

冠脉侧支循环的代谢调控机制研究进展

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[摘要] 冠脉侧支循环在冠脉狭窄或闭塞后形成, 能维持心肌灌注, 减轻缺血损伤。剪切力和信号通路在侧支形成中起重要作用, 代谢状态对个体间的侧支形成能力有关键影响。近年来, 代谢重编程被认为是内皮可塑性和血管再生潜能的基础。糖酵解、脂肪酸氧化及线粒体代谢在内皮细胞迁移、增殖和氧化还原稳态中发挥重要作用。衰老和代谢障碍通过影响这些代谢途径, 削弱侧支循环的形成能力。免疫代谢也深刻影响侧支循环, M2型巨噬细胞通过脂肪酸氧化促进血管生成。能量代谢、衰老代谢障碍及免疫代谢均对冠脉侧支循环产生影响, 代谢干预策略可能改善缺血性心脏病的侧支循环形成。

[关键词] 冠脉侧支循环; 代谢重编程; 内皮细胞; 衰老; 免疫代谢

Research progress on the metabolic regulatory mechanisms of coronary collateral circulation

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ABSTRACT

Coronary collateral circulation (CCC) develops in response to coronary artery stenosis or occlusion and helps maintain myocardial perfusion and attenuate ischemic injury. Shear stress and signaling pathways play crucial roles in collateral vessel formation, while metabolic status is a key determinant of individual variability in collateral growth capacity. In recent years, metabolic reprogramming has been recognized as a fundamental basis for endothelial plasticity and vascular regenerative potential. Glycolysis, fatty acid oxidation, and mitochondrial metabolism play essential roles in endothelial cell migration, proliferation, and redox homeostasis. Aging and metabolic disorders impair collateral

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vessel formation by disrupting these metabolic pathways. Immunometabolism also profoundly influences coronary collateral circulation, with M2 macrophages promoting angiogenesis through fatty acid oxidation. Energy metabolism, aging-related metabolic dysfunction, and immunometabolism all affect the development of coronary collateral circulation. Metabolic intervention strategies may therefore enhance collateral vessel formation in ischemic heart disease.

KEY WORDS

coronary collateral circulation; metabolic reprogramming; endothelial cells; aging; immunometabolism

冠脉侧支循环是机体在冠脉狭窄或闭塞后形成的一种天然代偿性血流通路^[1]。它能够在冠脉主干供血受限的情况下维持局部心肌灌注,从而减轻缺血损伤、限制梗死面积并改善预后^[2]。临床研究^[3]表明,具有良好侧支循环的患者在急性心肌梗死或慢性冠脉病变中往往表现出更高的缺血耐受性、更好的左室功能及较低的病死率。然而,不同个体间形成侧支的能力存在显著差异,因此,理解侧支循环形成差异的机制,将为冠心病患者的预后评估和干预策略提供潜在靶点。

早期研究多从血流力学和信号通路角度阐释侧支形成的过程。内皮细胞通过感受剪切力变化激活血管内皮生长因子(vascular endothelial growth factor, VEGF)、内皮型一氧化氮合酶(endothelial nitric oxide synthase, eNOS)及Notch等信号通路,从而引发细胞迁移、增殖及血管重塑。其中,VEGF及VEGF受体2/3(vascular endothelial growth factor receptor 2/3, VEGFR2/3)在内皮尖端细胞形成与血管芽生过程中发挥中心作用,而Notch-Delta信号通路促进动脉化形成^[4-5]。平滑肌细胞的重塑、基质金属蛋白酶介导的基底膜降解及炎症细胞的参与,共同构成了侧支循环成熟化的微环境^[6](图1)。

随着血管生物学研究的深入,学界逐渐认识到,单纯的剪切力变化或信号级调控不足以解释不同个体间侧支形成的差异。即使在相似的血流动力条件下,不同患者间的侧支丰富程度差异也可达数倍,提示存在其他影响侧支形成的决定性因素。近年来,代谢重编程被认为是内皮可塑性及血管再生潜能的关键基础^[7-8],内在的细胞代谢状态可能决定其对侧支形成的“响应阈值”。代谢不仅提供细胞生长与迁移所需的能量,还决定内皮细胞对外界刺激(如剪切力、缺氧及炎症)的反应能力。糖酵解水平高的内皮细胞表现出更强的迁移与分支能力,而线粒体氧化还原稳态则维持细胞存活及信号转导的平衡^[9]。脂肪酸氧化、氧化型烟酰胺腺嘌呤二核苷酸(oxidized nicotinamide adenine dinucleotide, NAD⁺)/SIRT1(sirtuin 1)轴及哺乳动物雷帕霉素靶蛋白(mammalian target of

rapamycin, mTOR)信号等代谢途径也在血管新生及修复过程中发挥重要作用^[10]。由此可见,代谢状态已从被动背景变量转变为决定侧支循环形成潜力的关键因素。

本综述围绕“代谢-内皮可塑性-免疫调控”这一主线,系统总结近年来关于能量代谢、衰老代谢障碍及免疫代谢对冠脉侧支循环形成的影响,旨在为理解侧支形成机制及开发代谢干预策略提供新的理论视角。

