

糖酵解重编程调控骨重建失衡与骨质疏松的机制研究

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摘要 骨质疏松症(osteoporosis, OP)的本质是骨形成与骨吸收长期失衡。近年来, 骨相关细胞的糖酵解重编程被认为是连接衰老、雌激素缺乏、糖尿病、低氧和慢性炎症与骨重建异常的重要代谢环节。糖酵解通过调节葡萄糖摄取与通量、三磷酸腺苷(adenosine triphosphate, ATP)和合成底物供给、氧化还原稳态、乳酸生成/转运及乳酸化修饰, 影响成骨细胞、破骨细胞和骨免疫细胞的命运与功能。成骨谱系中适度增强糖酵解有助于分化、基质合成和矿化, 而糖酵解适应失败可导致骨形成不足; 相反, 核因子- κ B受体活化因子配体(receptor activator of nuclear factor- κ B ligand, RANKL)/核因子- κ B(nuclear factor- κ B, NF- κ B)/缺氧诱导因子-1 α (hypoxia-inducible factor-1 α , HIF-1 α)驱动的破骨细胞糖酵解增强可通过6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶3(6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase 3, PFKFB3)、M2型丙酮酸激酶(pyruvate kinase M2, PKM2)、乳酸脱氢酶A(lactate dehydrogenase A, LDHA)/单羧酸转运蛋白(monocarboxylate transporter, MCT)等节点支持细胞融合、骨架重塑和吸收陷窝酸化, 促进骨吸收。腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)通过感知细胞能量状态并调控雷帕霉素机制靶蛋白(mechanistic target of rapamycin, mTOR)相关信号, 协调糖酵解介导的能量供给与合成代谢需求, 从而在糖酵解支持成骨分化及骨形成的过程中发挥关键的代谢检查点作用。乳酸/乳酸化呈明显“双刃剑”效应: 在短暂、适量且以组织修复和成骨耦联为主的微环境中, 乳酸可通过组蛋白乙酰转移酶p300(histone acetyltransferase p300, p300)/组蛋白H3第18位赖氨酸乳酸化(histone H3 lysine 18 lactylation, H3K18la)等途径促进成骨分化和骨形成; 在持续、高负荷且以慢性炎症和破骨优势为主的微环境中, 乳酸积累则可能协同酸化、MCT转运和免疫代谢重塑, 加重骨丢失。该文围绕糖酵解重编程调控骨重建失衡的关键节点、细胞特异性效应及潜在干预策略进行综述, 以期OP代谢靶向治疗提供新的理论依据和研究思路。

关键词 骨质疏松; 糖酵解重编程; 骨重建; 成骨细胞; 破骨细胞; 骨免疫; 乳酸化

Research on the Mechanism of Glycolytic Reprogramming Regulating Bone Remodeling Imbalance and Osteoporosis

