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低氧与氧化还原平衡耦合在组织再生中的作用

柳瑞璇[1,2]，周　炳[1,3]*
(1 北京航空航天大学医学科学与工程学院，北京 100191；2 北京航空航天大学生物与医学工程学院，北京 100191；3 北京航空航天大学北京大数据精准医学先进创新中心，北京 100191)

摘　要：在神经系统中，中枢神经或周围神经损伤引发线粒体功能障碍，导致能量代谢紊乱，继而出现氧化应激和炎症反应，使神经再生极为困难。研究表明，低氧环境广泛存在于组织再生、伤口愈合、免疫反应和肿瘤生长过程中。在低氧条件下，细胞通过代谢重编程适应能量需求和代谢物的重新分配，并调节关键代谢物来维持氧化还原平衡。因此，低氧环境下的代谢适应与氧化还原平衡是组织再生的关键。本文综述了低氧与氧化还原平衡在再生过程中的代谢耦合机制，为组织再生，尤其是神经再生的研究提供新思路。

关键词：低氧；代谢重编程；氧化还原平衡；代谢耦合；再生
中图分类号：{Q28}　　**文献标志码：**A

The role of hypoxia and redox balance coupling in tissue regeneration

LIU Rui-Xuan[1,2], ZHOU Bing[1,3]*
(1 School of Medicine and Engineering, Beihang University, Beijing 100191, China; 2 School of Biological Science and Medical Engineering, Beihang University, Beijing 100191, China; 3 Beijing Advanced Innovation Center for Big Data-Based Precision Medicine, Beihang University, Beijing 100191, China)

Abstract: In the nervous system, central or peripheral nerve injuries induce mitochondrial dysfunction, resulting in energy metabolism disorders, which subsequently cause oxidative stress and inflammatory responses, making nerve regeneration extremely difficult. Studies have shown that hypoxic environments are widely present in tissue regeneration, wound healing, immune responses, and tumor growth. Under hypoxic conditions, cells adapt to energy demands and the redistribution of metabolites through metabolic reprogramming and regulate key metabolites to maintain redox balance. Therefore, adaptation and redox balance in hypoxic environments are crucial for tissue regeneration. This review focuses on the metabolic coupling mechanisms of hypoxia and redox balance in the regeneration process, providing new insights for research on tissue regeneration, particularly nerve regeneration.

Key words: hypoxia; metabolic reprogramming; redox balance; metabolic coupling; regeneration

神经系统损伤往往会导致认知、感觉和运动功能的永久性缺陷，严重影响生活质量。在这种情况下，神经再生对于神经回路的修复和患者运动、认知功能的恢复至关重要[1]。促进神经再生不仅有助于减轻损伤后的病理变化，如神经元死亡[2]，而且对于揭示神经系统生长发育和损伤修复机制以及神经系统疾病的治疗具有重要意义。

氧气是细胞呼吸和能量产生的主要驱动力，低氧环境限制了氧气供应，对生物体构成挑战。为了适应低氧环境，细胞通过激活低氧诱导因子(hypoxia-inducible factor, HIF)调控葡萄糖代谢[3]和细胞存活[4]相关基因的表达。近年来，低氧对组织再生的影响已引起广泛关注。其中，代谢重编程和免疫反应等是促进组织再生的重要机制。

氧化还原平衡在保持代谢稳态中起着核心作用，涉及糖酵解、三羧酸(tricarboxylic acid, TCA)

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***通信作者：**E-mail: zhoub2@hotmail.com

循环和氧化磷酸化等过程[5, 6]。研究表明，维持氧化还原平衡有利于促进组织再生[7]。最近的研究发现，氧化还原平衡与低氧调控的代谢有关[8]。低氧会导致细胞代谢重编程和 HIF 激活，产生活性氧 (reactive oxygen species, ROS)。低氧诱导的 ROS 可以作为信号分子，参与调控氧化还原平衡，从而促进组织再生[9, 10]。

本文旨在综述再生过程中低氧和氧化还原平衡的代谢机制，并进一步阐明这两者之间的代谢耦合关系。通过深入理解这些过程，我们希望揭示细胞在再生环境中如何调节代谢，以期为神经系统损伤的治疗提供理论基础和新的策略。

1 低氧环境对细胞代谢的影响

低氧环境指组织或细胞暴露于低于正常氧 (约 21% 氧分压) 的状态，其氧分压通常介于 1%~5%[11]。低氧环境在多种生理和病理过程中发挥关键作用。Storz 等[12] 研究发现，高原环境中的大气压降低导致氧气分压下降，人体为了适应这种低氧状态，会通过增加红细胞数量改善血氧运输能力。此外，胚胎早期发育阶段的低氧环境对干细胞的增殖和分化至关重要[13]。在肿瘤微环境中，由于血管生成不足，快速增长的肿瘤细胞常处于低氧状态[14]。在组织损伤修复过程中，局部低氧环境能够通过调控干细胞活性和代谢重编程促进组织再生与修复[15]。然而，细胞在低氧环境下由于氧气供应不足，必须调整其代谢途径以适应这一挑战。最显著的代谢变化是细胞从依赖氧气的 TCA 循环和氧化磷酸化转向糖酵解途径，以确保能量供应的持续性以及通过合成代谢产生细胞生长构件 (building block)[16]。

