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REVIEW

The Role and Research Progress of Glycolytic Metabolic Reprogramming in Smooth Muscle Cells in Atherosclerosis

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Abstract: Atherosclerosis(AS) is a chronic vascular disease resulting from the combined effects of lipid deposition and inflammatory responses, in which the phenotypic plasticity of vascular smooth muscle cells (VSMCs) plays a central role in disease progression. Under aerobic conditions, VSMCs undergo a metabolic shift reminiscent of the "Warburg effect", supporting their proliferation, migration, and phenotypic modulation through enhanced glycolytic flux. Despite its pathophysiological significance, the mechanistic interplay between glycolytic reprogramming in VSMCs and atherosclerotic progression remains inadequately systematized. This review aims to bridge this knowledge gap by synthesizing emerging evidence on how glycolysis orchestrates VSMCs remodeling and contributes to the clinical manifestations of AS. Furthermore, we explore the synergistic coupling between glycolytic metabolism and electrophysiological dynamics in VSMCs—an emerging area with transformative potential. Our methodology integrates multidimensional strategies: first, we delineate the metabolic drivers of VSMCs phenotypic switching in AS; second, we combine in vitro and in vivo models to elucidate the role of VSMCs glycolysis in diabetes-accelerated AS and in-stent restenosis; lastly, we investigate metaboloelectrophysiological crosstalk and ion channel regulation as central mechanisms. This synthesis provides a conceptual and mechanistic foundation for targeting glycolytic pathways in AS and its complications, offering novel avenues for therapeutic intervention.

Keywords: smooth muscle cells, glycolysis, atherosclerosis

Background

Atherosclerosis(AS), as a chronic progressive vascular disease driven and stimulated by lipids, primarily affects medium and large arteries, characterized by persistent inflammatory responses and fibrous tissue proliferation.[1] Its pathological progression is a complex pathological change caused by multiple factors. With abnormal lipid metabolism, it leads to lipid deposition in the vascular intima, ultimately causing significant stenosis and dysfunction of vascular systems such as coronary arteries, carotid arteries, and peripheral arteries.[2] Traditional research on AS has primarily focused on abnormalities in lipid metabolism.[3] However, recent metabolomic analyses of human carotid atherosclerotic plaques by Tomas et al[4] have revealed that high-risk plaques exhibit metabolic characteristics such as increased glucose utilization, reduced fatty acid oxidation, and enhanced amino acid compensation. This metabolic phenotype closely resembles cellular "metabolic reprogramming", suggesting that similar adaptive metabolic alterations may occur within AS plaques. Further studies indicate that glycolytic metabolism—including both aerobic and anaerobic glycolysis—plays a critical role in the pathogenesis of AS. During AS progression, cellular metabolism and functional properties interact, inducing adaptive metabolic changes and triggering glycolytic reprogramming. While this process meets cellular energy demands, it also leads to the accumulation of intermediate metabolites. These metabolites alter the local inflammatory microenvironment in the vessel wall, exacerbating inflammatory responses within the plaques.[3,5] Simultaneously, research by Cao et al[6] has uncovered for the first time the synergistic role of glycolysis in VSMC phenotypic switching

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and neointima formation. Vascular injury induces the expression of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB). PFKFB-mediated glycolysis promotes VSMC dedifferentiation into a proliferative phenotype by supplying glycolytic-derived carbon and activating mTORC1 signaling, thereby facilitating neointima formation after vascular injury. Given the pivotal regulatory role of the glycolytic pathway in AS, targeted intervention in glycolysis holds promise for providing innovative therapeutic targets in clinical prevention and treatment. Based on this, this article reviews the regulatory role of glycolytic metabolism in vascular smooth muscle cells in the progression of AS.