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Abstract OP (osteoporosis) is fundamentally characterized by a long-term imbalance between bone formation and bone resorption. In recent years, glycolytic reprogramming in bone-associated cells has been recognized as an important metabolic link connecting aging, estrogen deficiency, diabetes, hypoxia, and chronic inflammation with abnormal bone remodeling. Glycolysis influences the fate and function of osteoblasts, osteoclasts, and bone immune cells by regulating glucose uptake and glycolytic flux, ATP (adenosine triphosphate) and biosynthetic substrate supply, redox homeostasis, lactate production/transport, and lactylation. In the osteogenic lineage, moderate enhancement of glycolysis facilitates osteogenic differentiation, matrix synthesis, and mineralization, whereas impaired glycolytic adaptation may result in insufficient bone formation. In contrast, RANKL (receptor activator of nuclear factor- κ B ligand)/NF- κ B (nuclear factor- κ B)/HIF-1 α (hypoxia-inducible factor-1 α)-driven enhancement of glycolysis in osteoclasts promotes bone resorption by supporting cell fusion, cytoskeletal remodeling, and acidification of resorption lacunae through metabolic nodes such as PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3), PKM2 (pyruvate kinase M2), and LDHA (lactate dehydrogenase A)/MCT (monocarboxylate transporter). AMPK (adenosine monophosphate-activated protein kinase) senses cellular energy status and modulates mTOR (mechanistic target of rapamycin) signaling to coordinate glycolytic energy supply with anabolic demands, thereby serving as a key metabolic checkpoint that determines how effectively glycolysis supports osteogenic differentiation and bone formation. Lactate/lactylation exhibits a pronounced “double-edged sword” effect: in transient and moderate microenvironments dominated by tissue repair and osteogenic coupling, lactate can promote osteogenic differentiation and bone formation through pathways involving p300 (histone acetyltransferase p300)/H3K18la (histone H3 lysine 18 lactylation); however, in persistent, high-lactate-burden microenvironments dominated by chronic inflammation and osteoclast activity, lactate accumulation may act in concert with acidification, MCT-mediated transport, and immunometabolic remodeling to aggravate bone loss. This review summarizes the key metabolic nodes, cell-specific effects, and potential intervention strategies involved in glycolytic reprogramming-mediated dysregulation of bone remodeling, with the aim of providing new theoretical insights and research directions for metabolism-targeted therapy of OP.

Keywords osteoporosis; glycolytic reprogramming; bone remodeling; osteoblast; osteoclast; osteoimmunology; lactylation

骨质疏松症(osteoporosis, OP)是以骨量降低、骨微结构破坏和骨折风险升高为主要特征的全身性骨代谢疾病,其本质是骨重建过程长期失衡^[1]。正常骨重建依赖成骨细胞介导的骨形成与破骨细胞介导的骨吸收保持动态平衡;当骨形成不足或骨吸收过度时,骨量和骨质量逐渐下降,最终导致OP及脆性骨折^[2]。因此,围绕骨重建失衡阐明OP的发生机制,是寻找新型干预靶点的重要基础。近年来,骨代谢研究逐渐从传统的激素调控、钙磷代谢和炎症因子调节,拓展至细胞能量代谢和代谢重编程领域。糖酵解不仅为骨相关细胞提供三磷酸腺苷(adenosine triphosphate, ATP),还通过调控代谢中间产物、氧化还原稳态、乳酸生成及表观遗传修饰参与细胞命运决定^[3]。已有研究表明,成骨细胞分化过程中糖酵解是满足能量需求的重要代谢方式,葡萄糖转运蛋白1(glucose transporter 1, GLUT1)、(葡萄糖转

运蛋白3(glucose transporter 3, GLUT3)、缺氧诱导因子-1 α (hypoxia-inducible factor-1 α , HIF-1 α)、无翅型小鼠乳腺肿瘤病毒整合位点家族(wingless-type mouse mammary tumor virus integration site family, Wnt)/雷帕霉素机制靶蛋白(mechanistic target of rapamycin, mTOR)等均可参与成骨细胞葡萄糖代谢调控^[4]。糖尿病相关骨量下降表明成骨细胞内源性葡萄糖代谢缺陷可导致骨形成受损,而增强成骨细胞糖酵解可在一定程度上改善骨形成不足^[5]。

与成骨细胞不同,破骨细胞糖酵解增强更多表现为促进骨吸收,破骨细胞在核因子- κ B受体活化因子配体(receptor activator of nuclear factor- κ B ligand, RANKL)和巨噬细胞集落刺激因子(macrophage colony-stimulating factor, M-CSF)诱导下分化成熟,其融合、骨架重塑、皱褶缘形成和酸化吸收陷窝均需要充足能量供应^[6]。RANKL可诱导破骨细胞发生

代谢重编程,提高葡萄糖利用和糖酵解通量;6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶3(6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase 3, PFKFB3)、乳酸脱氢酶A(lactate dehydrogenase A, LDHA)等糖酵解相关分子参与破骨细胞形成及功能维持,抑制相关节点可减少破骨细胞生成和降低骨吸收活性^[7]。这提示糖酵解在OP中的作用具有明显细胞特异性:成骨细胞糖酵解适应障碍可导致骨形成减少,而破骨细胞糖酵解增强则可推动骨吸收增加。