1 能量代谢与内皮细胞可塑性

1.1 糖酵解与内皮细胞迁移、芽生

在侧支循环形成过程中,内皮细胞的代谢方式与其功能状态密切相关。与多数依赖线粒体氧化磷酸化(oxidative phosphorylation, OXPHOS)的细胞不同,内皮细胞主要通过糖酵解获得能量。即使在氧气充足的条件下,约85%的内皮细胞ATP来源于糖酵解途径,而非线粒体呼吸^[11-12]。这种“有氧糖酵解偏好”被认为是内皮细胞适应血管微环境的代谢特征,可避免过度活性氧(reactive oxygen species, ROS)产生并确保在低氧、剪切力变化或炎症环境下仍具备能量供应优势。

糖酵解不仅为细胞提供能量,更直接调控内皮细胞的迁移与芽生能力。在血管新生过程中,内皮细胞分化为2种功能亚型:处于血管前缘的尖端细胞和负责管腔形成的柄细胞。尖端细胞需快速迁移、伸出伪足并感知外界生长因子梯度,其高代谢需求主要依赖糖酵解供能。研究^[13-14]发现,糖酵解关键酶6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶3(6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, PFKFB3)通过维持高水平的糖酵解通量,驱动内皮尖端细胞的伪足伸展与定向迁移。当PFKFB3被抑制时,内皮迁移受限,血管分支数目显著减少,提示PFKFB3驱动的糖酵解是血管芽生的必要条件。此外,糖酵解中间产物参与细胞骨架重塑与细胞间黏附调节。糖酵解增强可促进ATP在局部富集于前沿

伪足区域,驱动肌动蛋白聚合及细胞伸展。部分代谢酶(如烯醇化酶、丙酮酸激酶M2)还可在细胞质或细胞核中执行非代谢功能,调控细胞黏附分子表达与迁移相关基因转录^[15-17]。此类能量分配的空间特异性保证了细胞在血管分支形成时的方向性迁移与协调性。VEGF可通过蛋白激酶B(protein kinase B,

Akt)/mTOR通路上调PFKFB3表达,增强糖酵解通量,从而促进内皮细胞迁移与增殖^[18-20]。反之,Notch信号则通过抑制PFKFB3降低糖酵解速率,使柄细胞保持低代谢稳态,保证血管分支的维持^[13-14, 21]。因此,糖酵解被视为内皮亚型分化与血管形态建构的重要代谢“开关”(图2)。

