

Review

# The Regulatory Role and Mechanism of Energy Metabolism in Vascular Diseases

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## Abstract

Vascular diseases are amongst the most serious diseases affecting human life and health globally. Energy metabolism plays a crucial role in multiple vascular diseases, and the imbalance of energy metabolism in cells from the blood vessel wall can cause various vascular diseases. Energy metabolism studies have often focused on atherosclerosis (AS) and pulmonary hypertension (PH). However, the roles of energy metabolism in the development of other vascular diseases is becoming increasingly appreciated as both dynamic and essential. This review summarizes the role of energy metabolism in various vascular diseases, including AS, hemangioma, aortic dissection, PH, vascular aging, and arterial embolism. It also discusses how energy metabolism participates in the pathophysiological processes of vascular diseases and potential drugs that may interfere with energy metabolism. This review presents suggestions for the clinical prevention and treatment of vascular diseases from the perspective of energy metabolism.

**Keywords:** glycolysis; mitochondria; atherosclerosis; hemangioma; aortic dissection; pulmonary hypertension

## 1. Introduction

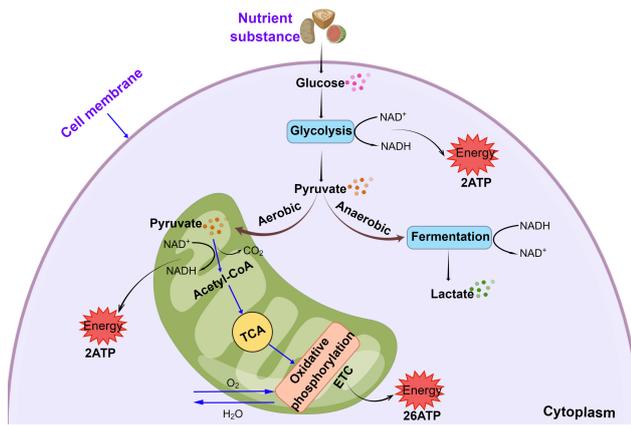
Various pathologies associated with the vasculature, including hypertension, atherosclerosis (AS), aortic aneurysm, aortic dissection, pulmonary hypertension (PH), and stenosis, are considered to be some of the most serious diseases affecting human life and health worldwide [1]. Furthermore, energy metabolism is known to play a crucial role in the etiology of a number of vascular diseases. An imbalance of energy metabolism has been closely associated with vascular diseases, such as AS [2], abdominal aortic aneurysm [3], PH [4], aortic dissection [5], and vascular aging [6]. Pathological changes in specific vascular diseases usually cause changes in the energy metabolism of cells in the vascular wall, including vascular endothelial cells (VECs), vascular smooth muscle cells (VSMCs), and macrophages [7–9].

Energy metabolism is critical for maintaining normal cell function and life. In eukaryotes, nutrients are converted by glycolysis to pyruvate, which then enters the mitochondria, where it is further decarboxylated to acetyl coenzyme A (acetyl-CoA). Under aerobic conditions, a acetyl-CoA enters the tricarboxylic acid (TCA) cycle where it is reduced through the oxidative respiratory chain pathway to produce nicotinamide adenine dinucleotide (NADH), with the generation of H<sub>2</sub>O, CO<sub>2</sub> as end-products. The energy released in this process leads to mitochondrial oxidative phosphorylation (OXPHOS) of adenosine diphosphate (ADP) to gen-

erate adenosine triphosphate (ATP), which is used to maintain the normal physiological functions of cells. However, under hypoxic conditions or when mitochondrial function is damaged, pyruvate can instead be converted to lactate for use in anaerobic glycolysis [10–12] (Fig. 1). OXPHOS and glycolysis maintain the energy metabolism homeostasis of cells. Imbalance of energy metabolism homeostasis is linked to various pathological conditions; for instance, obesity brain homeostasis, cardiovascular disease, and cancer [13–15].

Mitochondrial respiration and glycolysis are the major energy metabolism pathways in cells. However, they also regulate various cellular processes, including differentiation, proliferation, apoptosis, immune response, cell death, and the transmission of secondary signals to the nucleus, all of which play important roles in a variety of vascular diseases [16–18]. It is therefore imperative to study the role of energy metabolism in vascular diseases. This review will be elaborated the regulatory role and mechanism of energy metabolism in vascular diseases in two part. The first part of this review will summarize mechanisms responsible for the regulatory of energy metabolism in vascular diseases, such as AS, hemangioma, aortic dissection, PH, vascular aging, and arterial embolism. The second part will discuss drugs and clinical treatment strategies, which might help to improve energy metabolism function in vascular diseases.





**Fig. 1. Mitochondrial oxidative phosphorylation and glycolytic pathways.** Abbreviations: ATP, adenosine triphosphate;  $\text{NAD}^+$ , nicotinamide adenine dinucleotide; NADH, nicotinamide-adenine dinucleotide-reduced; TCA, tricarboxylic acid; ETC, electron transport chain. By Figdraw.

## 2. Atherosclerosis and Energy Metabolism

AS is a chronic inflammatory vascular disease driven by abnormal lipids and characterized by progressive thickening and the gradual formation of plaques on the blood vessel wall [19]. Cells of the arterial wall are very vulnerable to mitochondrial dysfunction due to their barrier and metabolic functions. Mitochondrial dysfunction in AS causes alteration in cellular metabolism and respiration, leading to the production of excessive amounts of reactive oxygen species (ROS) and resulting in oxidative stress [20]. Mitochondrial DNA (mtDNA) is more susceptible to oxidative stress, making it vulnerable to oxidation. Induction of mtDNA damage is a critical mechanism in the development of AS [21,22]. Damaged mtDNA is usually accompanied by a change in the number of abnormal mitochondria due to alterations in mitochondrial fusion and fission, thereby leading to abnormal energy metabolism in AS [23]. Mutations in mtDNA also lead to an increased number of pro-inflammatory macrophages. These phagocytose large amounts of lipid to form foam cells, resulting in cell death and necrotic plaque cores. The destruction of mitochondrial membranes, inhibition of the respiratory chain, and the reduction in mitochondrial enzyme activity, can also affect energy metabolism in AS [24]. Yu E, *et al.* [25] confirmed that mtDNA damage is seen early in AS in Apolipoprotein E knockout ( $\text{ApoE}^{-/-}$ ) mice. To then determine whether mtDNA damage promotes AS, they studied  $\text{ApoE}^{-/-}$  mice with deficient polymerase- $\gamma$  proof-reading activity ( $\text{polG}^{-/-}/\text{ApoE}^{-/-}$ ). The results suggested that mtDNA damage promotes AS and affects plaque composition independently of ROS in  $\text{polG}^{-/-}/\text{ApoE}^{-/-}$  mice through effects on VSMCs, monocytes, and hyperlipidemia [25].