除成骨和破骨细胞外,骨免疫炎症与乳酸代谢异常也是糖酵解重编程影响骨重建的重要环节。慢性低度炎症可促进巨噬细胞和T细胞代谢重编程,促进促炎因子释放,进而通过RANKL、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-1 β (interleukin-1 β , IL-1 β)、白细胞介素-6(interleukin-6, IL-6)、白细胞介素-17(interleukin-17, IL-17)等通路促进破骨细胞活化^[8]。乳酸作为糖酵解的重要产物,不仅参与局部酸性微环境形成,还可作为信号分子和表观遗传调控因子影响骨细胞功能。研究显示,葡萄糖代谢产生的乳酸可通过组蛋白乙酰转移酶p300(histone acetyltransferase p300, p300)介导的组蛋白乳酸化促进成骨分化;但在炎症或破骨优势微环境中,乳酸积累也可能加重骨吸收和免疫代谢异常^[9]。基于此,本文围绕糖酵解重编程调控骨重建失衡与OP的机制研究进展,重点从成骨细胞糖酵解适应障碍、破骨细胞糖酵解增强以及骨免疫炎症与乳酸代谢异常三方面进行综述,以期OP代谢机制研究和靶向干预提供参考。如图1所示,糖酵解重编程通过“病理刺激-代谢调控-细胞效应-骨重建结局”构成连续调控网络。衰老、雌激素缺乏、炎症、低氧及高糖等因素可经HIF-1 α 、核因子- κ B(nuclear factor- κ B, NF- κ B)和腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)/mTOR等信号调节葡萄糖转运蛋白(glucose transporter, GLUT)、己糖激酶2(hexokinase 2, HK2)、PFKFB3、M2型丙酮酸激酶(pyruvate kinase M2, PKM2)及LDHA/单羧酸转运蛋白(monocarboxylate transporter, MCT)轴,进而产生细胞特异性效应:成骨细胞糖酵解适应不足导致骨形成受损,而破骨细胞及促炎免疫细胞糖酵解增强则促进骨吸收;乳酸及乳酸化进一步介导代谢信号与表观遗传调控,最终推动骨重建失衡及OP发生发展。

1 糖酵解重编程调控骨重建的理论基础

骨重建是由成骨细胞介导的骨形成与破骨细胞介导的骨吸收共同维持的动态过程^[10]。糖酵解重编程是指细胞在分化、应激、炎症或病理刺激下,通过改变葡萄糖摄取、糖酵解通量、乳酸生成及乳酸转运等环节,以适应功能需求的代谢调节过程^[11]。在骨组织中,糖酵解不仅提供ATP,还参与代谢中间产物供应、氧化还原稳态维持、炎症信号放大和乳酸介导的细胞间交流。其对骨重建的影响具有明显细胞特异性(表1),成骨细胞适度糖酵解有利于骨形成,而破骨细胞及促炎免疫细胞糖酵解增强则可能促进骨吸收和炎症性骨丢失^[12]。

1.1 葡萄糖摄取与糖酵解通量:GLUT-HK2-PFKFB3-PKM2轴

GLUT1和GLUT3是成骨细胞常见的葡萄糖转运蛋白,可调控葡萄糖进入细胞的第一步;不同GLUT亚型对成骨细胞增殖和代谢的影响并不完全相同^[13]。Runx2相关转录因子2(runx-related transcription factor 2, Runx2)不仅是成骨分化转录因子,也可与葡萄糖摄取形成反馈,从而将细胞命运决定与代谢需求连接起来^[14]。Wnt/低密度脂蛋白受体相关蛋白5(low-density lipoprotein receptor-related protein 5, LRP5)和甲状旁腺激素(parathyroid hormone, PTH)等促成骨信号可通过雷帕霉素机制靶蛋白复合物2(mechanistic target of rapamycin complex 2, mTORC2)/蛋白激酶B(protein kinase B, AKT)等通路增强有氧糖酵解,支持胶原合成和矿化^[15-16]。