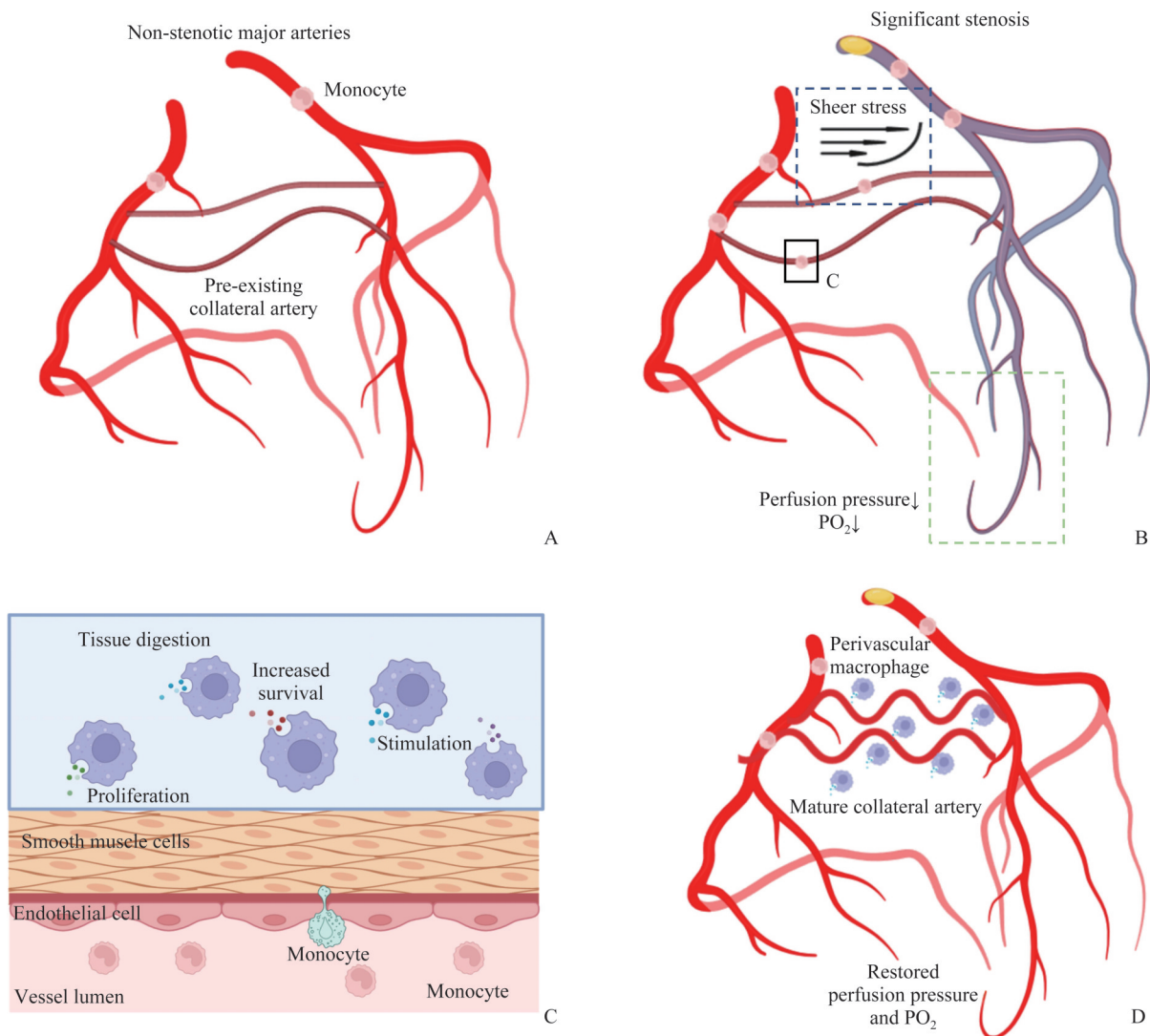


图1 冠脉侧支循环形成机制

Figure 1 Mechanism of coronary collateral circulation formation

A: Pre-existing collateral artery. B: Significant stenosis: Increased shear stress across pre-existing collateral arterioles triggers macrophage recruitment. C: Macrophages secrete pro-proliferative factors to promote collateral artery formation. D: Mature collateral artery restores blood perfusion. PO_2 : Partial pressure of oxygen.

1.2 脂质代谢与内皮功能

尽管糖酵解为内皮细胞的爆发性迁移提供了即时动能,然而,除ATP供应外,内皮细胞在增殖与管腔重塑过程中还需要充足的生物合成底物,以支持核酸复制、蛋白质更新及细胞膜扩增等过程。因此,血管重塑所需的代谢调控还依赖多种合成代谢

通路的协同参与。其中,细胞膜面积增加和膜结构重塑对脂质原料需求尤为显著,脂质代谢在持续性血管生成过程中具有重要作用。

脂肪酸氧化(fatty acid oxidation, FAO)不仅为内皮细胞提供非糖酵解能量来源,还维持三羧酸(tricarboxylic acid, TCA)循环活性,参与核苷酸合成

与细胞增殖^[22]。与以往认为内皮细胞能量代谢以糖酵解为主的传统观点不同, 近年研究^[22]发现FAO在维持内皮稳态与血管新生中具有独特功能。在分子层面, 肉碱棕榈酰转移酶1A(carnitine palmitoyltransferase 1A, CPT1A)是FAO的限速酶, 介导长链脂酰辅酶A进入线粒体。其核心功能不仅在于供能, 更在于通过补充TCA循环中间产物来支持内皮细胞的核苷酸生物合成与增殖。由此可见, FAO不仅提供能量, 更参与细胞合成代谢的物质供给, 在侧支血管形成中具有结构性代谢意义。

磷脂代谢与膜重塑也是调控内皮细胞可塑性的重要环节^[23-24]。在内皮细胞迁移与芽生过程中, 细胞膜需不断发生形态变化、伪足伸展及膜泡形成, 这

一系列过程依赖于膜脂成分的动态调控。磷脂酰肌醇(phosphatidylinositol, PI)及其磷酸化衍生物可通过磷脂酰肌醇3激酶(phosphoinositide 3-kinase, PI3K)/Akt信号通路调节细胞骨架重排和黏附复合物的组装^[25-26]。磷脂酰胆碱与磷脂酰乙醇胺比例变化则影响膜的流动性与弯曲度, 从而影响迁移速度与细胞极性^[27-28]。研究^[29]提示, 膜脂组成与膜相性质的微小改变会影响内皮细胞对流体剪切力的响应及下游信号转导; 脂质组学的数据和膜相成像研究为后续探讨血流剪切力与代谢耦合提供了新的研究方向^[30-31], 但关于这些脂质改变如何在分子层面整合为代谢信号仍需进一步的机制验证。