The Transformation and Functional Remodeling of Smooth Muscle Cells in Atherosclerosis

Recently, advancements in related research areas such as cell lineage tracing, single-cell RNA transcriptome sequencing, and high-throughput gene sequencing have led to new breakthroughs in the study of vascular smooth muscle cells (VSMCs). Studies have found that in atherosclerotic plaques, some cells highly expressing macrophage markers are not tissue-type macrophages but may be non-myeloid-derived macrophages (such as smooth muscle cells).[7,8] In atherosclerotic plaques, there is a group of cells that simultaneously highly express both VSMCs and macrophage markers. These findings suggest that VSMCs may be involved in the development of AS and participate in its progression.[9] The latest research evidence has once again confirmed the presence of macrophage-like cells in the progression of AS, which may originate from VSMCs, collectively promoting various pathogenic processes including vascular calcification, hyperplasia, and restenosis in the progression of AS.[10] VSMCs are primarily distributed in the vascular medial layer and are the main contractile and relaxing cells in blood vessels, exhibiting high plasticity. Under normal conditions, these cells are in a contracted state ("dormant" state), expressing more contractile-related protein molecules such as myosin heavy chains and regulatory proteins, which inhibit cell division activity. This special contractile phenotype is of great significance for maintaining normal vascular function.[11] When vascular tissues are damaged, the phenotype of VSMCs undergoes changes, and the dedifferentiated VSMCs (synthetic, proliferative, calcified, inflammatory, phagocytic, etc) exhibit impaired contractile properties. These various dedifferentiated vascular smooth muscle cell phenotypes are endowed with new functions, such as increased anabolism, enhanced proliferation, increased calcium salt deposition, release of pro-inflammatory factors, and enhanced phagocytic function, which adaptively contribute to the emergence of pathological vascular microenvironments.[12,13] Synthetic VSMCs downregulate the expression levels of contractile genes, which is accompanied by cytoskeletal remodeling and enhanced cell proliferation. Additionally, these cells secrete matrix metalloproteinases that play a critical role in the regulation of tissue repair processes. Current research elucidates the role of the redox state of vascular smooth muscle cells in the pathogenesis of vascular diseases, indicating that the imbalance between oxidation and antioxidation is a critical factor in the development and progression of AS in both elderly individuals and animal models.[14,15] Vascular injury stimulation or abnormal apoptosis can induce a proliferative state of VSMCs in atherosclerotic lesions. Existing literature indicates that age is an independent factor influencing specific redox-sensitive signaling pathways in VSMCs. As age advances, the balance between pro-oxidants and antioxidants becomes disrupted, leading to alterations in redox status that subsequently activate relevant signaling pathways. The alterations in these pathways promote VSMCs proliferation, migration, and extracellular matrix remodeling, ultimately leading to vascular wall thickening, enhanced inflammatory responses, and increased susceptibility to AS.[16] These biological changes collectively constitute the pathological basis for neointima formation following vascular injury.[17]

The Regulatory Role of Aerobic Glycolysis in the Proliferation and Migration of Vascular Smooth Muscle Cells

Under normal physiological conditions, cells primarily rely on the oxidative phosphorylation (OXPHOS) pathway in mitochondria to metabolize glucose, while the glycolysis pathway is typically significantly activated only under hypoxic conditions. However, Otto Warburg observed in his research that even in the presence of sufficient oxygen supply, malignant tumor cells still preferentially adopt the glycolysis method to obtain energy. This unique metabolic reprogramming provides the necessary material basis for their continuous proliferation.[2] This phenomenon is recognized as the "Warburg effect"[18] However, through the research of scholars, it has been discovered that this effect is not exclusive to cancer cells. Werle et al first reported the phenomenon of the Warburg effect in the study of VSMC proliferation: under the stimulation of platelet-derived growth factor-BB (PDGF-BB),