HK2催化葡萄糖磷酸化,PFKFB3通过提高果糖-2,6-二磷酸水平增加糖酵解通量,PKM2则参与糖酵解末端反应,并兼具代谢与信号调节功能^[17]。上述节点适度激活可满足成骨细胞分化和基质合成的代谢需求,而在破骨细胞及促炎免疫细胞中持续上调,则有利于维持高糖酵解、高乳酸生成及持续的炎症反应。因此,与单纯关注葡萄糖摄取水平相比,糖酵解关键调控节点及其代谢通量的变化,更能反映糖酵解对细胞功能的实际影响。Ma等^[18]在成骨细胞及卵巢切除小鼠模型中发现,烟酸可经沉默信息调节因子2相关酶2(sirtuin 2, SIRT2)/CCAAT/增强子结合蛋白 β (CCAAT/enhancer-binding protein β , C/EBP β)/双调蛋白(amphiregulin, AREG)-磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)/AKT轴提高PFKFB3活性和糖酵解水平,促进成骨分化。Cao等^[19]在骨髓间

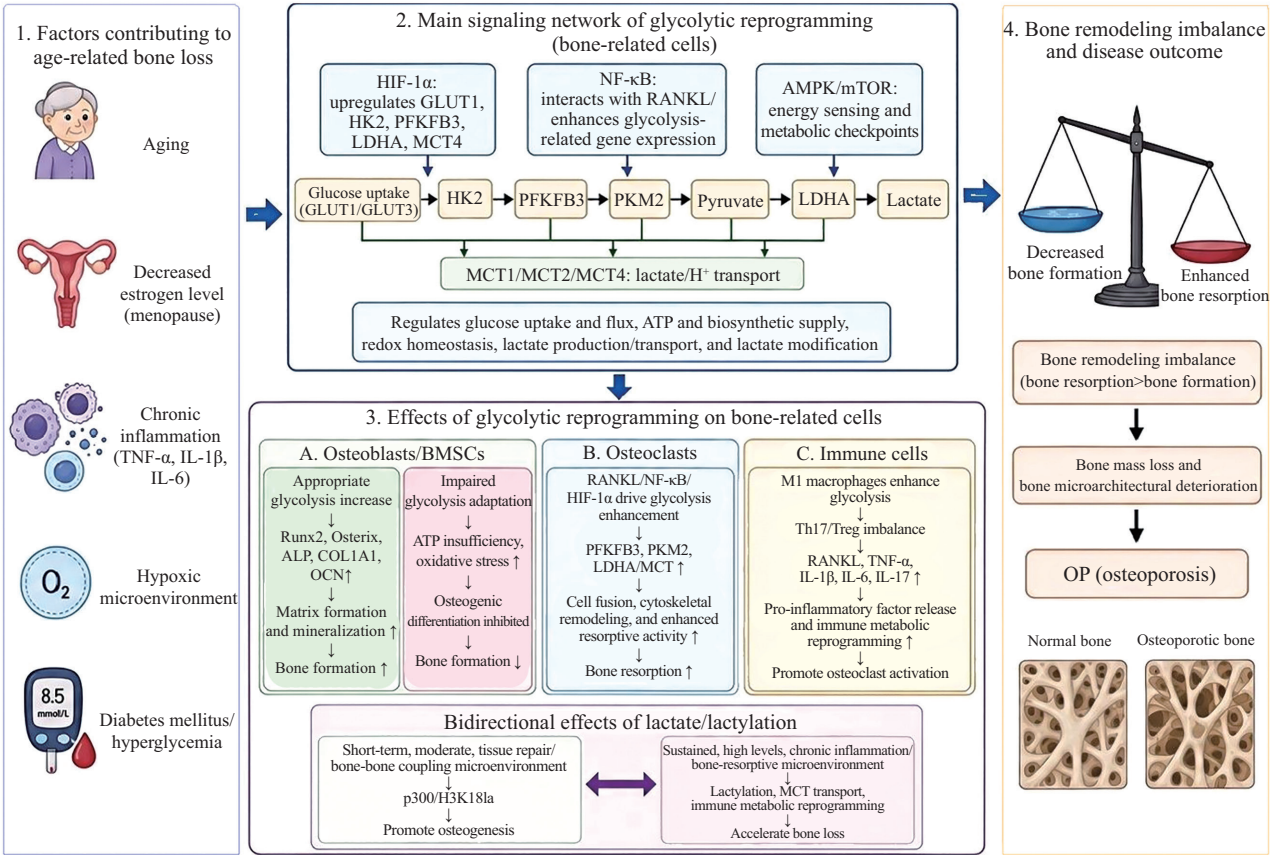


图1 糖酵解重编程调控骨重建失衡与OP的机制图

Fig.1 Mechanism diagram of glycolytic reprogramming regulating bone remodeling imbalance and osteoporosis

表1 糖酵解重编程关键节点及骨重建效应

Table 1 Key nodes of glycolytic reprogramming and effects on bone remodeling

关键节点	主要细胞/场景	在OP中的机制意义	参考文献
Key node	Major cell types/contexts	Mechanistic relevance to OP	References
GLUT1/GLUT3	Osteoblasts and osteoclasts	Moderate upregulation favors bone formation, whereas excessive upregulation in osteoclasts favors bone resorption	[13-16]
HK2	Osteoblasts and immune cells	Supports osteoblast metabolic adaptation and sustains pro-inflammatory phenotypes in inflammatory cells	[17]
PFKFB3	Osteoblasts and osteoclasts	Moderate activation in osteoblasts promotes bone formation, whereas upregulation in osteoclasts promotes bone resorption	[18-19]
PKM2	Osteoclasts and macrophages	Promotes precursor fusion and inflammatory osteoclastogenesis; a potential anti-resorptive target	[44-46]