1.1 低氧环境下细胞的代谢机制

1.1.1 HIF-1α的激活

为了应对低氧环境，细胞启动代谢调节机制。其中，HIF 是关键的调节因子，在低氧条件下被激活[17]。细胞通过 HIF-1 感知和适应氧气变化。HIF-1 异二聚体转录因子由 HIF-1α 和 HIF-1β 两个亚单位构成。在常氧条件下，HIF-1α 被脯氨酸羟化酶 (prolyl hydroxylases, PHDs) 羟基化，随后与 von Hippel Lindau (VHL) 蛋白结合，这一过程最终导致 HIF-1α 蛋白的泛素化并通过蛋白酶体降解。然而，当细胞处于低氧环境时，PHDs 的活性下降，导致 HIF-1α 羟基化减少，从而避免了与 VHL 结合。因此，HIF-1α 亚基得以稳定积累并转运至细胞核，与 HIF-1β 结合形成异二聚体，进而激活下游基因的转录 (图 1)[18]。

1.1.2 增强糖酵解途径

细胞在低氧环境中为了快速生成三磷酸腺苷 (adenosine triphosphate, ATP) 以提供能量，会通过稳定 HIF-1α 来诱导代谢重编程，从而增强糖酵解过程[19]。在此条件下，低氧环境以及双尾同源物 1 (bicaudal D homolog 1, BICD1) 和醛脱氢酶 3 A1 (aldehyde dehydrogenase 3A1, ALDH3A1) 的过表达，或甲硫腺苷磷酸酶 (methylthioadenosine phosphorylase, MTAP) 的敲除，都有助于稳定 HIF-1α[20-22]。低氧通过 HIF 依赖的机制激活一系列关键转录因子，包括 Kruppel 样因子 4 (Kruppel-like factor 4, KLF4)、SRY 盒转录

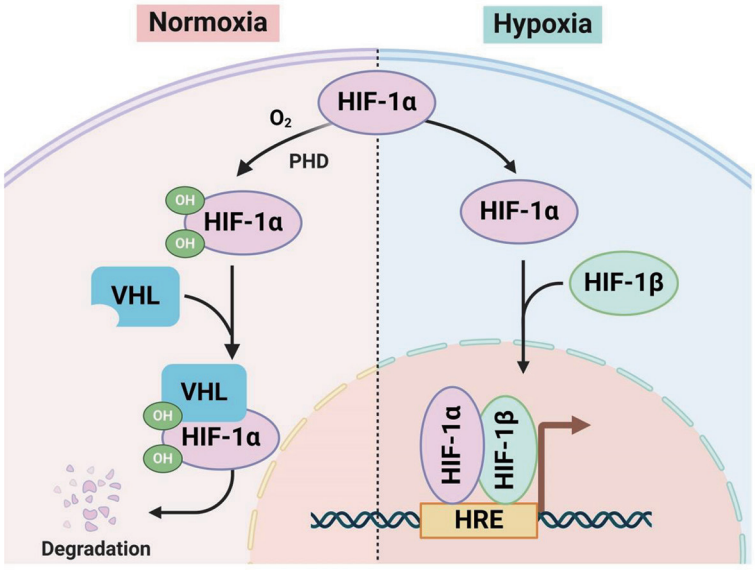

图1 常氧和低氧条件下HIF-1α调控机制示意图

因子 2 (SRY-box transcription factor 2, SOX2)、八聚体结合转录因子 4 (octamer-binding transcription factor 4, OCT4)、Lin-28 同源物 A (lin-28 homolog A, Lin28A) 和 Nanog 同源盒 (Nanog homeobox, Nanog)，从而诱导代谢重编程并促进细胞的去分化和增殖 [23, 24]。具体来说，HIF-1α 通过激活葡萄糖转运蛋白 1 (glucose transporter 1 protein, GLUT1)、己糖激酶 2 (hexokinase 2, HK2)、丙酮酸激酶 M2 (pyruvate kinase M2, PKM2)、乳酸脱氢酶 A (lactate dehydrogenase A, LDHA)、单羧酸转运蛋白 4 (monocarboxylate transporter 4, MCT4)、溶质载体家族 2- 成员 -4 基因 (solute carrier family-2-member-4-gene, Slc2a4) 和溶质载体家族 2- 成员 -1 基因 (solute carrier family 2 member 1, Slc2a1)，促进葡萄糖的摄取、增强糖酵解和增加乳酸产生 (图 2)[25-30]。在组织再生过程中，HIF-1α 通过代谢重编程激活与损伤反应和再生相关的基因，如血管内皮生长因子 A (vascular endothelial growth factor A, VEGFA) 和磷酸二酯酶 1B (phospho-diesterase 1b, PDE1B)(图 2)[31, 32]。这种代谢重塑在组织修复和再生中起到了重要作用。