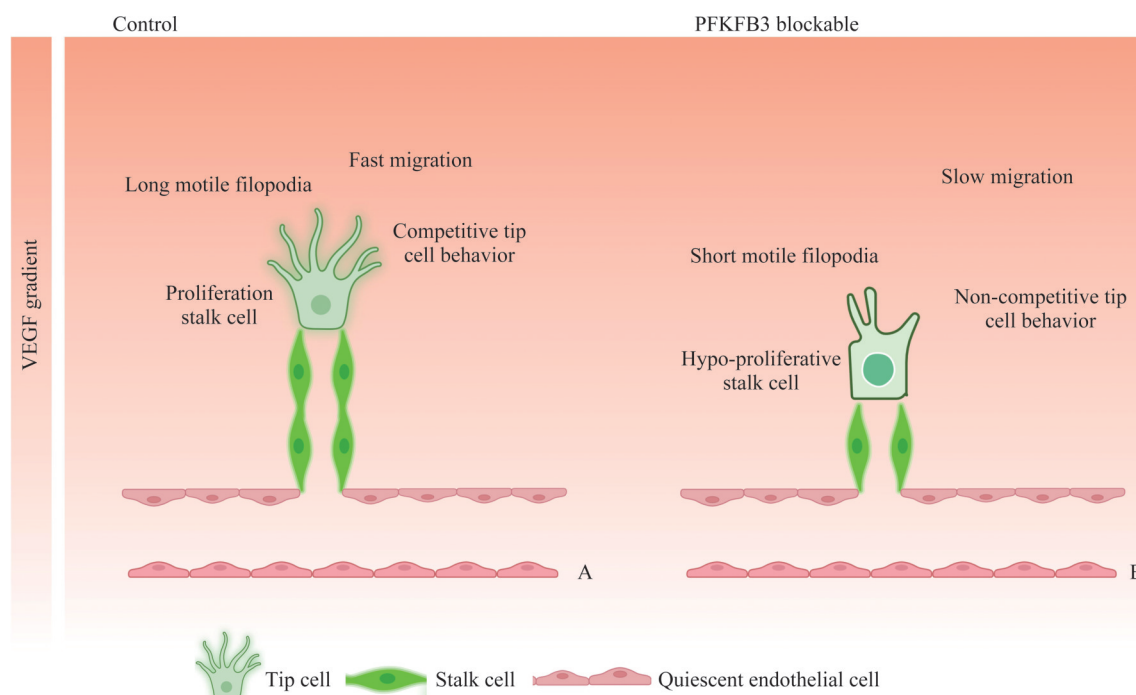


图2 糖酵解与血管再生

Figure 2 Glycolysis and vascular regeneration

A: ECs rely on glycolysis to promote vessel formation. B: Loss of the glycolytic activator PFKFB3 in ECs impairs vessel formation. VEGF: Vascular endothelial growth factor; ECs: Endothelial cells; PFKFB3: 6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3.

1.3 线粒体代谢与内皮氧化还原稳态

无论是糖酵解的产物还是脂肪酸 β -氧化的产物, 最终均需通过进入线粒体进行TCA循环来满足细胞的生物合成需求与维持氧化还原平衡。线粒体在侧支循环形成中的作用已超越了传统的能量生产范畴。它通过精密的氧化还原监控系统, 将上述代谢产生的化学信号整合为驱动内皮表型转换的分子指令, 从而使内皮细胞对缺血应激具有高灵敏度。

首先, 线粒体代谢在维持 NAD^+ /还原型烟酰胺腺

嘌呤二核苷酸(reduced nicotinamide adenine dinucleotide, NADH)平衡和生物合成中扮演核心角色。通过TCA循环和电子传递链, 线粒体能够调控细胞的氧化还原状态, 从而影响糖酵解速率、脂肪酸氧化及核苷酸合成等代谢通路。研究^[32]显示, 内皮细胞中适度的线粒体活性有助于满足血管再生所需的生物合成需求, 而当线粒体功能受损时, NAD^+ 再生不足会导致细胞代谢紊乱和迁移能力下降。其次, 线粒体来源的ROS是血管生成的重要信号分子^[33-34]。

适度水平的ROS可通过氧化修饰关键蛋白质,激活下游信号通路,如VEGF、缺氧诱导因子-1 α (hypoxia-inducible factor 1 alpha, HIF-1 α)和AMP依赖的蛋白激酶(AMP-activated protein kinase, AMPK),从而促进内皮细胞增殖、迁移^[35]。在冠脉缺血环境中,轻度氧化应激可诱导适应性反应,促进侧支血管的形成和灌注重建。相反,持续或过量的ROS积累会引发线粒体DNA损伤、电子传递链失衡及细胞凋亡,从而抑制血管新生^[32, 36-37]。此外,线粒体的动态平衡(融合与分裂)也与内皮细胞可塑性密切相关。线粒体分裂蛋白在血管萌芽过程中上调,有助于提供局部ATP供给和调节细胞迁移方向^[38];而过度分裂或融合受阻则会削弱细胞对剪切力与代谢应激的适应能力,导致血管结构不成熟^[39-40]。最后,代谢-氧化还原网络的协调对血管成熟度具有决定性意义。在血管形成的早期阶段,ROS介导的信号促进内皮细胞激活与迁移;而在血管重塑与成熟阶段,抗氧化系统需及时介入以清除过量自由基,防止内皮屏障破坏和炎症反应。因而,维持线粒体代谢与氧化还原稳态的动态平衡,是实现内皮细胞从激活态向稳态转变、形成功能性侧支血管的重要条件。

综上所述,糖、脂与线粒体代谢共同构成了内皮细胞表型可塑性的代谢基础。这种代谢网络的动态平衡是侧支循环得以正常建立的基础,而一旦这种平衡被年龄增长或病理生理因素打破,便会导致侧支形成不良。

2 衰老代谢障碍对侧支循环的抑制

衰老是导致冠脉侧支循环形成能力下降的重要生物学因素。随着年龄增长,机体代谢状态、内皮细胞功能及信号调控网络均发生显著改变,最终导致冠脉缺血后的代偿性侧支生成能力显著下降^[41-44]。