LDHA/MCT1/MCT4	Osteoclasts, osteoblasts, and immune cells	Promotes acidification and bone resorption in osteoclastic environments, while moderate lactate regulates differentiation in osteogenic environments	[24-26,48]
HIF-1 α	Hypoxic bone microenvironment and inflammatory environment	Supports hypoxic adaptation in osteoblasts but enhances bone resorption in osteoclasts and inflammatory settings	[42,58-60]
AMPK/mTOR	Osteoblasts and bone marrow mesenchymal cells	Imbalance may impair osteogenic metabolic adaptation, requiring distinction between energy conservation and insufficient anabolism	[23,36,38]
NF- κ B	Osteoclast precursors, macrophages, and T cells	Links RANKL/inflammatory signals to glycolytic activation, driving osteoimmune bone loss	[41,50-60]

充质干细胞(bone marrow mesenchymal stem cells, BMSCs)和条件性基因模型中进一步发现, 硫氧还蛋白相互作用蛋白基因(hioredoxin-interacting protein gene, *Txnip*)过低或过高表达均可破坏糖酵解与三羧酸循环的平衡并损害骨稳态。近年机制研究进一步明确了PFKFB3在成骨谱系中的通量意义, PFKFB3并非单向“促成骨开关”, 其有益效应取决于糖酵解通量与线粒体氧化及合成代谢的动态匹配。

1.2 HIF-1 α 、NF- κ B与AMPK/mTOR: 低氧、炎症和能量检查点

骨髓和骨表面存在动态低氧梯度。HIF-1 α 稳定化可上调*GLUT1*、*HK2*、*PFKFB3*、*LDHA*和单羧酸转运蛋白4(monocarboxylate transporter 4, *MCT4*)等基因, 并通过血管-成骨耦联促进骨形成^[20]。PTH诱导的成骨效应也伴随葡萄糖代谢和线粒体呼吸的重塑, 在糖尿病性骨量减少中, 激活成骨细胞HIF-1 α 通路可部分改善成骨不足^[21]。然而, HIF-1 α 在破骨前体和炎症髓系细胞中又可促进糖酵解和骨吸收, 因此其作用方向取决于细胞类型。