1.1.3　抑制氧化磷酸化

氧化磷酸化是细胞能量代谢的核心过程，它依赖于氧气作为电子传递链的最终受体。在低氧环境下，细胞为了适应氧气供应的不足，会抑制线粒体的氧化磷酸化过程。Kim 等 [33] 的研究表明，HIF-1α 通过激活丙酮酸脱氢酶激酶 1 (pyruvate dehydrogenase kinase 1, PDK1) 的表达，进而抑制丙酮酸脱氢酶 (pyruvate dehydrogenase, PDH) 的活性。这一变化阻断了丙酮酸进入 TCA 循环，导致代谢通量转向糖酵解。此外，AMP 活化蛋白激酶 (AMP-activated protein kinase, AMPK) 水平的下降会引起 HIF-1α 水平的升高，这促进了脂肪酸和蛋白质的生物合成，并伴随着氧化磷酸化的降低 [34]。microRNA (miRNA) 也是调控氧化磷酸化的重要因子。例如，miR-424 通过降低异柠檬酸脱氢酶 3α (isocitrate dehydrogenase 3α, IDH3α) 表达，抑制氧化磷酸化 [35]。Jin 等 [36] 发现，HIF-1α 可以直接与三个 miRNA (miR-23a、miR-27a 和 miR-24) 的启动子结合，特异性地抑制 TCA 循环中的关键代谢酶，从而实现从氧化磷酸化向糖酵解的代谢转换。长期低氧或慢性 HIF-1α 激活还会进一步损害线粒体能量代谢功能 [37]。这表明，尽管在低氧条件下细胞倾向于依赖糖酵解来产生能量，但线粒体在代谢中间体的生成、ATP 的补充合成以及细胞凋亡调控方面仍然发挥着不可或缺的作用 [38]。此外，HIF-1α 长时间表达会导致新生儿缺血缺氧性脑损伤 [39]。