2.1 衰老相关代谢改变:糖酵解下降、脂质积累与线粒体功能衰退

在衰老过程中,内皮细胞的代谢特征发生系统性重塑。糖酵解能力下降被认为是限制内皮迁移与血管新生的关键环节。研究^[45-46]表明,老龄内皮细胞中PFKFB3、己糖激酶2(hexokinase 2, HK2)等糖酵解限速酶的表达降低,导致ATP供应不足,从而削弱了细胞在低氧或剪切力刺激下的迁移与分支能力。多项研究^[47-49]表明,衰老伴随组织与细胞层面的脂质代谢失衡,包括内皮细胞中脂滴积聚与脂质处置异常,这与内皮功能障碍、氧化应激、慢性炎症相关。研究^[50]提示,脂质过载可通过诱导线粒体功能损伤、增加ROS与激活炎症通路而损害内皮细胞的迁移和增殖能力;与此同时,衰老相关的FAO与线粒

体代谢异常在多种组织与免疫细胞中被报道,这些代谢改变可能是导致脂质累积与炎症激活的重要背景,但在不同模型中表现出一定的异质性^[51-53]。上述证据支持“脂质代谢和FAO的失衡在老化相关的内皮功能受损与再生能力下降中具有重要作用”,但具体的因果链条和在冠脉侧支形成中的端到端证明仍需更多针对性研究。此外,线粒体功能衰退贯穿于血管衰老的全过程。线粒体DNA损伤、氧化磷酸化效率下降及过量ROS积累,均导致内皮细胞能量供应不足与氧化应激加剧,使其从可塑性状态向衰老表型转变。

2.2 能量感应通路失衡:AMPK、SIRT1与mTOR

内皮细胞衰老与多条能量感应信号通路的失衡密切相关。AMPK作为细胞能量感应器,在能量不足时被激活,促进糖酵解和脂肪酸氧化以恢复能量平衡^[54]。然而,在衰老内皮中,AMPK活性普遍下降,使细胞无法有效应对能量压力^[55]。SIRT1通过去乙酰化调控代谢酶和抗氧化因子,是维持内皮年轻化和代谢稳态的关键蛋白质^[56]。SIRT1表达下降会导致线粒体功能紊乱、一氧化氮(nitric oxide, NO)生成减少及炎症信号上调,从而削弱血管新生能力^[57]。相反,mTOR通路在衰老过程中常持续活化^[58]。mTOR过度活跃抑制自噬和线粒体更新,造成代谢废物累积和氧化应激上升,进一步加速内皮功能衰退^[54](图3)。

2.3 衰老与侧支形成受损的临床与实验依据

老年冠心病患者的冠脉侧支循环发育显著低于年轻患者,即便在相似的血流阻断程度下,老年患者的侧支供血灌注评分明显下降。这提示衰老本身削弱了血管再生的潜能,而不仅仅是合并疾病或危险因素所致。动物实验^[59-60]进一步证实了这一现象:老龄缺血模型小鼠的侧支血管密度、流速恢复及内皮细胞增殖率均明显低于年轻对照组。分子分析显示,老龄动物内皮中AMPK、SIRT1水平均下调,eNOS活性下降,伴随氧化应激升高和炎症因子上调,这些改变共同导致侧支循环形成受阻^[61]。此外,代谢性疾病如糖尿病、肥胖症、代谢综合征常与衰老相伴,其共同特征是代谢灵活性下降和慢性炎症持续存在。衰老通过影响糖酵解、脂质代谢与线粒体功能,引起能量感应通路(AMPK-SIRT1-mTOR)的失衡,从而削弱内皮细胞的代谢可塑性和血管再生能力。这种代谢与信号的双重退化,是冠脉侧支循环形成能力随年龄增长而下降的根本机制。未来研究应聚焦于恢复代谢感应网络平衡及线粒体功能重塑,以探索延缓血管老化、改善侧支循环的新干预方向。