NF- κ B主要感知RANKL和TNF- α 、IL-1 β 等炎症刺激信号, 并与HIF-1 α 形成交叉调控, 驱动破骨前体细胞及免疫细胞发生代谢重编程^[22]。AMPK则位于该网络的能量感知层: 当ATP不足时, AMPK促进底物利用和稳态恢复, 并限制过度雷帕霉素机制靶蛋白复合物1(mechanistic target of rapamycin complex 1, mTORC1)介导的蛋白合成消耗, mTORC2/AKT则参与促成骨信号驱动的糖酵解适应^[23]。AMPK/mTOR轴因此不是简单的“促成骨”或“抑成骨”开关, 而是决定能量供给、合成消耗和细胞功能能否匹配的代谢检查点。

1.3 LDHA/MCT与乳酸/乳酸化: 代谢产物、信号和表观遗传的交汇

LDHA将丙酮酸还原为乳酸并再生氧化型烟酰胺腺嘌呤二核苷酸(oxidized nicotinamide adenine dinucleotide, NAD⁺), 单羧酸转运蛋白1(monocarboxylate transporter 1, *MCT1*)、单羧酸转运蛋白2(monocarboxylate transporter 2, *MCT2*)和*MCT4*介导乳酸及氢离子(hydrogen ion, H⁺)的跨膜转运。乳酸不再被视为单纯代谢废物: 组蛋白赖氨酸乳酸化可将细胞糖酵解状态转化为染色质和基因转录变化^[24]。在骨相关细胞中, LDHA介导的乳酸生成或外源乳酸可增强组蛋白乳酸化, 进而促进成骨分化。血管内皮细胞来源乳酸还能诱导BMSC 组蛋白H3第18位

赖氨酸(histone H3 lysine 18, H3K18)乳酸化并加强血管-成骨耦联^[25]。与此同时, 破骨细胞和促炎免疫细胞的高糖酵解可造成乳酸持续生成与外排。此时乳酸主要通过维持NAD⁺再生、支持高糖酵解通量、改变局部pH值并调节免疫细胞表型参与骨吸收。由此, 乳酸效应至少由浓度、持续时间、细胞来源、MCT亚型、氧张力和炎症阶段共同决定^[26]。

综上, 糖酵解重编程通过多个关键节点参与骨重建调控: GLUT决定葡萄糖摄取, HK2、PFKFB3和PKM2调控糖酵解通量, LDHA/MCT轴介导乳酸生成和转运, HIF-1 α 、AMPK和NF- κ B则分别从低氧适应、能量感知和炎症反应层面调节糖酵解网络。其核心特征是细胞特异性与情境依赖性: 成骨细胞糖酵解适应不足可导致骨形成下降, 破骨细胞糖酵解增强可促进骨吸收, 骨免疫炎症和乳酸代谢异常则进一步放大骨重建失衡。因此, 未来针对糖酵解的干预不宜采取单纯促进或抑制的策略, 而应根据不同细胞类型、疾病阶段及关键代谢节点进行精准调控。

2 成骨细胞糖酵解适应障碍与骨形成不足

成骨细胞是介导骨形成的核心效应细胞, 其分化、骨基质合成和矿化过程均依赖充足的能量供应与代谢底物支持^[27]。研究发现成骨细胞主要依赖线粒体氧化磷酸化不同, 糖酵解是成骨细胞分化过程中满足ATP需求的重要代谢方式。成骨细胞在分化早期即出现葡萄糖摄取量增加、糖酵解通量提高和乳酸生成水平升高等代谢特征, 这种类似“有氧糖酵解”的代谢模式有助于为细胞增殖、胶原合成、碱性磷酸酶活性增强及矿化结节形成提供能量和合成原料^[28]。