1.1.4　其他代谢途径

细胞还通过调节其他代谢途径适应低氧环境。Sun 等 [40] 研究发现，肝脏中甘油三酯和游离脂肪酸

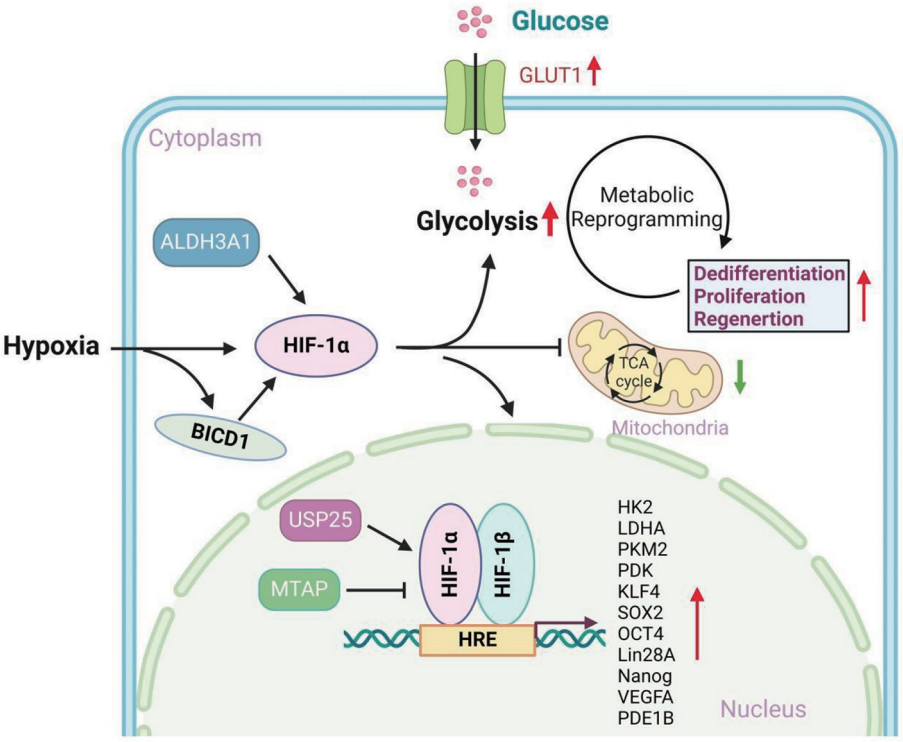

图2　低氧通过诱导代谢重编程调控细胞的去分化、增殖和再生

的积累增加，表明脂肪酸代谢增强。Olkowicz 等 [41] 研究发现，在动脉粥样硬化性血脂异常小鼠心脏中，细胞的能量生成主要依赖脂肪酸氧化，而不是依赖于糖酵解。Li 等 [42] 研究表明，心肌细胞中脂肪酸氧化的缺失可以提高抗低氧能力，刺激心肌细胞增殖，使缺血 - 再灌注损伤后心脏再生。谷氨酰胺代谢在低氧环境中有助于调节能量代谢。Smith 等 [43] 研究发现，线粒体谷氨酸丙酮酸转氨酶 2 (glutamate pyruvate transaminase 2, GPT2) 是糖酵解和 TCA 循环的重要连接点，可激活糖酵解并促进谷氨酰胺回补到 TCA 循环。Shigeta 等 [44] 研究表明，IDH2 诱导还原性谷氨酰胺代谢，增强有氧糖酵解和磷酸戊糖途径 (pentose phosphate pathway, PPP)。

以上研究表明，低氧环境通过增强糖酵解、抑制氧化磷酸化以及动员脂肪酸代谢等途径适应能量需求。这些适应性反应有助于生物体在低氧环境下生存，但同时也可能导致一些病理生理变化。例如，在阿尔茨海默病的进展过程中，观察到糖酵解代谢表型得到显著增强 [45]。

1.2 低氧对细胞表型和组织再生的代谢与免疫调控机制

成熟的细胞可以通过去分化、增殖和再分化重新进入细胞周期从而形成新的细胞发挥功能 [46]。低氧环境通过代谢和免疫调控机制，显著影响细胞表型和组织再生 (图 3)。在代谢层面，低氧促进细胞经历去分化，恢复至更原始的未分化状态，赋予成熟细胞干细胞样特性，支持组织再生 [42]。例如，α- 烯醇化酶的过表达激活 α 丝氨酸 / 苏氨酸蛋白激酶 (RAC-α serine/threonine-protein kinase, AKT) 通路，推动细胞向糖酵解的代谢重编程及去分化 [47]。同时，表观遗传修饰如 DNA 甲基化在低氧 / 缺血诱导神经再生中发挥重要作用 [48]。miR-34a 和线粒体丙酮酸转运体 (mitochondrial pyruvate carrier, MPC) 缺失调节组蛋白甲基化，促进细胞去分化，改善脑损伤后的认知功能 [49, 50]。心肌梗死后，α- 酮戊二酸通过含十字形结构域蛋白 -3 (Jumonji domain-containing protein 3, JMJD3) 依赖性去甲基化促进心肌细胞增殖和心脏再生 [51]。

在免疫层面，低氧调节免疫反应以促进细胞增殖 [52]，如巨噬细胞通过分泌 VEGFA 响应低氧，维持免疫系统稳态 [53]；通过髓系细胞触发受体 1 (triggering receptor expressed on myeloid cells 1, TREM-1) 和 mTOR/HIF-1α 途径激活核苷酸结合域样受体蛋白 3 (nucleotide-binding domain (NOD)-like receptor protein 3, NLRP3) 炎症小体 [26]，以及通过 Toll 样受体 3 (Toll-like receptor 3, TLR3)- 核因子 κB (nuclear factor-κB, NF-κB) 信号通路促进 HIF-1α 表达，增强糖酵解和谷氨酰胺水解，帮助 T 细胞适应能量需求 [54, 55]。低氧还通过白细胞介素 4 (interleukin-4, IL-4) 和 TLR2 途径调节免疫反应，促进炎症消退和组织修复 [56, 57]。然而，持续的低氧刺激也可能抑制 T 细胞功能，促进肿瘤生长 [58]。总之，低氧环境通过调控代谢途径影响免疫反应，促进细胞增殖和组织再生。

2 氧化还原平衡与再生过程

氧化还原平衡是指细胞内氧化剂和还原剂之间的平衡状态，是细胞代谢的关键因素。氧化还原平衡失调 (如过度产生 ROS) 会导致细胞损伤和死亡，从而抑制再生。因此，维持氧化还原平衡对于促进细胞增殖和组织修复至关重要。氧化还原平衡主要通过维持烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, NAD^+)/ 还原型烟酰胺腺嘌呤二核苷酸 (reduced nicotinamide adenine dinucleotide, NADH) 比值、调控氧化还原信号和提供抗氧化防御代谢机制促进细胞增殖和组织再生 (图 4)。