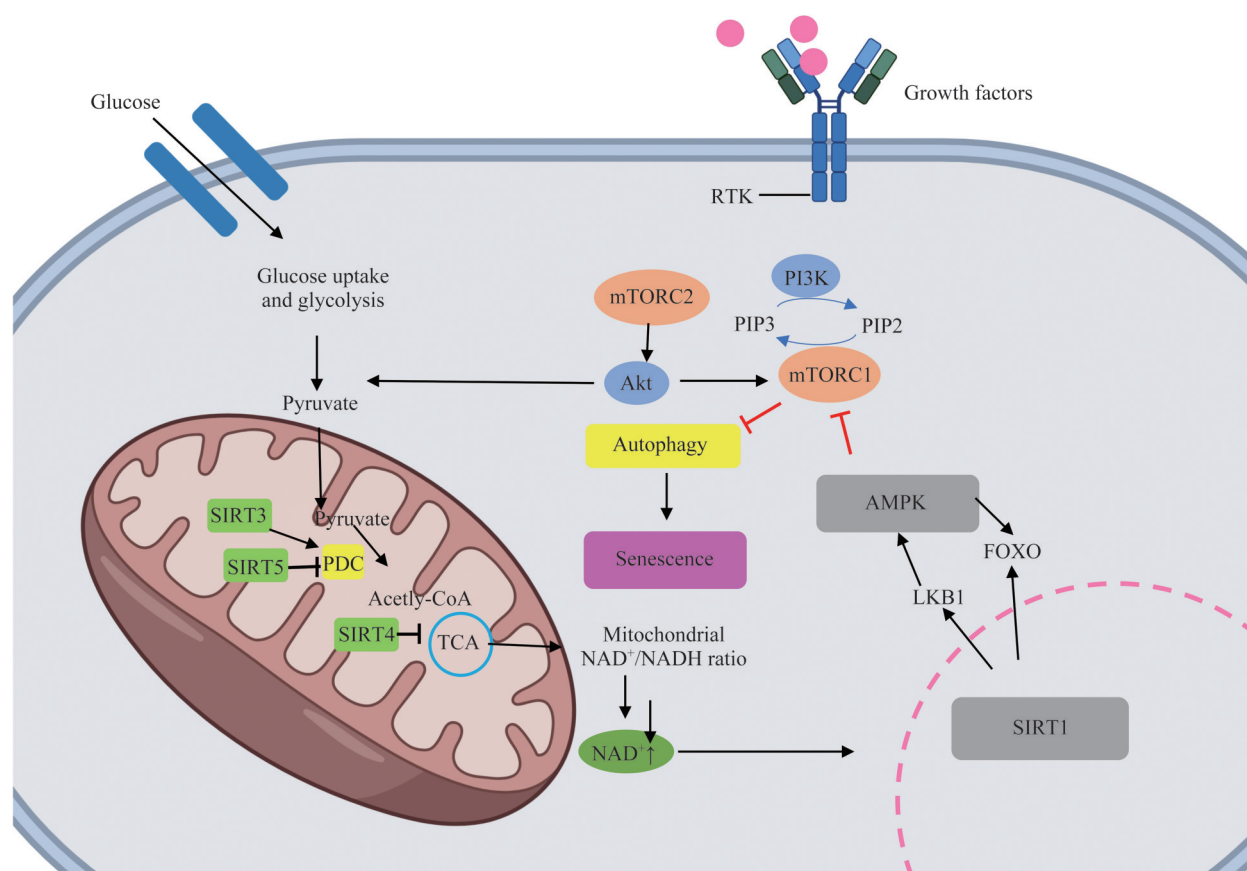


图3 内皮细胞衰老与能量感应通路失衡

Figure 3 Aging of endothelial cells and imbalance of energy sensing pathways

RTK: Receptor tyrosine kinase; mTORC2: Mammalian target of rapamycin complex 2; PI3K: Phosphoinositide 3-kinase; Akt: Protein kinase B; PIP2: Phosphatidylinositol 4,5-bisphosphate; PIP3: Phosphatidylinositol (3,4,5)-trisphosphate; AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; FOXO: Forkhead box O; LKB1: Liver kinase B1; SIRT: Sirtuins; TCA: Tricarboxylic acid; NAD^+ : Oxidized nicotinamide adenine dinucleotide (oxidized form); NADH: Reduced nicotinamide adenine dinucleotide; LKB1: Liver kinase B1.

3 免疫代谢与侧支循环

冠脉侧支循环的形成不仅依赖内皮细胞的代谢可塑性与机械信号响应, 还受免疫细胞代谢状态的深刻影响。不同免疫细胞亚型的代谢特征决定其在侧支形成中的作用方向, 其中以M2型巨噬细胞的促血管效应最为关键。

缺血组织中的巨噬细胞可分化为促炎的M1型或修复性的M2型。M1型以糖酵解为主, 释放肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)、白细胞介素(interleukin, IL)-1 β 等炎症介质; M2型则依赖FAO与OXPHOS, 分泌IL-10、转化生长因子 β (transforming growth factor- β , TGF- β)、VEGF等因子以促进修复。M2型巨噬细胞通过血管生长因子和基质重塑酶促进内皮迁移和管样结构形成, 从而增强灌注^[62-63]。其依赖FAO代谢产生活性代谢物(如柠檬酸、乙酰辅酶A)调控组蛋白乙酰化, 维持抗炎和促

血管表型^[22, 64]。巨噬细胞与内皮细胞之间存在紧密的代谢信号耦合。在缺血条件下, HIF-1 α 被激活: 在巨噬细胞中促进糖酵解与乳酸生成, 在内皮中诱导VEGF、ANGPT2等基因表达以驱动血管新生^[65-67]。M2型巨噬细胞分泌的IL-10和TGF- β 可通过STAT3-SIRT1轴上调内皮线粒体生物发生、抗氧化防御及脂肪酸代谢, 维持血管稳定^[68]。这种免疫-代谢互动维持炎症与修复间的动态平衡。在慢性缺血或老龄化组织中, 免疫代谢常出现糖酵解持续激活、FAO受阻的失衡状态, 使巨噬细胞长期维持M1型促炎表型^[69]。过量乳酸、琥珀酸可激活NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor pyrin domain containing 3, NLRP3)炎症小体, 形成正反馈抑制M2型巨噬细胞转化并损伤内皮^[70]。铁死亡及脂质过氧化积聚进一步破坏巨噬细胞与内皮功能, 削弱血管生成与成熟^[71]。总体而言, 免疫代谢通过重塑巨噬细胞功能, 调控其与内皮细胞剪切力信号的耦合, 进而