2.1 糖酵解参与成骨分化、基质合成与矿化

在BMSCs向成骨细胞分化过程中, Runx2、成骨特异性锌指转录因子(osteoblast-specific zinc finger transcription factor, Osterix)、碱性磷酸酶(alkaline phosphatase, ALP)、I型胶原 α 1链(collagen type I α 1 chain, COL1A1)和骨钙素(osteocalcin, OCN)等成骨标志物逐渐上调, 伴随胶原分泌、非胶原蛋白合成和矿化基质沉积增加^[29]。糖酵解可为上述过程提供ATP、NAD⁺循环及三碳/六碳中间产物, 参与氨基酸、脂质和核苷酸合成, 从而支持基质形成。Wnt、PTH等促成骨信号可提高成骨细胞葡萄糖利用率和糖酵解通量; GLUT1/GLUT3等转运蛋白则构成成骨细胞葡萄糖摄取的重要入口^[30]。Lee等^[31]研究发现糖酵

解是成骨细胞满足分化期间能量需求的主要代谢方式, GLUT1和GLUT3是成骨细胞中主要葡萄糖转运蛋白, Wnt、PTH等促骨形成信号均可增强成骨细胞糖酵解。

骨基质矿化同样依赖糖酵解维持细胞代谢活性。成骨细胞糖酵解增强可促进ALP活性、胶原沉积和矿化结节形成; 相反, 当葡萄糖摄取或糖酵解通量受限时, 成骨分化和矿化能力下降^[32]。由此可见, 成骨细胞糖酵解并非单纯的供能过程, 而是成骨分化、基质成熟和矿化共同依赖的代谢基础。

2.2 成骨细胞糖酵解适应障碍导致骨形成不足

在OP相关病理状态下, 成骨细胞糖酵解适应障碍可能成为骨形成不足的重要原因。衰老、雌激素缺乏、糖皮质激素暴露、高糖环境和慢性炎症均可影响成骨细胞代谢稳态, 使其出现葡萄糖摄取不足、糖酵解通量下降、线粒体功能异常和氧化应激增强等改变^[33]。Liu等^[34]研究发现, 老龄小鼠骨组织及OP患者骨组织中叉头框蛋白K1(forkhead box K1, FOXK1)表达水平降低; 在成骨谱系细胞中特异性缺失Foxk1可下调多种糖酵解酶相关基因表达并降低有氧糖酵解水平, 进而抑制成骨细胞增殖与分化、减少骨形成, 而在老龄小鼠成骨前体细胞中过表达Foxk1则可增加骨量并改善骨力学性能, 该效应可被2-脱氧-D-葡萄糖(2-deoxy-D-glucose, 2-DG)削弱。因此, “衰老-FOXK1下调-有氧糖酵解减弱-骨形成受损”为衰老相关成骨功能下降提供了较直接的代谢机制证据。相比之下, 雌激素缺乏所致成骨障碍目前更多与线粒体生物能受损及糖酵解-氧化磷酸化协同失衡相关, 尚缺乏其普遍抑制成骨细胞糖酵解的直接证据。雌二醇/雌激素受体 α (estrogen receptor α , ER α)可上调核编码和线粒体编码的呼吸链复合体基因, 提高线粒体膜电位、酶活性和ATP生成量并促进成骨细胞矿化^[35]。在卵巢切除小鼠及MC3T3-E1细胞中, 17 β -雌二醇还可通过抑制基质金属蛋白酶8(matrix metalloproteinase 8, MMP8)并激活大鼠肉瘤相关蛋白(rat sarcoma-associated protein, Ras)通路, 恢复线粒体膜电位、氧耗、ATP生成和线粒体动态, 降低活性氧(reactive oxygen species, ROS)水平并改善成骨分化^[36]。雌激素缺乏可降低ER α 介导的线粒体能量供给能力, 并损害线粒体质量控制, 进而破坏糖酵解与氧化磷酸化之间的代谢协同, 导致成骨细胞能量代谢适应受损。雌激素缺乏是否直