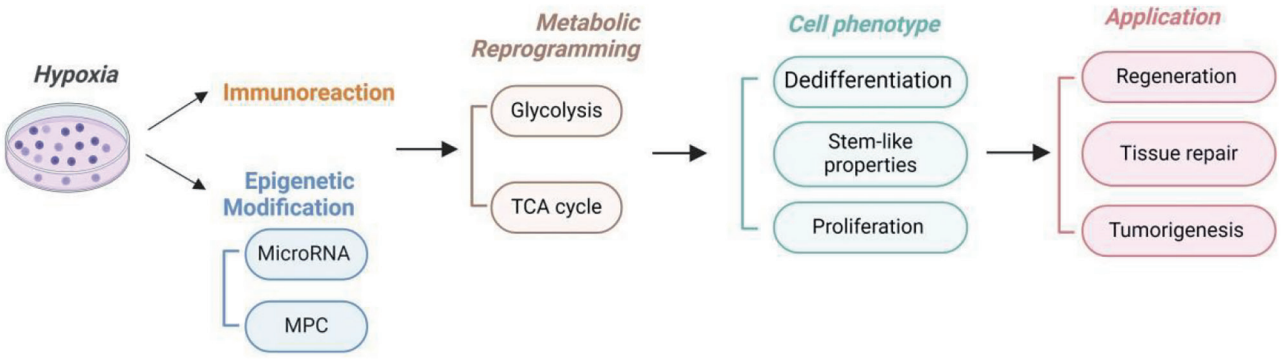

图3 低氧环境下代谢重编程对细胞表型的影响

2.1　NAD⁺/NADH比值

NAD⁺ 及其还原形式 NADH 是细胞内关键的氧化还原对。NAD⁺ 作为氧化剂，在糖酵解、TCA 循环和氧化磷酸化等代谢途径中发挥关键作用，为细胞提供能量，并维持细胞内的氧化还原状态稳定。NADH 则作为还原剂，通过电子传递链将电子传递给氧气，生成 ATP。NAD⁺/NADH 比值的变化直接影响细胞的氧化还原状态，调控细胞增殖、再生和修复过程。

高水平的 NAD⁺ 有助于维持代谢稳态。在低氧环境下，激活磷脂酰肌醇 3- 激酶 (phosphoinositide 3-kinase, PI3K)-AKT 通路可以稳定 HIF-1α 并降解肿瘤抑制蛋白 p53 (tumor suppressor p53)，维持细胞内 NAD⁺/NADH 比值的平衡，促进细胞增殖 [59]。HIF-1α 还可通过促进环状 RNA MYH9 (circular RNA MYH9, CircMYH9) 的表达来抑制 p53，从而提高 NAD⁺/NADH 比值 [60]。Kalucka 等 [61] 及 Yuan 等 [62] 研究表明，NAD⁺ 的再生有助于维持内皮细胞静息状态和血管保护，并且改善衰老人骨髓间充质干细胞 (human mesenchymal stem cells, hMSCs) 的氧化还原平衡，恢复其活力及促进组织再生。NAD⁺ 水平下降或 NADH 过多会导致氧化应激积累，与疾病发展相关。例如，降低溶质载体家族 25- 成员 -51 基因 (solute carrier family 25 member 51, SLC25A51) 水平会导致线粒体内 NAD⁺ 水平降低，从而显著增加急性髓细胞性白血病 (acute myeloid leukemia, AML) 细胞的凋亡 [63]。

NAD⁺ 是长寿蛋白去乙酰化酶 (sirtuin, SIRT) 家族的必需辅因子。通过改变 NAD⁺/NADH 比值，可以调节 SIRT1 和 SIRT2 的活性，从而调控氧化应激、炎症反应和组织修复。Li 等 [64] 研究表明，羟基红花黄色素 A (hydroxysafflor yellow A, HSYA) 通过增加 NAD⁺/NADH 比值以恢复 SIRT1 活性，保护脑微血管内皮细胞免受氧化应激。Zhang 等 [65] 研究发现，巨噬细胞中的 NAD⁺ 增加通过维持线粒体电子传递链的氧化还原平衡，激活 SIRT1 与前 B 细胞白血病同源盒蛋白 1 (pre-B-cell leukemia homeobox 1, PBX1)，诱导抗炎重编程，促进心脏损伤后的组织修复。

小分子化合物如丹参酮 IIA (tanshinone IIA)[66]，通过减少巨噬细胞的糖酵解并提高其 NAD⁺/NADH 比值，增强 SIRT2 活性，从而抑制炎症反应。反过来，SIRT1 也调控 NAD⁺ 的水平，通过阻断糖酵解激活 SIRT1，即使在低氧条件下也能抑制 HIF-1α，恢复 NAD⁺ 水平 [67]。另有研究发现，在缺血性脑损伤后，星形胶质细胞通过一氧化碳释放分子 -2 (carbon monoxide releasing molecule-2, CORM-2) 激活 SIRT1，