VSMCs exhibited a significant enhancement of aerobic glycolysis activity and an increase in glucose metabolic flux, with phosphofructokinase 1 (PFK1) involved in regulating this metabolic flux change process. More importantly, the activation of aerobic glycolysis in PDGF-induced VSMCs plays a critical regulatory role in their cellular proliferation and migration capabilities.[19] Heiss et al reported that the motility of VSMCs is accompanied by an increase in glycolysis. Through stimulation with PDGF, VSMCs significantly enhance aerobic glycolysis activity and the influx of glucose metabolic flux. Furthermore, the indirubin derivative indirubin-3′-monoxime (I3MO) specifically targets the STAT3 signaling pathway, inhibiting the glycolytic activity of VSMCs.[20] Research indicates that lactate dehydrogenase A (LDHA), a key rate-limiting enzyme in glycolysis, functions as a promoter of VSMCs proliferation and migration. Inhibition of LDHA activity can diminish the glycolytic rate in VSMCs stimulated by PDGF, subsequently leading to a reduction in VSMC proliferation and migration.[21] Furthermore, Zhao et al experimentally demonstrated that oxidized low-density lipoprotein (ox-LDL) significantly activates the glycolytic metabolic pathway via the pyruvate kinase-M2 (PKM2) pathway, ultimately promoting the proliferation and migration of vascular smooth muscle cells.[22] A substantial body of experimental evidence indicates that exogenous high concentrations of glucose serve as the sole substrate for aerobic glycolysis in VSMCs under unstimulated conditions. Alongside the phenotypic changes in VSMCs, their energy metabolism undergoes alterations, characterized by a significant increase in glycolytic flux and a marked elevation in lactate levels. According to metabolomic findings, approximately 30% of ATP production in VSMCs is derived from aerobic glycolysis, with 80% to 90% of glucose metabolized into lactate within this pathway.[23] Therefore, it can be seen that aerobic glycolysis contributes significantly to ATP generation in the overall energy metabolism of VSMCs (Figure 1).