Besides mitochondrial metabolism, the glycolytic process is the chief source of rapid energy production in re-

sponse to environmental changes, with the rate of glycolysis playing a critical role in maintaining cellular homeostasis. Intermediates produced during glycolysis can affect cell viability and thus increase the risk of AS [26,27]. Moreover, abnormalities in mitochondrial and glycolytic energy metabolism can affect the function of VECs, the proliferation of VSMCs, and the polarization of macrophages, which ultimately promote the progression of AS lesions (Fig. 2).

### 2.1 Energy Metabolism of Vascular Endothelial Cells and Atherosclerosis

Endothelial dysfunction is a key early event in the pathogenesis of AS. Unlike other cell types, the energy required for the physiological function of VECs primarily derives from glycolysis [28]. Even when oxygen is sufficient, VECs preferentially catabolize glucose through aerobic glycolysis rather than OXPHOS [29,30]. Therefore, aerobic glycolysis provides various substrates for cell proliferation and DNA synthesis.

VECs that are exposed to disturbed flow patterns in areas of arterial bifurcation or curvature are more vulnerable to injury and loss of integrity, and show increased glycolysis both *in vitro* and *in vivo* [31]. Multiple mechanisms are involved in this process, protein kinase AMP-activated catalytic subunit alpha 1 (PRKAA1)/AMP-activated protein kinase  $\alpha 1$  ( $\text{AMPK}\alpha 1$ ), is a major regulator of endothelial glycolytic metabolism, and is upregulated under pathological shear stress. Increased levels of PRKAA1/ $\text{AMPK}\alpha 1$  signaling promote the expression of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ). This, in turn, drives the transcription of glycolytic enzymes, thereby increasing glycolysis in VECs. PRKAA1/ $\text{AMPK}\alpha 1$ -mediated glycolysis is critical for increased VEC proliferation, thus helping to preserve the integrity of the VEC barrier in regions that are vulnerable to AS and protecting against the development and progression of AS in a mouse model [27,29]. Similarly, impaired endothelial glycolysis is associated with various vascular pathologies, including impaired angiogenesis and the development of AS. Interferon- $\gamma$  inhibits basal glycolysis through global transcriptional suppression of glycolytic enzymes in quiescent primary human coronary artery ECs leading to basal reduced intracellular guanosine 3', 5'-cyclic monophosphate (cGMP), impaired endothelial migration, and a shift towards a pro-inflammatory state [32].

Although aerobic glycolysis is beneficial for VEC proliferation; pathological angiogenesis also increases [33]. Aerobic glycolysis can bypass OXPHOS, so that the rate of glucose hydrolysis is faster. This can produce large amounts of energy very rapidly for VECs, thus accelerating their migration and proliferation, and promoting the formation of AS plaques [34]. The new vessels developed as a consequence of aerobic glycolysis are immature and have structural and functional abnormalities, thereby leading to plaque hemorrhage which is a major risk factor for the de-

velopment of AS [34,35]. Thus, aerobic glycolysis in VECs can have both beneficial and harmful roles in the development of AS.

Mitochondrial respiration is not the main energy metabolism pathway in VECs, but the disruption of mitochondrial redox homeostasis in VECs can cause chronic inflammation, which then contributes substantially to AS development [36]. Recently, the disruption of mitochondrial redox homeostasis in VECs was shown to be a key factor in triggering inflammation. Reducing or neutralizing mitochondrial ROS levels may therefore be an effective strategy to mitigate inflammation, promote endothelial repair, and inhibit AS development [37]. The primary enzymatic source of ROS during cardiovascular pathogenesis is the nicotinamide adenine dinucleotide phosphate oxidase (NOX) family of proteins. These are mainly expressed in VECs and provoke oxidative inactivation of nitric oxide (NO) and the consequent uncoupling of endothelial nitric-oxide synthase (eNOS), leading to sustained oxidative stress [38] (Fig. 2B). NOX has become a target for drug therapy in AS, Tanshinone IIA, for example, can attenuates oxidative stress by decreasing NOX2 and NOX4 levels and downregulating the nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling pathway, which may help to ameliorate AS [39].

## 2.2 Energy Metabolism of Vascular Smooth Muscle Cells and Atherosclerosis

Abnormal proliferation of VSMCs promotes plaque formation in the early stage of AS lesions, but the apoptosis and senescence of VSMCs and VSMC-derived macrophage-like cells may promote inflammation and plaque rupture in the late stages of AS. Therefore, VSMCs are beneficial during the advanced stage of plaques, for example, by preventing the fibrous cap from rupturing [40,41]. A major event leading to AS development is the change in VSMC phenotype from a physiological contractile state to an adverse proliferative or synthetic state, accompanied by enhanced aerobic glycolysis [42].

Aerobic glycolysis is the main energy metabolism pathway in VSMCs. Even though approximately 90% of glucose is used in aerobic glycolysis, this pathway only produces about 30% of the ATP is produced [42]. Currently there are two hypotheses to explain this: The first is that the ATP produced by glycolysis and glucose oxidation provides energy for different physiological processes. For example, ATP produced by glycolysis is used to supply energy for sodium and potassium transport, whereas ATP produced by OXPHOS supplies energy for other physiological processes [43]. The second is that the large amount of lactate produced by glycolysis can enhance the reserve capacity of mitochondria. The lactate can then be converted to pyruvate by lactate dehydrogenase after entering the mitochondria and being completely oxidized to produce CO<sub>2</sub> and H<sub>2</sub>O. In this process, all of the energy stored in lactate is completely released and participates in various biochemical

activities in cells and organisms. Under ATP-deficient conditions, glycolysis can promote the proliferation of VSMCs by producing lactate [44–46] (Fig. 2C).