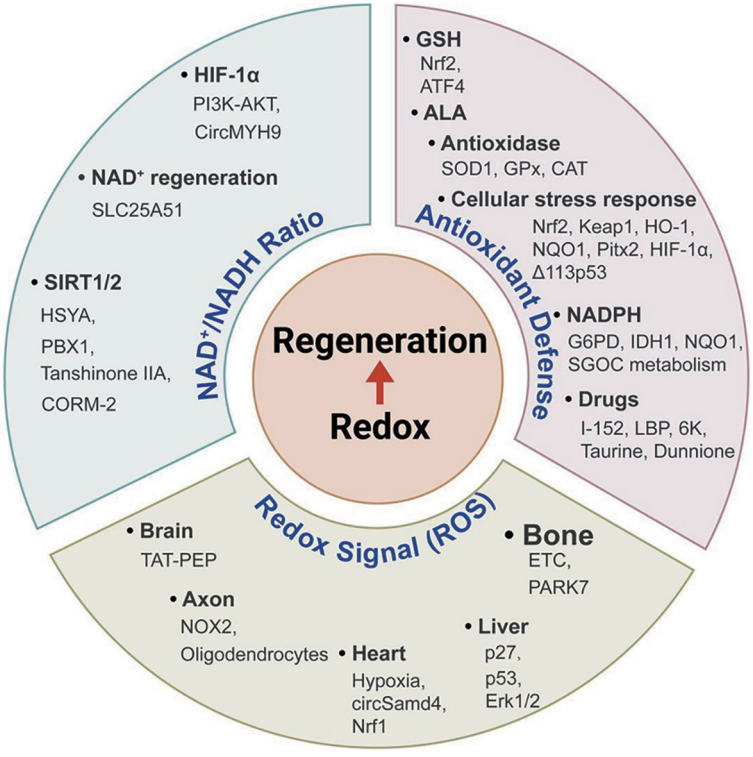

图4　氧化还原平衡促进组织再生的代谢机制

增加 NAD^+ 生物合成，促进 VEGF 的表达 [68]。这些研究表明，维持 NAD^+/NADH 平衡在改善氧化应激和调控炎症反应、细胞增殖、组织再生与修复中的关键作用。

2.2 氧化还原信号

ROS 作为细胞内重要的氧化还原信号分子，在调节氧化还原平衡和促进组织再生中发挥重要作用。ROS 包括超氧化物阴离子 ($O_2^{\cdot}$)、过氧化氢 (H_2O_2) 和羟基自由基 ($^{\cdot}OH$) 等类型，主要在细胞代谢过程中产生，尤其是在线粒体内。适量的 ROS 对细胞信号转导、基因表达和免疫反应是必要的，但过量的 ROS 则会导致氧化应激、损伤细胞结构，并与多种疾病的发生发展密切相关 [69, 70]。

在生理条件下，ROS 的适度增加对组织再生具有积极作用。Hervera 等 [71] 研究发现，ROS 通过激活 NADPH 氧化酶 2 (NADPH oxidase 2, NOX2)-PI3K-p-AKT 信号通路，促进背根神经节 (dorsal root ganglion, DRG) 细胞的轴突再生。线粒体来源的 H_2O_2 的短暂增加，通过降低靶基因周期蛋白依赖性激酶抑制剂 p27 (cyclin-dependent kinase inhibitor p27) 的表达，有助于肝脏再生 [72]。此外，少突胶质细胞在神经损伤后通过产生 ROS 启动再生过程，而过度使用抗氧化剂如褪黑素反而抑制这一过程 [73]。

然而，过量的 ROS 持续引发氧化应激，不利于组织再生。多项研究揭示了通过降低 ROS 水平减轻氧化应激促进组织再生的机制。例如，转录激活因子 PirB 细胞外肽 (transactivator of transcription-PirB extracellular peptide, TAT-PEP) 通过降低 ROS 积累，减轻线粒体损伤，改善脑缺血 / 再灌注 (ischemia/reperfusion, I/R) 损伤后的神经功能 [74]。在心脏再生过程中，低氧环境和环状 RNA Samd4 (circRNA Samd4, circSamd4) 的过表达通过抑制线粒体呼吸和阻止线粒体通透性转换孔的开放，减少 ROS 的产生 [75, 76]。Cui 等 [77] 研究发现，核因子 E2 相关因子 1 (nuclear factor erythroid 2-related factor 1, Nrf1) 通过增强抗氧化基因的表达清除过量 ROS，从而减轻心肌损伤和促进心脏再生。此外，p53 通过诱导细胞色素 P450 2A5 (cytochrome P450 2A5, CYP2A5) 和细胞色素 P450 2A6 (cytochrome P450 2A6, CYP2A6) 的表达促进 ROS 解毒，减轻氧化应激对肝细胞的损伤 [78]。Lao 等 [79] 发现，激活细胞外信号调节激酶 1/2 (extracellular signal-regulated kinase 1/2, Erk1/2) 有助于维持 NO/ROS 平衡，从而促进肝脏再生。Agriesti 等 [80] 认为，通过降低线粒体呼吸产生的 ROS 可以提高骨再生效率。也有研究报道，帕金森病蛋白 7 (Parkinson disease protein 7, PARK7) 通过促进 Nrf2 入核，激活抗氧化酶基因表达来清除 ROS，从而促进骨髓间充质干细胞 (bone marrow mesenchymal stem cells, BMSCs) 修复股骨头坏死 [81]。