深度参与侧支循环调控。维持M2型FAO/OXPHOS代谢并矫正炎症性代谢失衡,可能成为改善缺血性心脏病血管重建的重要策略^[72](图4)。

效应性T细胞依赖糖酵解支持增殖与炎症反应,而调节性T细胞(regulatory T cells, Tregs)主要依赖FAO和OXPHOS,具有免疫抑制与组织保护作用^[73]。缺血心肌中Tregs聚集与毛细血管密度及心功能恢复呈正相关^[74]。Tregs通过IL-10、VEGF-A及AMPK-SIRT1通路改善内皮线粒体稳态并抑制炎症^[75-76]。相反,糖酵解活跃的效应性T细胞产生 γ 干扰素(interferon- γ , IFN- γ)、TNF- α 等因子,导致内皮损伤与血管再生受抑^[77]。因此,T细胞代谢分化构成缺血

修复中的关键免疫调控环节。

未成熟树突状细胞(dendritic cell, DC)依赖OXPHOS与FAO维持稳态,激活后则转向糖酵解以增强抗原呈递和炎症反应^[78-79]。此转变虽强化免疫反应,却抑制血管修复;抑制mTOR或增强FAO可使DC趋向耐受性表型,减轻内皮损伤^[80-81]。中性粒细胞早期依赖糖酵解供能,其过度活化可产生ROS损伤血管,但部分N2型亚群通过脂质代谢与中性粒细胞胞外诱捕网(neutrophil extracellular traps, NETs)释放促进血管生成,提示其不同阶段可能具有双向作用^[82-83]。

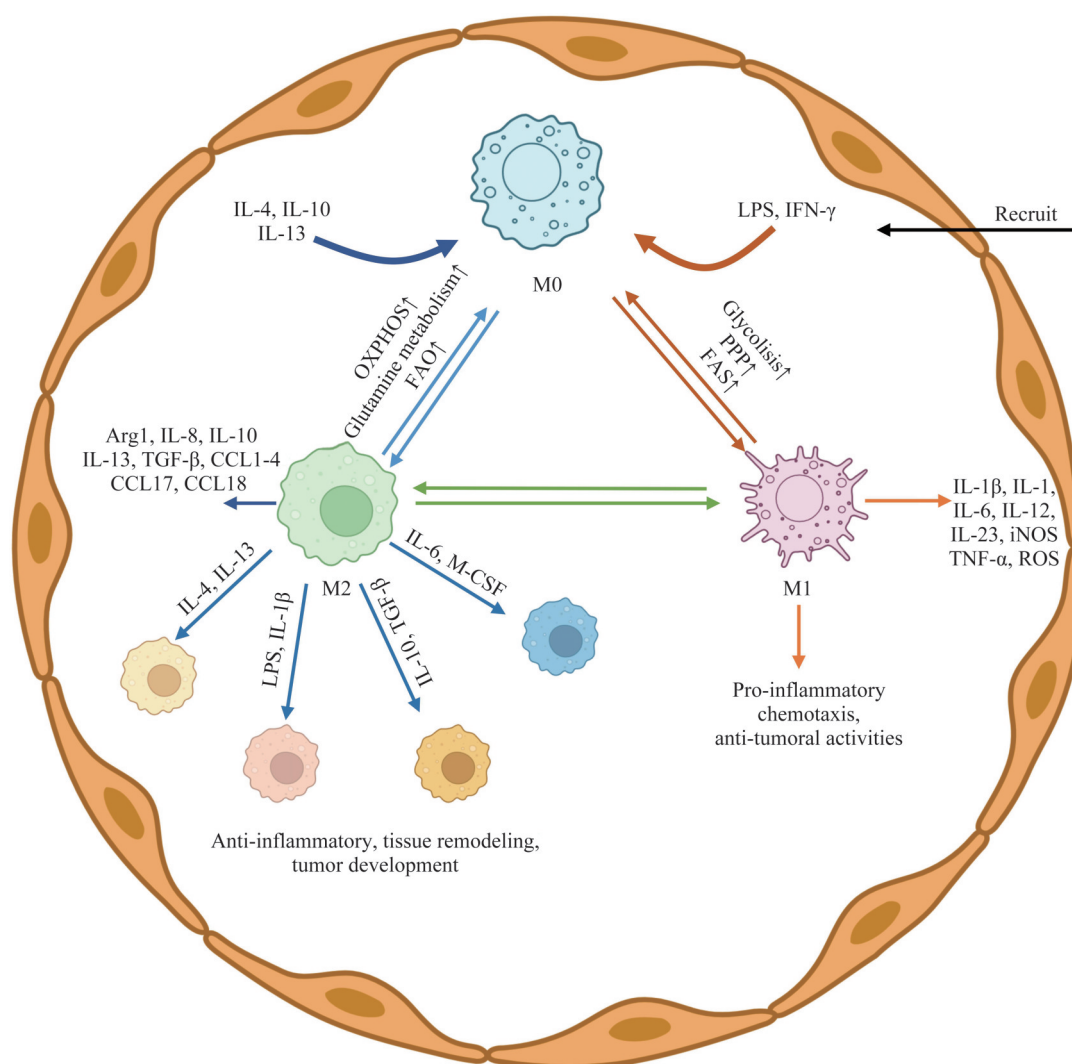


图4 巨噬细胞表型转换与代谢调控

Figure 4 Phenotypic transformation and metabolic regulation of macrophages

IL: Interleukin; LPS: Lipopolysaccharide; IFN- γ : Interferon-gamma; iNOS: Inducible nitric oxide synthase; OXPHOS: Oxidative phosphorylation; FAO: Fatty acid oxidation; PPP: Pentose phosphate pathway; FAS: Fatty acid synthase; ROS: Reactive oxygen species; TNF- α : Tumor necrosis factor-alpha; Arg1: Arginase-1; CCL: Chemokine (C-C motif) ligand; TGF- β : Transforming growth factor-beta; M-CSF: Macrophage colony-stimulating factor.