The uptake of carbohydrates in VSMCs is determined by glucose transporter 1 (GLUT1), which can further affect energy metabolism and especially the glycolytic pathway [47,48]. The GLUT1-mediated glycolytic pathway in VSMCs has been closely associated with AS [49]. In one study, GLUT1 overexpression led to a 44% increase in intracellular glucose concentration in rat aortic smooth muscle cell lines (A7r5) and in human VSMC lines. An increase in the glucose flux through glycolysis and the TCA cycle further promotes the proliferation of VSMCs [42] (Fig. 2C). Overexpression of GLUT1 can also inhibit VSMC apoptosis by inhibiting caspase-8 activation in mouse primary VSMCs, thereby promoting cell proliferation [50]. Metabolic reprogramming may be involved in VSMC phenotypic transition. Prohibitin 2 is a pleiotropic scaffold protein involved in the regulation of energy metabolism and proliferation, which maintains VSMC contractile phenotype by interacting with heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) to counteract hnRNPA1-mediated pyruvate kinase isoform M2 (PKM2) alternative splicing and glucose metabolic reprogramming [45].

Furthermore, VSMCs were recently found to rely on a combination of mitochondrial and glycolytic metabolism, with the energy switch occurring at different stages in the AS disease process. Mitochondrial dysfunction and DNA damage are defining traits of aged VSMCs in AS [51]. Klotho is an anti-aging protein that could play a significant role in improving the VSMC phenotype. Targeting Klotho during early stages of AS could induce energy switching and improve VSMC survival in the plaque [51]. A follow-up study demonstrated that phosphatase and tensin homolog deleted on chromosome ten (PTEN) induced putative kinase 1 (Pink1) kinase can regulate mitochondrial homeostasis and the recycling of dysfunctional organelles that are critical for maintaining energetic homeostasis [52]. Energy switching between oxidative and glycolytic metabolism were found to be regulated by Pink1.

## 2.3 Energy Metabolism of Macrophages and Atherosclerosis

Macrophages exist in two distinct subsets: the classically activated M1 macrophages, and the alternatively activated M2 macrophages [53]. Glycolysis is the main energy pathway in M1 macrophages, and the TCA cycle and OXPHOS are impaired in these cells. In contrast, M2 macrophages are more dependent on mitochondrial OXPHOS [54]. GLUT1 is a rate-limiting glucose transporter in pro-inflammatory polarized macrophages. Overexpression of GLUT1 in macrophage/monocyte-like leukemia cells (RAW264.7) resulted in a significant enhancement of glucose uptake and metabolism, and increased production of

pentose phosphate pathway intermediates [55]. With increased the enhancement of glycolytic metabolism, the proportion of M1 macrophages also increases, followed by reduced lipid oxidative metabolism and lipid accumulation [56]. The polarization of M1 macrophages induces AS by increasing ROS levels, which then cause OXPHOS dysfunction. This in turn increases the rate of glycolysis and stimulates pro-inflammatory reactions and the synthesis of inflammatory factors [57]. As a consequence, glycolysis is increased in M1 macrophages together with the levels of NADH:NAD<sup>+</sup> and glutathione (GSH):glutathione disulfide (GSSG), while the O<sub>2</sub> consumption rate (OCR) and O<sub>2</sub> consumption both decrease. In contrast, glycolysis is decreased in M2 macrophages, together with NADH:NAD<sup>+</sup> and GSH:GSSG levels, whereas the OCR and O<sub>2</sub> consumption levels increase (Fig. 2D) [58,59].

Recent studies highlight the importance of mitochondria in the metabolic and signaling pathways necessary to maintain macrophage effector functions [60]. Lipoprotein, oxidized phospholipid, and oxidized low-density lipoprotein (ox-LDL) present within AS plaques can cause oxidative stress-induced damage to macrophage mitochondria [61]. Mild oxidative stress damages the mitochondrial respiratory chain, stimulates mtDNA replication and transcription, and increases the mtDNA copy number. However, under severe oxidative stress the damaged mitochondria gradually lose the ability to self-regulate, which then leads to decreased rates of replication and transcription and a decrease in mtDNA copy number. This ultimately affects mitochondrial function and leads to abnormal energy metabolism [62]. Concurrently, oxidative stress damage to mitochondria in macrophages causes dysfunction of the mitochondrial electron transport chain (ETC), leading to stalled electron transport and increased ROS production [63]. Macrophage polarization is activated by increased ROS through a variety of signaling pathways. For example, activation of the mitogen-activated protein kinase (MAPK)-dependent nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathways by ROS-induced cytotoxicity ultimately increases the transcription of pro-inflammatory cytokines and other inflammatory mediators that promote polarization of M1 macrophages in RAW264.7 cells [64]. Consequently, ROS is generated in AS plaques as a result of damaged ETC function and further induces the polarization of M1 macrophages. Once polarized, the energy metabolism of macrophages relies mainly on glycolysis, meaning that fat metabolism is reduced and leading to further lipid accumulation and the deterioration of AS plaques [65,66].

In addition to oxidative stress damage to mitochondria in macrophages, HIF-1 $\alpha$  is involved in ox-LDL-induced effects in macrophages, including the inflammatory response, angiogenesis, and metabolic reprogramming. HIF-1 $\alpha$  signaling promotes the accumulation of triglycerides and cholesterol in macrophages. Hypoxia and HIF-1 $\alpha$  increase