总之，ROS 在维持细胞的氧化还原平衡和促进再生过程中具有双重作用。一方面，适度的 ROS 水平对细胞信号转导和再生过程至关重要；另一方面，过量的 ROS 会引起氧化应激，导致细胞损伤。因此，精准调控 ROS 水平以维持氧化还原平衡是促进组织再生和修复的关键。未来的研究应当关注如何在不同的生理和病理条件下，有效调控 ROS 的生成和清除，以期实现更好的组织再生效果。

2.3 抗氧化防御

抗氧化防御系统构成了细胞和机体对抗氧化应激损害的核心防线，其功能主要体现在两个方面：一是抗氧化剂的直接作用，二是细胞应激反应的调控。这两者相互配合，共同维系体内的氧化还原平衡，保障细胞和机体的正常生理功能。

抗氧化剂作为抵御氧化应激的第一道防线，包括 GSH、超氧化物歧化酶 (superoxide dismutase, SOD)、谷胱甘肽过氧化物酶 (glutathione peroxidase, GPx) 和过氧化氢酶 (catalase, CAT) 等。其中，GSH 是关键的抗氧化剂，其合成依赖于谷氨酰半胱氨酸连接酶 (γ-glutamylcysteine ligase, γ-GCL) 和谷胱甘肽合成酶 (glutathione synthetase, GS)。γ-GCL 作为这一过程的限速酶，由谷氨酰半胱氨酸连接酶催化亚基 (glutamate-cysteine ligase catalytic subunit, GCLC) 和谷氨酰半胱氨酸连接酶调节亚基 (glutamate-cysteine ligase modifier subunit, GCLM) 共同作用，在 Nrf2 和活化转录因子 4 (activating transcription factor 4, ATF4) 等的调控下促进 GSH 的生成，从而增强细胞的抗氧化能力 [82]。Sanadgol 等 [83] 发现，内源性抗氧化剂 α- 硫辛酸 (α-lipoic acid, ALA) 能够清除 ROS，促进髓鞘再生。

最近的研究表明，一些小分子药物可以通过调节特定的酶信号通路来增强抗氧化防御系统的效能。例如，Bruschi 等 [84] 研究表明，N-(N- 乙酰基 -L- 半胱氨酸基)-S- 乙酰基半胱氨酸 [N-(N-acetyl-l-cysteinyl)-S-acetylcysteamine, I-152] 在低氧环境下通过上调抗氧化酶的表达来清除 ROS。Barbiera 等 [85] 发现，牛磺酸 (taurine) 通过增加 SOD1、CAT、GPx1 的表达来减轻氧化应激，从而增强老年小鼠骨骼肌的再生能力。

此外，烟酰胺腺嘌呤二核苷酸磷酸 (nicotinamide adenine dinucleotide phosphate, NADPH) 通过保持 GSH 等抗氧化剂的还原状态，有效清除 ROS[86]。在细胞应对氧化应激过程中，特别是在低氧条件下，细胞会通过增加葡萄糖 -6- 磷酸脱氢酶 (glucose-6-phosphate dehydrogenase, G6PD) 的表达来促进 NADPH 的生成 [87]。Itsumi 等 [88] 研究表明，IDH1 通过降低细胞内氧化型烟酰胺腺嘌呤二核苷酸磷酸 (oxidized form of nicotinamide adenine dinucleotide phosphate, $NADP^+$)/NADPH 比值，保护肝细胞免受氧化应激的损害。此外，通过使用靶向 NAD(P)H 醌 : 氧化还原酶 1(NAD(P)H:quinone dehydrogenase 1, NQO1) 的药物，如邻苯二甲酰亚胺 (dunnione)，可以提高 $NADP^+$/NADPH 的比值，从而减轻急性胰腺炎所引起的损伤 [89]。在维持线粒体氧化还原平衡方面，丝氨酸 - 甘氨酸 - 一碳 (serine-glycine-one-carbon, SGOC) 代谢通过调节 NAD(P)/NAD(P)H 的比值发挥作用 [90-92]。

近年来，除了抗氧化剂之外，细胞应激反应机制，特别是氧化应激在组织再生中的作用逐渐受到关注。在氧化应激条件下，Nrf2 与 Kelch 样 ECH 相关蛋白 1 (Kelch-like ECH-associated protein 1, Keap1) 解离并进入细胞核，激活抗氧化反应元件 (antioxidant response element, ARE) 驱动的基因表达 [93]，从而提升抗氧化剂水平并减轻氧化应激 [94, 95]。Chen 等 [96] 研究表明，在心脏受损时，Nrf2 的激活通过上调抗氧化基因如血红素氧合酶 1 (heme oxygenase-1, HO-1) 和 NQO1 等的表达，显著减少心肌细胞的氧化应激，促进心脏再生。也有研究发现，成对样同源域转录因子 (paired-like homeodomain transcription factor 2, Pitx2) 和 p53 异构体 Δ113p53 能够通过增强与 Nrf2 的互作或者激活抗氧化基因的表达，促进心脏修复 [97, 98]。激活的 Nrf2 还能通过 HIF-1α 依赖机制，抑制低氧诱导的神经营养素 6A 亚型受体 (semaphorin 6A, Sema6A)，促进血管再生 [99]。