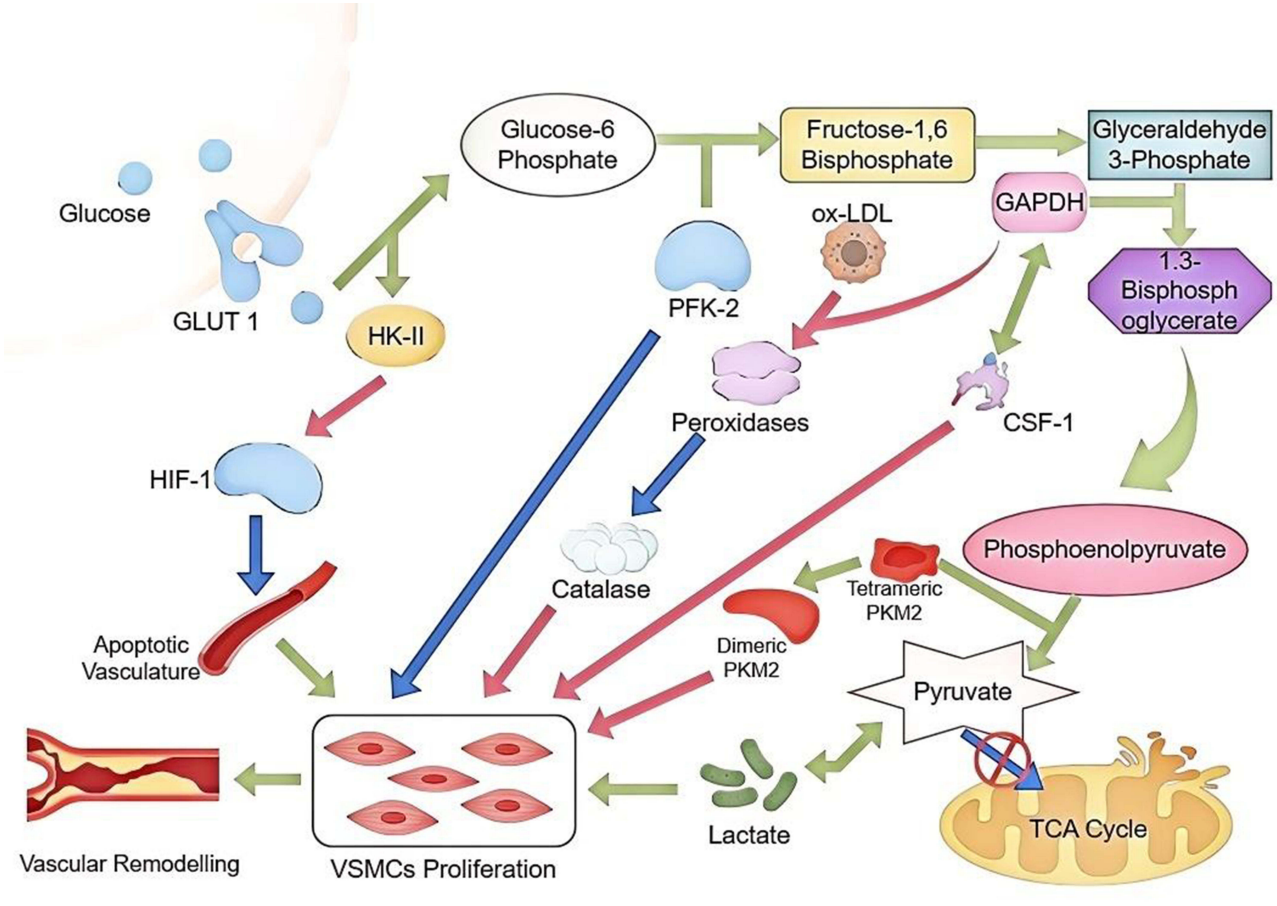

Figure 1 Depicts the link between glycolysis and VSMCs proliferation. Exogenous glucose is transported via GLUTs, thereby initiating the glycolytic pathway. An increase in glycolytic flux leads to the stimulation of HIF-1 activity by HK-II. Furthermore, the overexpression of PFK-2 has been shown to reduce apoptosis and promote VSMC proliferation. GAPDH interacts with CSF-1, which further facilitates cell proliferation. Additionally, the phenotypic switch of VSMCs is triggered by the conversion of tetrameric PKM2 to its dimeric form. The stimulation of LDHA and subsequent lactate release also contribute to VSMC proliferation and vascular remodeling.
Abbreviation: CSF-1, Colony-stimulating factor-1; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; GLUTs, Glucose transporters; HIF-1, Hypoxia-inducible factor; HK-II, Hexokinase-II; LDHA, Lactate dehydrogenase-A; PFK-2, Phosphofructokinase-2; PKM2, Pyruvate kinase-M2.

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Therefore, Among glycolytic regulators in VSMCs, GLUT1, HK-II, PKM2, LDHA and pyruvate dehydrogenase kinase (PDK1) represent the most druggable targets, as they are central to glycolytic flux and phenotypic switching while already supported by available small-molecule modulators in preclinical or clinical development.[24,25] Local delivery strategies, such as drug-eluting stents or nanoparticle-based carriers, may further enhance selectivity and safety, thereby strengthening their translational potential in the treatment of atherosclerosis and restenosis. Future studies should focus on systematically evaluating these candidates in clinically relevant models to clarify their efficacy, safety, and combinatorial potential with existing therapies.

Mechanism Study of Abnormal Glucose Metabolism in Vascular Smooth Muscle Cells in Clinical Diseases

In the LDL receptor knockout (LDLR-/-) mouse model, Wall et al found that abnormalities in VSMCs glucose metabolism synergize with metabolic syndrome, collectively promoting the development of AS.[26]