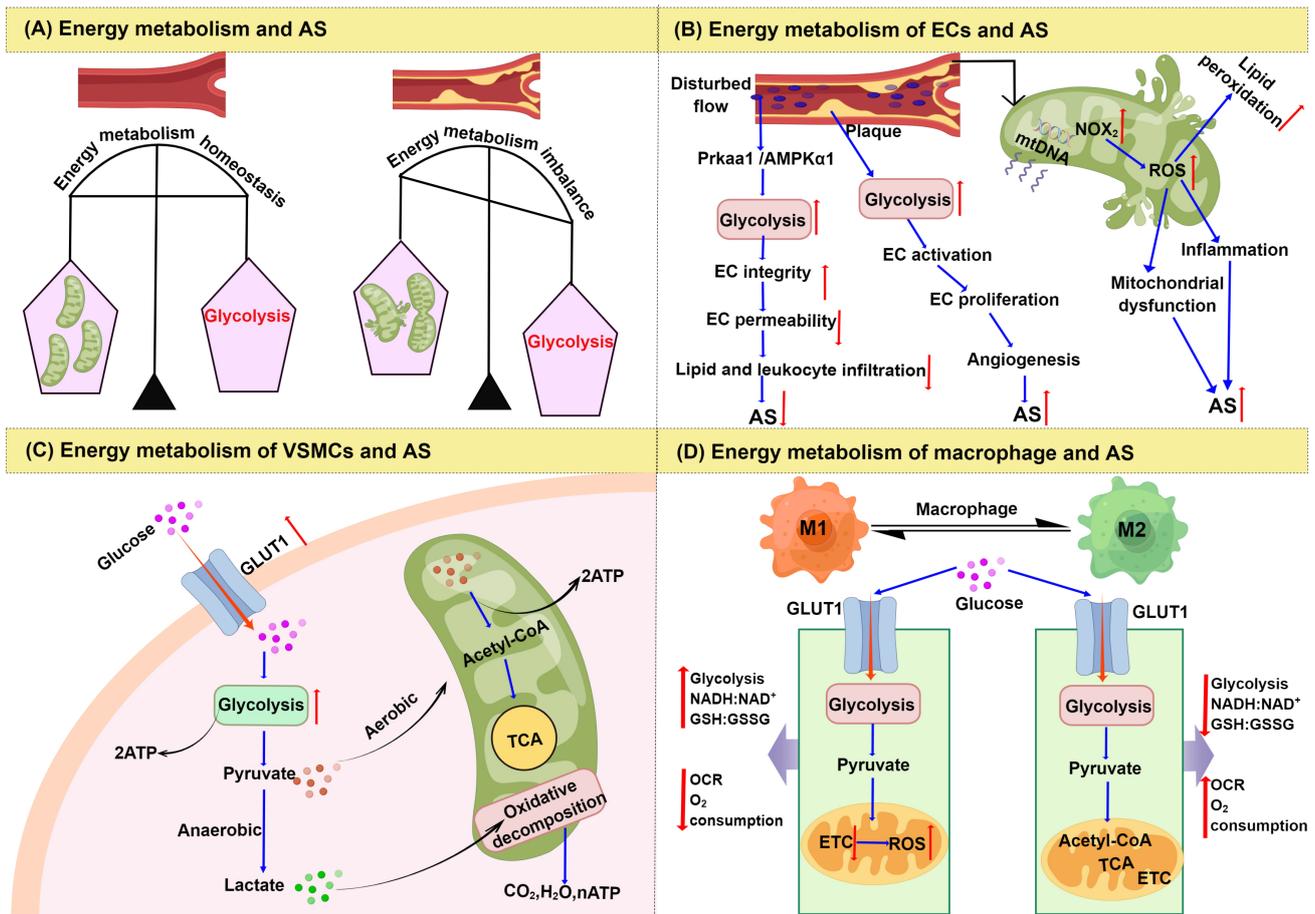
the uptake of ox-LDLs, promote cholesterol and triglyceride synthesis, and decrease cholesterol efflux. The effect of HIF-1 $\alpha$  on cholesterol homeostasis within macrophages, and activation of the inflammatory response by oxysterols via HIF-1 $\alpha$ , could have deleterious consequences in AS [67]. HIF-1 $\alpha$  can also activate the glycolytic pathway in macrophages. Meanwhile, mitochondrial function in these cells is decreased, thereby changing the mode of energy metabolism, increasing the level of inflammatory factors, accelerating macrophage polarization to the M1 type, and hence causing the progression of AS [57,68].

### 3. Energy Metabolism and Hemangioma

Hemangioma is the most common benign tumor of infancy and is caused by dysfunction during embryogenesis and vasculogenesis. Hemangiomas progress during fetal life and manifest fully at birth. They arise in the skin and soft tissues and can occur at birth or shortly after birth [69]. The primary characteristics of hemangioma are a high incidence rate and strong destructiveness. Hypoxia and abnormal glucose metabolism are considered to be key factors in the pathogenesis of this disease [70].

Under normoxic and hypoxic conditions, glucose consumption and ATP production occur at higher levels in hemangioma-derived endothelial cells compared to human umbilical vein endothelial cells [70]. In addition, several glycolysis-related genes are expressed at higher levels, including GLUT1, hexokinase 2 (HK2), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), PKM2, and lactate dehydrogenase A (LDHA). Inhibition of glycolytic-related genes in hemangioma-derived ECs can reduce the proliferation, migration, and angiogenesis of these cells. The above results suggest that increased glycolytic metabolism is an important cause of infantile hemangioma [70,71]. Some genes related to glycolysis are also highly expressed in infantile hemangioma. For example, the expression of LncRNA MCM3AP-AS1 is significantly upregulated in infantile hemangiomas and also promotes their progression by increasing glycolysis via regulation of the miR-138-5p/HIF-1 $\alpha$  axis [72].

Although tumor cells rely on glycolysis for energy supply, mitochondrial transformations in bioenergetics, metabolism, and fission-fusion dynamics are also likely to be important. This is especially true for rapidly growing tumor cells that rely on mitochondrial function for their sustenance [73]. However, some studies have identified tumorigenic cell populations that rely more on mitochondrial respiration than on glycolysis [74–76]. Mouse hemangioendothelioma ECs have been used to study the mechanism of hemangioendothelioma, which depend heavily on mitochondria to thrive. The targeting of mitochondria may therefore be an effective strategy for the management of hemangiomas [77].



