosis's status as a leading cause of cardiovascular disease globally, driven by inflammatory processes influenced by various T cell subsets. By targeting specific inflammatory pathways and T cell functions, researchers can refine prevention and treatment strategies, potentially mitigating disease progression and its associated complications [2, 84].

8.5 Advances in Metabolic Profiling Techniques

Recent advancements in metabolic profiling techniques have significantly enhanced our understanding of atherosclerosis by providing detailed insights into the complex metabolic networks involved. Techniques such as mass spectrometry-based metabolomics, nuclear magnetic resonance (NMR) spectroscopy, and advanced imaging modalities facilitate comprehensive metabolite analysis, enabling the identification of metabolic alterations associated with atherosclerosis. Integrating these techniques with computational approaches like Expectation Propagation offers a more accurate and efficient means of estimating marginal distributions of metabolic fluxes, surpassing traditional Monte Carlo methods [81].

Advanced profiling techniques, including spatial multi-omics, allow researchers to intricately analyze the metabolic pathways involved in atherosclerosis. These methodologies identify critical metabolites and metabolic pathways dysregulated in this disease, shedding light on inflammation, lipid accumulation, and endothelial dysfunction mechanisms contributing to cardiovascular complications. By integrating multiple data modalities, researchers can better understand the molecular circuits governing atherosclerosis, potentially uncovering novel biomarkers and therapeutic targets for more effective prevention and treatment strategies [2, 14, 20, 7, 18]. This has led to discovering potential biomarkers for early detection and risk stratification, as well as identifying novel therapeutic targets. Mapping metabolic changes in atherosclerosis at a systems level provides a holistic view of the disease, offering insights into the interactions between lipid metabolism, glycolysis, and mitochondrial dynamics.

Furthermore, exploring mitochondrial dynamics through these profiling techniques has revealed their critical role in cellular metabolism and atherosclerosis. Understanding the molecular pathways regulating mitochondrial dynamics is essential for developing therapeutic strategies aimed at modulating these processes to prevent or treat atherosclerosis [49]. As research progresses, elucidating these pathways will be crucial for advancing our knowledge of the disease and improving therapeutic outcomes.

In addition to metabolic profiling, identifying specific stem cell populations and their regulatory mechanisms presents a promising avenue for regenerative therapies in vascular diseases, including atherosclerosis. Future research should prioritize developing targeted therapies that harness the regenerative capabilities of these stem cells, potentially offering new treatment modalities for atherosclerosis [61]. Integrating metabolic profiling with stem cell research could further enhance our understanding of the disease and lead to innovative therapeutic approaches.

9 Conclusion

Atherosclerosis is characterized by intricate biological processes involving lipid metabolism, glycolysis, mitochondrial dynamics, vascular remodeling, oxidative stress, and cellular metabolism. These interconnected processes play pivotal roles in the formation, stability, and progression of plaques, highlighting the systemic nature of atherosclerosis and the need for comprehensive management strategies. Lipid metabolism, modulated by hormonal and genetic factors, is crucial in plaque development, influencing lipid synthesis, breakdown, and transport. Glycolysis contributes to energy production and inflammatory responses within plaques, affecting glucose metabolism and disease progression. Mitochondrial dynamics significantly impact cellular functions and vascular health, regulated by mechanotransduction in response to mechanical stimuli.

Structural changes in blood vessels, mediated by inflammatory cells, perivascular adipose tissue, and fibrous cap dynamics, are critical for plaque stability. Oxidative stress exacerbates vascular inflammation and plaque progression, with therapeutic strategies targeting oxidative stress showing potential in mitigating these effects. Understanding the integration of metabolic pathways and immune cell metabolism is essential for a comprehensive view of atherosclerosis.

Future research should focus on elucidating the molecular pathways regulating mitochondrial dynamics in immune cells and explore therapeutic strategies targeting these pathways to modulate immune functions. Advanced modeling techniques could enhance our understanding of atherosclerosis complexities and its risk factors. Multi-dimensional data integration is crucial for a comprehensive understanding of coronary artery disease and developing precision medicine approaches tailored to individual patients. Investigating cardiac morphology and cardiovascular risk factors will further highlight the interconnectedness of biological processes in atherosclerosis.

Key areas for future investigation include understanding the molecular mechanisms of atherosclerosis, particularly the roles of microRNAs and lncRNAs, and examining the impacts of gut microbiota and sex differences. Targeting inflammatory pathways, such as the NLRP3 inflammasome and PCSK9, may offer promising strategies for treating atherosclerosis and improving patient outcomes. Multi-omics approaches represent a powerful tool for discovering novel causal mediators of disease, enhancing our understanding of complex biological interactions, and informing personalized medicine. Understanding immune mechanisms in atherosclerosis is vital for developing targeted therapies that effectively modulate immune responses to improve patient outcomes. Lastly, refining therapeutic strategies to more effectively and safely target inflammation, alongside exploring emerging trends in personalized medicine based on genetic and inflammatory biomarkers, remains a priority. These research directions underscore the need for a multifaceted approach to address the complexities of atherosclerosis and enhance cardiovascular outcomes.

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