鉴于 Nrf2 在抗氧化和细胞保护中的重要作用，针对 Nrf2 的药物开发被认为是一种具有潜力的新疗法。例如，Gallyas 等 [100] 验证了枸杞多糖 (*Lycium barbarum* polysaccharides, LBP) 通过激活 Nrf2/HO-1 通路减轻脑损伤，增强神经再生。Qi 等 [101] 指出，Keap1-Nrf2 蛋白 - 蛋白相互作用的抑制剂 6K 能够通过调节细胞的氧化还原平衡，促进组织再生 [101]。总之，抗氧化防御系统通过抗氧化剂和细胞应激反应等，为细胞和机体提供了有效的抗氧化保护。

3　再生过程中低氧与氧化还原平衡的耦合机制

线粒体在组织再生中发挥重要作用 [95, 102]。研究发现，低氧通过抑制线粒体的氧化磷酸化，导致线粒体功能下降，这一过程伴随着 ROS 的产生和氧化应激的暂时性增加 [103-105]。为了适应这种环境，细胞通过激活 HIF-1α 信号通路来启动一系列保护机制。HIF-1α 信号通路不仅增强线粒体自噬，清除受损的线粒体，还通过诱导线粒体生物生成来维持线粒体功能的稳定 [106-109]。具体而言，线粒体自噬是一个关键过程，它通过降解损伤的线粒体来保护细胞免受氧化应激的损害。同时，线粒体生物生成的增强有助于补充因低氧而受损的线粒体，保证细胞能量代谢的顺利进行。然而，这一调控过程需要精确控制，因为长期的低氧或 HIF-1α 的过度激活可能导致线粒体呼吸能力降低，最终引发细胞死亡 [110]。因此，在组织再生过程中，低氧与氧化还原平衡的耦合可能调节线粒体稳态从而促进组织再生。

在低氧条件下，糖酵解的增强会改变细胞内的 NAD^+/NADH 比值。由于线粒体氧化磷酸化被抑制，NADH 无法快速氧化为 NAD^+，细胞通过增加乳酸发酵来维持这一比值，进而参与维持氧化还原平衡 [111]。这一过程在低氧环境下尤为重要，因为它不仅影响能量代谢，还与细胞生存和再生密切相关。目前，关于低氧如何通过 NAD^+/NADH 比值与氧化还原平衡之间的代谢耦合机制来影响组织再生，尤其是神经再生，尚缺乏深入研究，这可能是未来研究的一个重要方向。此外，低氧环境还可以通过 HIF-1α 促进线粒体自噬和生物生成，以及增强谷氨酰胺酶介导的 GSH 合成来调节氧化还原平衡，从而支持移植骨后骨细胞的存活 [112]。这些研究结果表明，低氧通过 ROS、NAD^+/NADH 比值以及 GSH 与氧化还原平衡实现代谢耦合，进而促进组织再生。

在医学研究领域，低氧与氧化还原平衡的耦合作用可能在多种疾病中起重要作用，包括癌症 [113]、心血管疾病 [114] 和神经退行性疾病 [115]。之前的研究主要聚焦于直接促进神经元再生的策略上 [116]。深入理解低氧与氧化还原平衡的耦合机制，不仅有助于揭示这些疾病的发病机制，还有望为开发神经再生的新型治疗方法提供理论基础。

4　结论和展望

对再生过程中低氧引起代谢适应理解的最新进展为支持氧化还原平衡在促进组织再生中的转化应

用提供了新的研究契机。深入探讨低氧条件下的代谢重编程，将有助于理解低氧如何通过代谢调控维持氧化还原平衡，从而促进组织再生。在治疗策略方面，应注重于将代谢调控机制应用于临床研究，通过实证优化治疗方法。例如，通过操纵特定的代谢途径，如增加抗氧化剂的产生或调节细胞内 NAD^+ 水平，来减轻氧化应激以促进神经再生。肿瘤和免疫细胞中的代谢机制为理解和借鉴低氧适应提供了宝贵经验。例如，肿瘤细胞在快速增殖过程中能够通过代谢重编程适应低氧微环境，同时利用多种代谢途径 (如增加抗氧化分子的生成) 来维持氧化还原平衡。而免疫细胞在伤口处聚集并释放代谢因子，改善局部微环境，也为再生研究提供了启示。然而，将这一代谢适应范式应用于难再生的神经再生领域时，我们仍面临重大挑战。因此，需借助如单细胞代谢组学等前沿技术，更全面地解析低氧环境与氧化还原平衡在神经再生中的耦合机制。通过这些深入研究，期望能够为神经再生等领域提供新的科学见解，最终推动临床治疗方法的创新与进步。

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