**Fig. 2. Changes of energy metabolism in AS.** (A) Energy metabolism imbalance and AS. (B) Signaling regulation of glycolysis and mitochondrial dysfunction in endothelial cells. (C) Signaling regulation of the glycolysis pathway in vascular smooth muscle cells. (D) Comparison of energy metabolism between M1 and M2 macrophages. Abbreviations: AS, atherosclerosis; ECs, endothelial cells; NOX<sub>2</sub>, NADPH oxidase 2; ROS, reactive oxygen species; GLUT1, Glucose transporter protein 1; M1, M1 macrophage; M2, M2 macrophage; GSH, glutathione; GSSG, glutathione disulfide; OCR, oxygen consumption rate. By Figdraw.

#### 4. Energy Metabolism and Aortic Dissection

Aortic dissection is a life-threatening condition in which blood in the aortic cavity enters the aortic medial membrane from a tear in the aortic intima, resulting in separation of the different layers of the aortic wall. Although the incidence of aortic dissection is low, it has a major clinical impact due to its high mortality and poor prognosis [78]. The potential mechanisms underlying energy metabolism-induced aortic dissection primarily involve two aspects: ROS and inflammation [79,80].

Fan LM, *et al.* [81] investigated the special role of endothelial ROS in the development of aortic dissection by establishing a mouse model with endothelium-specific Nox2 overexpression. These workers then determined the susceptibility of the Nox2 over-expressing mice to aortic dissection after infusion with angiotensin II (Ang II). Compared to wild-type mice, a specific increase in endothelial ROS production in the Nox2 transgenic mice was sufficient to cause Ang II-mediated aortic dissection. Increased expression of Nox2 in VECs can lead to increased ROS production, up-

regulated expression of vascular cell adhesion molecule-1 (VCAM-1), enhanced matrix metalloproteinase activity, and accelerated CD45 inflammatory cell infiltration. Compared to controls, ECs from Nox2-overexpressing mice grown in conditioned medium induced greater phosphorylation of extracellular-regulated kinase 1/2 (ERK1/2) in VSMCs by secreting cyclophilin A (CypA). These findings suggest that VEC-derived ROS plays a critical role in determining the susceptibility of the aortic wall to dissection mediated by Ang II. The ROS-dependent secretion of CypA by VECs is an important signaling mechanism that regulates the susceptibility of aortic wall structural components to aortic dissection. These results suggest that endothelial ROS and CypA are potential therapeutic targets for the prevention of aortic dissection [81].

Aortic dissection is a severe inflammatory vascular disease associated with the metabolic reprogramming of macrophages. The effect of macrophage metabolic reprogramming has been studied in a mouse model by inducing aortic dissection with  $\beta$ -amiopropanitrile (BAPN, a lipoxy-

genase inhibitor) and then collecting tissue samples from the vessels. Changes in the macrophage levels of HIF-1 $\alpha$  in the animal model and in the tissues of patients with aortic dissection were evaluated by immunohistochemistry, immunofluorescence, Western blotting, and quantitative polymerase chain reaction. Macrophage HIF-1 $\alpha$  expression was upregulated in the aorta of patients with aortic dissection, as well as in the mouse model. Mechanistically, activated HIF-1 $\alpha$  in macrophages triggers vascular inflammation, extracellular matrix degradation, and elastic plate disruption by increasing the secretion of disintegrin and metalloprotease. Meanwhile, BAPN was found to impair mitochondrial oxidative phosphorylation in macrophages by enhancing HIF-1 $\alpha$  activation and glycolytic metabolism, and by promoting metabolic reprogramming. Therefore, HIF-1 $\alpha$  is activated by the metabolic reprogramming of macrophages, which subsequently favors aortic dissection. Inhibition of macrophage HIF-1 $\alpha$  may therefore be a potential treatment strategy for aortic dissection [80].

## 5. Energy Metabolism and Pulmonary Hypertension

Pulmonary Hypertension (PH) is a pulmonary vascular disease with complex etiology. It is characterized by the remodeling and occlusion of small peripheral pulmonary vessels, and a progressive increase in pulmonary vascular resistance. This eventually leads to hypertrophy of the right ventricle and right heart failure [82]. The pathological characteristics of PH are excessive proliferation and apoptosis tolerance of VSMCs, adventitial fibroblasts and VECs, eventually leading to continuous pulmonary vascular wall thickening and pulmonary vascular remodeling [83]. Changes in metabolism and bioenergetics are increasingly recognized as universal hallmarks of PH in patients and in animal models of this disease [84].

Excessive proliferation of pulmonary artery smooth muscle cells (PASMCs) is the main cause of hypoxic PH. Molecules that induce abnormal proliferation of VSMCs may trigger PH [85]. For example, the increase in the main end products of intracellular lipid peroxidation, 4-HNE, leads to abnormal proliferation of VSMCs, thus promoting the development of PH. Therefore, inhibiting the intracellular increase of 4-HNE can prevent the occurrence and progression of PH. Aldehyde dehydrogenase 2 (ALDH2) is a detoxifying enzyme for 4-HNE, which can regulate mitochondrial fission and VSMC proliferation through the 4-HNE/HIF-1 $\alpha$ /Drp1 (dynamin-related protein 1) signaling pathway. Ultimately, this mechanism helps prevent hypoxia-induced PH [86]. Other enzymes in the ALDH family, such as ALDH1A3, can also regulate glycolysis in SMCs, thereby regulating the proliferation of SMCs [87]. The latest research shows that elevated ALDH1A3 can orchestrate changes in metabolism needed both for cell energy and for targeted epigenetic and transcriptional regulation of genes required by dividing cells. To elucidate mechanisms

accounting for ALDH1A3-mediated PH PASMC proliferation, Li D, *et al.* [88] compared the transcriptome of PAH PASMC under basal conditions and when ALDH1A3 was reduced. They found that ALDH1A3-dependent regulation of mRNA levels of genes related to cell cycle and metabolism. Dihydrolipoyl dehydrogenase (DLD), PKM2, and isocitrate dehydrogenase 1 (IDH1) contribute to the metabolic shift initiated by ALDH1A3 in PH PASMC and also impact nucleotide synthesis via PKM2 and cell cycle genes required for cell proliferation [88].