4 代谢干预策略

代谢重编程不仅决定细胞能量供应方式,也深刻影响其表型与功能。针对衰老和缺血状态下侧支循环形成受损的代谢失衡,调控免疫与内皮细胞代谢状态被认为是重塑促血管新生微环境的重要方向。

M2型巨噬细胞代谢依赖FAO与线粒体OXPHOS,支持其抗炎与修复表型,促进侧支形成,因此,FAO/OXPHOS上调促进替代激活和促血管因子分泌^[62]。缺血或低氧激活HIF-1 α ,增强糖酵解和促血管因子(如VEGF、ANGPT2)表达^[84];而IL-10、TGF- β 等抗炎因子可通过SIRT1-AMPK通路提升线粒体代谢与抗氧化能力,改善内皮功能和血管稳定性^[85-86]。HIF-1 α 与SIRT1的动态平衡被视为维持血管再生的关键节点:前者驱动能量供应应对低氧,后者维持线粒体稳态,二者协同决定侧支循环的质量与持续性。

在衰老或代谢紊乱状态下,糖酵解过度、OXPHOS受损及铁稳态失衡会削弱巨噬细胞的修复极化并诱导铁死亡,导致内皮损伤、脂质过氧化及血管成熟受阻。基于此,恢复线粒体代谢、抑制铁死亡及改善脂质稳态成为新型干预策略^[87]。动物与临床研究^[88-89]表明,激活AMPK、增强FAO或提升NAD⁺水平(如二甲双胍、白藜芦醇、吡格列酮等)均可改善缺血组织血流恢复、提高内皮功能并减少炎症反应。未来研究需明确代谢通路在侧支形成各阶段的时间特异性,以推动代谢重塑在血管再生领域的精准应用。

5 展望

冠脉侧支循环的形成是机体在心肌缺血状态下的一种关键代偿机制,对维持灌注、减轻梗死范围及改善预后具有重要意义。近年来,代谢生物学的发展为理解侧支循环形成的分子基础提供了新的视角。能量代谢、氧化还原平衡及免疫代谢重编程在内皮细胞的机械感知、迁移与重塑中均发挥核心作用。

当前研究多聚焦于代谢通路的静态描述,忽视了代谢干预的时空特异性。冠脉侧支循环的形成是一个涵盖剪切力响应启动、内皮芽生进展及血管重塑成熟的动态过程。未来的研究重点应从单一途径的“开启”或“关闭”转向对代谢开关的精准调控:在侧支形成早期,需重点强化由PFKFB3驱动的糖酵解通量以提供芽生动力;在血管重塑后期,则应转向维持线粒体氧化还原稳态,以确保侧支血管的结

构稳定与长期存续。

关于冠脉侧支循环代谢调控的研究虽不断深入,但在模型可靠性、机制整合性及时空分辨率等方面仍存在明显局限。首先,不同动物模型和实验条件间存在显著差异。多数研究^[90-91]依赖小鼠或大鼠的缺血模型,但其冠脉解剖结构与人类存在本质区别,其结果在临床转化中具有不确定性。其次,侧支形成的代谢机制研究相对碎片化,往往聚焦于单一通路(如糖代谢、脂代谢或氧化应激),缺乏系统性的能量网络解析。再次,目前尚缺乏能同时反映细胞类型特异性与空间分布特征的研究,难以精准揭示侧支形成中不同细胞间代谢互作的动态过程。

在技术层面,未来应突破传统整体组织代谢分析的局限,深度结合“空间多组学”与“动态代谢流监测”技术。在单细胞甚至亚细胞水平上,实时绘制侧支循环形成过程中的代谢全景图,从而精准识别驱动血管再生的代谢亚群。针对代谢干预的“脱靶”风险,应探索利用靶向纳米材料或外泌体载体,实现对特定细胞类型(如内皮细胞或M2型巨噬细胞)的分阶段精准给药,为临床转化提供更具可操作性的方案。

随着代谢干预理念的兴起,代谢调控已成为促进冠脉侧支循环的新突破口。靶向AMPK、SIRT1、PPAR通路的药物,以及能够改善线粒体稳态、抑制氧化应激的化合物,均展现出改善内皮功能与促进血流重建的潜力。未来的代谢干预不应局限于全局性的代谢增强,而应聚焦于组织特异性代谢调节。例如,研发仅在低氧或高剪切力环境下激活的代谢修饰药物,或利用纳米载体将PFKFB3激动剂精准递送至缺血冠脉末梢,以规避全身性代谢干预可能带来的毒副作用。此外,建立基于循环代谢物谱的侧支代偿能力评估模型,将有助于实现冠心病患者预后的个体化精准分层。综上所述,代谢调控为理解与促进侧支循环提供了新的研究范式。通过多组学技术整合与代谢信号网络解析,未来有望实现对冠脉侧支形成过程的动态调控,从而为心肌缺血性疾病的防治开辟新的方向。

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