The mechanism indicates that smooth muscle cells surrounding atherosclerotic lesions exhibit high expression of the glucose transporter protein 1(GLUT1), primarily driven by inflammatory response cells such as tumor necrosis factor (TNF-α) released from the lesion sites. This process initiates glycolysis and the polyol synthesis pathway, leading to increased expression of GLUT1 and enhanced generation of chemokines. These factors synergistically promote the formation of AS, exacerbating vascular complications around the lesions. In the microenvironment of AS, vascular smooth muscle cells in the lesion area demonstrate a characteristic overexpression of GLUT1. This mechanism involves the glycolytic pathway, which promotes abnormal polyol metabolism and increases the secretion of chemokines, thereby accelerating plaque formation. Clinicopathological analyses confirm that VSMCs in the fibrous caps of arterial plaques, observed in both human and animal models, exhibit significant characteristics of metabolic reprogramming. This reprogramming is accompanied by impaired OXPHOS and activated glycolysis.[26,27] In vivo imaging techniques targeting glycolytic metabolic reprogramming in VSMCs, particularly ^{18}F-FDG PET, hold great potential for assessing plaque vulnerability. ^{18}F-FDG, a glucose analog, is taken up by cells and becomes metabolically trapped, with its uptake level directly reflecting cellular glucose metabolic activity.[28] These techniques enable noninvasive, quantitative visualization of metabolic activity within plaques, providing functional information beyond conventional anatomical assessment. Clinical studies have confirmed[29] that ^{18}F-FDG uptake in plaques at sites such as the carotid artery is highly correlated with the density of inflammatory cells within the plaque (with macrophages being the primary contributors, although activated SMCs also contribute), making it an effective tool for evaluating plaque inflammation and vulnerability. Furthermore, lactate, the end product of glycolysis, serves as a direct indicator of the Warburg effect. Reprogrammed SMCs produce substantial amounts of lactate. Using hyperpolarized ^{13}C-pyruvate MRI, pyruvate is largely converted to lactate in metabolically active plaques. By measuring the conversion rate from ^{13}C-pyruvate to ^{13}C-lactate, the glycolytic flux within plaques can be directly and quantitatively assessed.[30] But clinical imaging technologies still face challenges in translational application. In addition, the metabolic reprogramming of VSMCs is not limited to atherosclerosis but also plays a critical role in other vascular disorders, such as aneurysm formation. Costa et al demonstrated[31] that VSMC phenotypic transitions and extracellular matrix remodeling are central mechanisms in aneurysms, closely paralleling the synthetic switching observed in atherosclerosis. These similarities imply that metabolic cues may underlie both diseases, highlighting a potential cross-disease therapeutic perspective. For instance, glycolysis-targeting strategies explored in atherosclerosis could also inform novel treatment approaches for aneurysms, thereby broadening the clinical relevance of VSMC metabolism as a therapeutic target.

In clinical practice, physicians recognize that insulin resistance and diabetes are significant risk factors for the development of AS. Insulin resistance (IR) exerts profound effects on VSMCs by disrupting normal insulin signaling pathways.[32] Under physiological conditions, insulin activates the PI3K/Akt pathway, which promotes NO production and maintains the contractile phenotype of VSMCs. In the setting of IR, this pathway is impaired, resulting in reduced NO bioavailability, while the MAPK/ERK pathway remains activated, thereby enhancing VSMC proliferation and migration. Such imbalanced signaling drives the phenotypic switch of VSMCs from a contractile to a synthetic state, characterized by extracellular matrix production and inflammatory mediator release.[33] These changes accelerate vascular remodeling,

contribute to neointimal hyperplasia, and play a pivotal role in the initiation and progression of atherosclerosis. Recent research by Fu et al has demonstrated that insulin mediates numerous critical cellular functions through receptors and signaling cascades, particularly in the transport and delivery of nutrients to VSMCs. Disruption of these pathways can lead to insulin resistance, thereby accelerating endothelial dysfunction, AS, and heart failure. This mechanism provides new insights for clinical treatment, as the precise targeting of VSMCs may prevent the development of insulin resistance in patients and effectively block the malignant complications associated with diabetes-related vascular diseases.[34]