An emerging metabolic theory for PH suggests that cellular and mitochondrial metabolic dysfunction underly the pathology of this disease [89]. Zhang *et al.* [89] showed that high expression of polypyrimidine tract-binding protein 1 (PTBP1), controlled by decreased expression of miR-124, underlies the elevated PKM2/PKM1 ratio and subsequent metabolic reprogramming of pulmonary adventitial fibroblasts isolated from calves and humans with severe PH. These findings are similar to those made in cancer cells and support the idea that pyruvate metabolism can be exquisitely controlled by miR-124 and by PTBP1 [89].

Metabolic changes together with endothelial dysfunction that favor increased glycolysis are important in the pathophysiology of PH [90]. Lung ECs express high levels of glucose metabolic enzymes, such as PFKFB3, and consequently produce large amounts of glucose metabolites. Low levels of HIF-1 $\alpha$  and HIF-2 $\alpha$  were noted in PFKFB3-knockdown pulmonary artery endothelial cells (PAECs), whereas high levels of HIF-1 $\alpha$  and HIF-2 $\alpha$  were observed in PFKFB3-overexpressing PAECs. Knockdown of HIF-2 $\alpha$ , but not HIF-1 $\alpha$ , reduced the elevated expression of growth factors and proinflammatory cytokines in PFKFB3-overexpressing PAECs. This indicates the critical involvement of HIF-2 $\alpha$  in PFKFB3-mediated expression of growth factors and proinflammatory cytokines in PAECs [7]. Furthermore, the blocking of endothelial PFKFB3 inhibits PH development in rodent models, suggesting that targeting of glucose metabolic enzymes may be a promising strategy for the treatment of PH. Recent research has shown that intracellular chloride channels regulate endothelial metabolic reprogramming in PH. In particular, chloride intracellular channel 1 (CLIC1) and CLIC4 are highly expressed in the lung endothelium of patients with PH and preclinical models of PH. Moreover, their activation has been linked with better endothelial repair, apoptosis resistance, and angiogenesis [91], CLIC1/4 is localized in the inner and outer mitochondrial membranes of VECs. Common and unique CLIC1- and CLIC4-interacting partners create a link between CLIC signaling, mitochondrial dysfunction, and mitofusin-2 deficiency in PH endothelium [4].

## 6. Energy Metabolism and Vascular Aging

Vascular aging involves a deterioration in the normal function of vessels, resulting in increased arterial stiffness and pulse wave propagation rate and accumulation of ox-

oxidative damage. Vascular aging also greatly increases the incidence of AS and PH [92,93]. Mitochondrial dysfunction plays a critical role in disease progression. For example, mitochondria-targeted esculetin alleviates AS in the setting of aging by delaying vascular senescence and pro-inflammatory processes, and by improving mitochondrial biogenesis and function [92].

Senescence appears to be closely linked with changes in cell metabolism. Replicative senescent VECs show up-regulation of glycolytic and oxidative glucose metabolism compared to young VECs. This was demonstrated by metabolic profiling and glucose flux measurements, and by analyzing the expression of key metabolic enzymes. Senescent cells exhibit higher glycolytic activity and lactate production, enhanced expression of LDHA, and increased activity of the TCA cycle and mitochondrial respiration [6].

Age-related endothelial dysfunction is mediated primarily by the reduced bioavailability of NO. Impaired NO-mediated endothelial function is largely due to excessive production of ROS, which reacts with NO to reduce its bioavailability. The resulting arterial oxidative stress leads in turn to vascular aging and dysfunction [94]. The effects of oxidative stress on vascular aging also correlate with endothelium-dependent dilation (EDD), which is a marker of endothelial dysfunction. Impaired or reduced EDD can promote vascular aging and the stiffening of arteries by increasing the tension in arterial activity. Increased expression of NADPH oxidase and abnormal mitochondrial function lead to increased ROS production, decreased NO bioavailability, damaged EDD, and age-related endothelial dysfunction [95]. Furthermore, the expression of serine biosynthetic enzyme phosphoglycerate dehydrogenase (PHGDH) is significantly reduced due to decreased transcription of the activating transcription factor 4 (ATF4) during senescence, which leads to reduction of intracellular serine. Mechanistically, PHGDH interacts with PKM2, which prevents p300/CBP-associated factor (PCAF)-catalyzed PKM2 K305 acetylation and subsequent degradation by autophagy. In addition, PHGDH facilitates p300-catalyzed PKM2 K433 acetylation, which promotes PKM2 nuclear translocation and stimulates its activity to phosphorylate H3T11 and regulate the transcription of senescence-associated genes. Vascular endothelium-targeted expression of PHGDH and PKM2 ameliorates ageing in mice. This findings reveal that enhancing serine biosynthesis could become a therapy to promote healthy ageing [96].

## 7. Energy Metabolism and Arterial Embolism

Arterial embolism involves the narrowing or occlusion of the lumen due to AS, thus making it difficult to transport nutrients in the blood to the limbs and resulting in ischemia and serious tissue necrosis [97]. The occurrence of arterial embolism causes changes in energy

metabolism. Insufficient blood supply and hypoxia not only lead to changes in energy metabolism, but also decrease mitochondrial activity and increase the carbon dioxide level, which may cause hypercapnia [98]. However, most of research on the relationship between energy metabolism and arterial embolism was carried out in the 1990s, with almost no recent research. The reason may be that the inducing factors for arterial embolism are related to hypertension, hyperlipidemia, AS, etc. Therefore, study of the inducing factors for arterial embolism and energy metabolism may be more important for the prevention of arterial embolism. Here, we review the research progress on arterial embolism and energy metabolism during the 1990s.

In one study, cerebral ischemia was induced in rats by administering microspheres into the right carotid canal, and the time course of changes in brain energy metabolism was examined on day 7 post-surgery. Nearly 50% of the operated rats showed the typical symptoms of stroke, i.e., cerebral ATP and creatine phosphate (PCr) were significantly decreased in the right hemisphere of microsphere-induced cerebral ischemia from day-1 to day-7, while tissue lactate levels were increased on day-1, -3, and -5 after embolism [99]. These results indicate that ischemia alters the energy metabolism of rat cerebra. Subsequently, Takeo *et al.* [98] studied the sustained damage to cerebral regions of rat brain induced by cerebral ischemia. These workers examined animal behavior and cerebral energy metabolism after microsphere embolization. On day-1 of post-microsphere embolization, the lactate content increased to its peak, and the ATP and PCr contents decreased to their lowest level in these cerebral regions in the right hemisphere. The glucose and glycogen content in these regions increased to their peak on day-3. Although these markers returned to control levels over time, metabolic changes in all of these areas persisted for up to 28 days post-surgery. The behavioral scoring as a result of the temporal changes after microsphere embolization showed stroke-like symptoms on day-1 after embolization, with the symptoms disappearing relatively quickly with the passage of time. These observations indicate that microsphere embolization in brain regions can cause extensive and sustained damage to energy metabolism [98].