High glucose levels induce persistent oxidative stress and a significant increase in glucose-6-phosphate dehydrogenase (G6PDH) activity in VSMCs. The underlying molecular mechanisms involve synergistic actions across multiple pathways, including disturbances in the protein kinase C(PKC) signaling system and sustained activation of advanced glycation end products (AGEs). AGEs regulate a dose-dependent upregulation of PDK4 during vascular calcification, which accelerates the transition of VSMCs to the glycolytic metabolic pathway, ultimately leading to the deposition of calcium salts in the vasculature. This finding elucidates the molecular basis for the high incidence of vascular calcification observed in diabetic patients.[35] Regarding hypertensive vascular remodeling, alterations in glucose uptake and metabolism in VSMCs may be associated with contractile dysfunction in specific types of hypertension, such as deoxycorticosterone acetate-induced salt-sensitive hypertension. In rat models of this hypertension, researchers observed a significant decrease in GLUT4 protein expression levels and glucose transport capacity was observed. This finding highlights the potential mechanism linking glucose metabolism disorders in VSMCs to hypertensive vascular dysfunction from the perspective of energy metabolism.[36] Simultaneously, VSMCs are implicated in the metabolism associated with in-stent restenosis. Jain et al have demonstrated that the phenotypic transformation of VSMCs is a critical pathological mechanism underlying the occurrence of in-stent restenosis. Analysis of tissue samples following coronary bare metal stent implantation revealed that, compared to normal vascular medial tissue, the expression levels of the key glycolytic enzyme pyruvate kinase were significantly elevated in the neointimal region, particularly within VSMCs-enriched areas. Building on this discovery, the research team conducted experiments using a large animal stent model, confirming that targeted inhibition of PKM2 effectively reduces the degree of in-stent stenosis. For the first time, this study elucidates the molecular mechanism by which PKM2 promotes neointimal hyperplasia through the regulation of VSMC phenotypic transformation, thereby providing a novel therapeutic direction for the clinical prevention and treatment of in-stent restenosis.[37]

It is well established that carbohydrate metabolism and lipid metabolism are closely interconnected.[38] In VSMCs, glycolysis and lipid metabolism converge through acetyl-CoA, a central metabolic intermediate.[39] Glycolysis-derived pyruvate enters mitochondria and is converted into acetyl-CoA by pyruvate dehydrogenase, subsequently fueling the tricarboxylic acid (TCA) cycle and driving oxidative phosphorylation. Similarly, fatty acid β-oxidation generates acetyl-CoA, which also enters the TCA cycle and provides a parallel source of energy. Notably, under pathological conditions such as atherosclerosis, excessive reliance on glycolysis may alter the availability of acetyl-CoA, thereby impairing lipid metabolism and promoting abnormal lipid accumulation within VSMCs. This metabolic interplay highlights acetyl-CoA as a pivotal node linking glycolytic reprogramming with lipid handling, ultimately influencing VSMC phenotypic switching and vascular pathology.[6] Moreover, targeting this glycolysi-lipid metabolism axis may offer a novel therapeutic strategy for vascular diseases.

The Dual Regulatory Mechanism of Metabolic-Electrophysiological Coupling in Vascular Smooth Muscle Cells and Its Role in Vascular Function

The regulation of VSMCs in vascular function exhibits a dual regulatory mechanism. Research indicates that the maintenance of VSMC function relies not only on the glycolytic metabolic pathway but also significantly on alterations in ion channels, which dynamically regulate the expression and activity of K^+ and $Ca2^+$ ions. Electrophysiological remodeling of VSMCs is another crucial determinant involved in the regulation of vascular tension. Regarding energy metabolism, the aerobic glycolysis pathway is closely associated with the transmembrane transport of K^+ ions, while mitochondrial oxidative phosphorylation directly provides energy for the contractile activities of VSMCs. This