Hepatic energy metabolism and oxidative attack were also studied following transcatheter arterial embolization (TAE) and chemoembolization (TAC) in the left and median lobes of the liver in a rat model with thioacetamide-induced liver cirrhosis. The energy charge of the embolized lobes of the lungs decreased from 0.86 to 0.78 and 0.74 one hour after the TAE and TAC processes, respectively, but recovered after 3 h. The ATP and total adenine nucleotide content of embolized and non-embolized lobes were also temporarily reduced. Total hepatic blood flow in the catheter-embolized and chemo-embolized lobes decreased by nearly 50% and returned to normal after 1 week. After chemoembolization for 3 h, the total liver glutathione content de-

creased from 7.02  $\mu\text{mol/g}$  to about 4.5  $\mu\text{mol/g}$ , while after chemoembolization for 6 h the malondialdehyde content increased from 196.94 nmol/g to more than 300 nmol/g. However, these parameters did not change in the catheter-embolized liver. The above results suggest that hepatic energy metabolism is temporarily altered by ischemia after treatment with TAE and TAC [100].

## 8. Discussion and Perspective

The regulation of energy metabolism in various tissues and cells helps the body adapt to environmental changes. These regulatory disturbances are closely related to the molecular pathology of many vascular diseases, including AS, PH and hemangioma [70,84,101]. Under specific pathological conditions, glycolysis and the mitochondrial energy pathway can affect VEC function, macrophage polarization, and VSMC proliferation [51,102,103]. Abnormal glycolysis metabolism in VECs, VSMCs, and macrophages is related to AS, infantile hemangioma, and PH [70,84,101]. In addition to glycolysis, mitochondrial metabolism is also crucial for vascular diseases such as AS, aortic dissection, PH, vascular aging, and arterial embolism [20,90,104]. *In vitro* and *in vivo* studies indicate that regulation of energy metabolism-related molecules and pathways is used to maintain cellular metabolic homeostasis and to prevent vascular diseases. The mechanisms for preventing vascular diseases include multiple genes and signaling pathways involved in energy metabolism, such as PRKAA1/AMPK $\alpha$ 1 [29], GLUT1 [47], Prohibitin 2 [45], NOX [39], Klotho [51], Pink1 [105], ROS- and MAPKs-dependent Nrf2/HO-1 signaling pathways [64], HIF-1 $\alpha$  [67], key glycolytic enzymes (HK2, PFKFB3, PKM2, and LDHA) [70], ALDH2 [86], ALDH1A3 [87], microRNA-124/PTBP1 [89], CLIC1/CLIC4 [4], and PHGDH [96].

Through literature analysis, GLUT1 is closely associated with the energy metabolism of various vascular diseases, which overexpressed in high glycolytic flux, resulting in the overproduction of pyruvate, alanine, and lactate [106]. Concurrently, VECs and VSMCs display characteristics of cell proliferation and migration, while the polarization of M1 macrophages also increases [48,107,108]. NOX2, ROS, Pink1 and NF- $\kappa$ B are important molecules closely related to mitochondrial metabolism. Excessive ROS can directly target mitochondria, decouple mitochondrial ETC, and reduce ATP production. ROS is therefore highly deleterious to mitochondria and can lead to several vascular diseases [109,110]. HIF-1 $\alpha$  is involved in various pathophysiological processes, such as oxygen supply and cell metabolism, and is also important in AS, infantile hemangioma, and aortic dissection [58,72,80]. Inhibition of HIF-1 $\alpha$  helps to shift from glycolysis to normal aerobic oxidation. Therapeutic targeting of HIF-1 $\alpha$  can also partially reverse the promoting effect of glycolysis on infantile hemangioma by upregulating the expression of LncRNA MCM3AP-AS1 [72].

Treatment strategies for vascular diseases that target energy metabolism have attracted much attention, especially the use of drugs. Pharmacotherapies that target endothelial dysfunction caused by energy metabolism disorders can potentially be used to treat AS and many other vascular diseases [111]. For example, the small molecule 3PO (3-[3-pyridyl]-1-[4-pyridyl]-2-propen-1-ketone) may exert beneficial effects against plaque formation by partially inhibiting the glycolysis-mediated impairment of new angiogenesis without affecting plaque composition, as well as by increasing the number of autophagosomes in VECs [112]. 3PO is known to be an inhibitor of PFKFB3. Heterozygous global deficiency of Pfkfb3 was shown to protect mice from developing hypoxia-induced PH, while administration of 3PO almost completely prevented PH in rats treated with Sugen 5416/hypoxia [7]. Tetrahydrobiopterin (BH4) has been shown to reduce endothelial NO synthase uncoupling, reverse oxidative stress-mediated inhibition of EDD, and improve EDD in the elderly, thereby alleviating vascular aging [95]. Furthermore, natural products may be a good primary source of drugs for the treatment of vascular diseases. Extracts of *Rhodiola* and Salidroside have been suggested to provide beneficial effects for metabolic disorders and AS. The postulated mechanisms for *Rhodiola* extracts and Salidroside in the treatment of AS involve energy metabolism and include oxidative stress, inflammation, mitochondria, and cell death [113]. Apocynin, extracted from the roots of *Apocynum cannabinum* and *Picrorhiza kurroa*, is an inhibitor of NADPH oxidase and could therefore restore EDD and NO levels *in vitro* and alleviate vascular aging [95,114]. Oral apigenin supplementation can reverse two clinically important and age-related indicators of arterial dysfunction, namely vascular endothelial dysfunction and large elastic artery stiffening [115]. This novel work also showed that apigenin prevents foam cell formation in an established cell culture model of early AS. The above preclinical findings provide an experimental basis for future translational studies to assess the potential of natural products in treating arterial dysfunction and reducing vascular disease risk. In addition, the non-selective-adrenergic receptor antagonist propranolol is already in clinical use and is becoming the first line therapy as an approved treatment for infantile hemangioma. The latest evidence showed that propranolol-induced apoptosis in VECs may occur via mitochondrial stress [116]. Thus, it would be advantageous to discover the mechanisms related to energy metabolism for drugs that are already used in clinical practice.