synergistic coupling of metabolism and electrophysiology collectively sustains VSMC function.[40] In aerobic glycolysis, two major reactions are dependent on potassium ions. In the initial stage of glycolysis, potassium ions regulate the conversion of glucose to glucose-6-phosphate. In the terminal stage, potassium ions influence the conversion of phosphoenolpyruvate to pyruvate and the generation of ATP. Furthermore, studies have demonstrated that physiological concentrations of lactate, the end product of glycolysis, can dynamically regulate the signaling expression and function of Kv channels in VSMCs.[41,42] This discovery reveals a novel mechanism of ion metabolic coupling: the dysfunction of potassium ion channels impairs glycolytic metabolic efficiency by interfering with key enzymatic reactions. The membranes of VSMCs are densely populated with various subtypes of voltage-gated potassium channels (Kv). In addition to regulating membrane potential and influencing vascular tension, these channel proteins also play a crucial role in regulating cell proliferation and differentiation, significantly contributing to pathophysiological changes such as vascular remodeling and phenotypic transformation.[43] Mueed's research team has discovered that enhancing the potassium ion current in VSMCs significantly improves the abnormal contractile function of atherosclerotic blood vessels. The molecular mechanism underlying this protective effect involves several key processes: the opening of potassium channels facilitates K^+ efflux, leading to membrane hyperpolarization, which inhibits the activation of voltage-dependent $Ca2^+$ channels. This inhibition further reduces intracellular $Ca2^+$ concentration, ultimately resulting in vasodilation. Notably, the activation of K^+ channels in VSMCs also regulates intracellular reactive oxygen species (ROS) levels by modulating the function of the mitochondrial electron transport chain.[44]

Prolonged exposure to hyperglycemia impairs the normal physiological regulatory capacity of blood vessels while simultaneously inhibiting the functional activity of voltage-gated potassium channels (Kv channels). Research perspectives indicate that selective inhibition of the Kv1.3 channel subtype has a dual effect: it prevents the abnormal proliferation of VSMCs in vitro and significantly alleviates the pathological changes associated with vascular intimal thickening in vivo.[45] The influx of extracellular calcium ions significantly influences the phosphorylation level of myosin light chain by modulating the activity of myosin light chain kinase. This regulatory mechanism is crucial for the contractile function of VSMCs and also plays a vital role in their proliferation.[46] The metabolic reprogramming of VSMCs plays a pivotal regulatory role in cell proliferation and phenotypic transformation. This biological process is closely associated with the pathological progression of various vascular disorders in clinical settings. Inhibitors that target key effector molecules, such as specific enzymes or regulatory proteins within metabolic pathways, effectively suppress the pathological alterations in VSMCs.[11] However, due to the complex nature of the metabolic regulatory network and its intricate interactions with multiple pathways, translating current research findings into clinical applications continues to face significant challenges. There is an urgent need for more systematic and comprehensive large-scale clinical studies to validate their therapeutic efficacy.

Conclusion

Comprehensive studies have demonstrated that the phenotypic switching of VSMCs is closely linked to the reprogramming of glycolytic energy metabolism. By specifically targeting key metabolic pathways and enzymes involved in glycolysis, it is possible to effectively inhibit the transformation of VSMCs from the normal contractile phenotype to the abnormal synthetic phenotype. This finding provides novel insights for the prevention and treatment of restenosis following coronary interventions and stent implantation. Notably, therapeutic strategies directed at critical metabolic nodes have shown promising efficacy in various preclinical animal models, highlighting their potential as a novel therapeutic approach for delaying AS and enhancing vascular repair responses in patients with coronary heart disease post-stent implantation.

To address current limitations, future prospective studies should focus on multicenter, randomized clinical trials evaluating the long-term efficacy and safety of glycolysis-targeted metabolic interventions in patients undergoing coronary stent implantation. Furthermore, exploring the crosstalk between glycolysis and other metabolic pathways, such as oxidative phosphorylation and fatty acid metabolism, may uncover a more comprehensive network regulating VSMC phenotypic switching. The development of highly targeted small molecules or nanodelivery systems could further enhance the precision and effectiveness of these interventions.

In summary, glycolytic metabolic reprogramming serves as a central driver of VSMC phenotypic switching and represents a key determinant in the progression of AS and post-stent restenosis. Translating these insights into novel therapeutic strategies has significant potential to improve clinical management and patient outcomes, underscoring the critical importance of targeting metabolic pathways in coronary heart disease.

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Disclosure

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