In terms of clinical research, a mitochondrial-targeted antioxidant (MitoQ) has been shown to improve vascular mitochondrial function. Acute oral administration of the MitoQ (80 mg) can effectively improve endothelial function and superoxide dismutase in patients with peripheral artery disease (PAD). In addition, acute intake of MitoQ has also been found to be effective in improving maximum walking capacity and delaying claudication onset in PAD

patients [117]. Pyruvate dehydrogenase kinase (PDK), an inhibitor of the mitochondrial enzyme pyruvate dehydrogenase in the pulmonary arteries of human PH compared to healthy lungs. In a 4-month, open-label study, DCA (PDK inhibitor dichloroacetate, 3 to 6.25 mg/kg b.i.d.) administered to patients with idiopathic PH already on approved idiopathic PH therapies led to reduction in mean pulmonary artery pressure and pulmonary vascular resistance and improvement in functional capacity [118].

Besides medication, there may be other potential therapeutic methods for the treatment of vascular diseases, such as cytotherapy. ALDHs are a superfamily that includes 19 subtypes in humans. ALDH2 is the mitochondrial isoform of ALDH and a key metabolizer of acetaldehyde. It is known to be a protective factor for vascular diseases such as AS, aortic dissection, aortic aneurysm, and PH by clearing toxic aldehydes generated from lipid peroxidation [86,119,120]. A Bayesian network meta-analysis of randomized controlled trials showed that intra-arterial injection of large amounts of ALDH-positive cells could improve the activity of daily living in ischemic stroke patients [121]. Therefore, we speculate that cytotherapy is a potential treatment for vascular disease.

## 9. Conclusions

Cellular energy metabolism is a crucial factor in vascular disease, with a number of studies having been conducted over the years to investigate its role. The vascular disease types related to energy metabolism include AS, hemangioma, aortic dissection, PH, vascular aging, and arterial embolism. Some drugs can directly or indirectly affect the expression of key rate-limiting enzymes in glycolysis, or regulate the mitochondrial energy metabolism pathway. In summary, this review should increase our understanding of energy metabolism in various vascular diseases. It may also help to guide future research efforts aimed at exploring the pathogenesis of vascular diseases and clinical treatment methods.

## Abbreviations

Acetyl-CoA, acetyl coenzyme A; ADP, adenosine diphosphate; ALDH1A3, aldehyde dehydrogenase 1A3; ALDH2, aldehyde dehydrogenase 2; AMPK $\alpha$ 1, AMP-activated protein kinase  $\alpha$ 1; Ang II, angiotensin II; ApoE $^{-/-}$ , Apolipoprotein E knockout; AS, atherosclerosis; ATF4, activating transcription factor 4; ATP, adenosine triphosphate; A7r5, aortic smooth muscle cell lines; BAPN,  $\beta$ -amiopropanitrile, a lipoxygenase inhibitor; BH4, Tetrahydrobiopterin; cGMP, guanosine 3', 5'-cyclic monophosphate; CLIC, Chloride intracellular channel; Cr, creatine; CypA, cyclophilin A; DLD, Dihydrolipoyl dehydrogenase; Drp1, dynamin-related protein 1; ECs, endothelial cells; EDD, endothelium-dependent dilation; eNOS, endothelial nitric-oxide synthase; EOMA, Mouse hemangi endothelioma endothelial cells; ERK1/2,

extracellular-regulated kinase 1/2; ETC, electron transport chain; GLUT1, glucose transporter 1; GSH, glutathione; GSSG, glutathione disulfide; HIF-1 $\alpha$ , hypoxia-inducible factor-1 $\alpha$ ; HIF-2 $\alpha$ , hypoxia-inducible factor-2 $\alpha$ ; HK2, hexokinase 2; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; H3K27, lysine 27 on histone H3; IDH1, isocitrate dehydrogenase 1; LDHA, lactate dehydrogenase A; LDLR $^{-/-}$ , low-density lipoprotein receptor-deficient; MAPK, mitogen-activated protein kinase; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NFYA, nuclear transcription factor Y subunit alpha; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NO, nitric oxide; NOX, Nicotinamide adenine dinucleotide phosphate oxidase; NOX2, NADPH oxidase 2; NOX4, NADPH oxidase 4; Nrf2/HO-1, nuclear factor erythroid 2-related factor 2/heme oxygenase-1; OCR, O<sub>2</sub> consumption rate; ox-LDL, oxidized low-density lipoprotein; OXPHOS, oxidative phosphorylation; PAECs, pulmonary artery endothelial cells; PASMC, pulmonary-artery smooth muscle cells; PH, pulmonary hypertension; PCAF, p300/CBP-associated factor; PCr, creatine phosphate; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PINK1, PTEN induced putative kinase 1; PKM2, pyruvate kinase isoform M2; polG $^{-/-}$ , polymerase- $\gamma$  proofreading activity; PRKAA1, protein kinase AMP-activated catalytic subunit alpha 1; PTBP1, polypyrimidine tract-binding protein 1; PTEN, phosphatase and tensin homolog deleted on chromosome ten; RAW264.7, macrophage/monocyte-like leukemia cells; ROS, reactive oxygen species; TAC, chemoembolization; TAE, transcatheter arterial embolization; TCA, tricarboxylic acid; VCAM-1, vascular cell adhesion molecule-1; VECs, vascular endothelial cells; VSMCs, vascular smooth muscle cells; 3PO, 3-[3-pyridyl]-1-[4-pyridyl]-2-propen-1-ketone; 4-HNE, 4-hydroxynonenal.

## Author Contributions

QT designed the study. TS, WY, YW and DL performed the literature research. TS and WY wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflicts of interest for this work.

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