接降低成骨细胞糖酵解通量, 仍需通过细胞外酸化率(extracellular acidification rate, ECAR)、稳定同位素示踪和细胞特异性ER α 模型进一步验证。研究发现, 地塞米松可抑制成骨细胞中HIF-1 α /丙酮酸脱氢酶激酶1(pyruvate dehydrogenase kinase 1, PDK1)信号通路, 而恢复HIF-1 α 或PDK1的表达可通过激活AKT/mTOR信号通路改善成骨功能并增加骨量^[37]。此外, 过量糖皮质激素还可干扰骨微环境的局部营养供应, 尤其是脂肪酸转运, 进而同时抑制骨形成和骨吸收, 使骨组织呈现低骨转换状态^[38]。因此, 糖皮质激素所致代谢异常应表述为HIF-1 α /PDK1/AKT/mTOR及多底物利用的重塑, 而不宜简单等同于糖酵解通量下降。在高糖/糖尿病方面, 2型糖尿病模型中成骨细胞内源性葡萄糖代谢缺陷可同时削弱糖酵解和线粒体代谢, 提高HIF-1 α 或PFKFB3相关通量可改善骨形成^[39], 1型糖尿病骨组织稳定同位素示踪亦显示糖酵解受损, 单纯过表达GLUT1不能挽救骨量, 而过表达Pfkfb3可保护皮质骨和松质骨^[40]。上述结果提示, 糖尿病相关成骨障碍的关键代谢缺陷可能主要涉及糖酵解通量异常及其与线粒体代谢的协调失衡, 而非单纯的葡萄糖摄取量不足。一方面, 在慢性炎症状态下, TNF- α 可抑制人骨髓间充质干细胞(human bone marrow mesenchymal stem cells, hBMSCs)的成骨分化, 并削弱成骨分化过程中由糖酵解向氧化磷酸化转换所需的线粒体呼吸能力^[41]; 另一方面, 在炎症伴低氧的微环境中, HIF稳定化及沉默信息调节因子2相关酶6(sirtuin 6, SIRT6)下调可伴随LDHA表达上调和乳酸生成量增加, 过度糖酵解及乳酸积累反而可能促进成骨细胞凋亡^[42]。因此, 慢性炎症可导致不同形式的代谢适应障碍, 既可表现为糖酵解向氧化磷酸化转换受阻, 也可表现为糖酵解代偿性增强但未能有效支持成骨, 最终均可导致骨形成不足。总体而言, 衰老、雌激素缺乏、糖皮质激素暴露、高糖及慢性炎症均可扰乱成骨细胞代谢稳态, 但其作用方向及主导代谢环节具有病因和阶段特异性。因此, 成骨细胞糖酵解适应障碍更宜理解为糖酵解通量、线粒体氧化、NAD⁺/还原型烟酰胺腺嘌呤二核苷酸(reduced nicotinamide adenine dinucleotide, NADH)氧化还原平衡及合成代谢之间的协调失衡, 最终表现为ATP及合成底物供应不足、氧化应激增强、成骨分化受阻、基质合成减少及矿化能力下降, 而不宜简单概括为“糖酵解降低”。

2.3 HIF-1 α /GLUT1/HK2轴与AMPK/mTOR轴共同调控成骨细胞代谢适应

HIF-1 α /GLUT1/HK2轴与AMPK/mTOR轴并非两条孤立通路,而是共同构成成骨细胞代谢适应的核心调控网络。前者主要在低氧、糖代谢障碍或组织修复微环境中促进葡萄糖摄取和糖酵解,后者则通过能量感知及蛋白合成调控,决定糖酵解增强能否有效支持成骨分化、基质合成和矿化^[43]。一般而言,HIF-1 α 稳定化可上调GLUT1、HK2、PFKFB3、LDHA等糖酵解相关分子表达,使成骨细胞获得更强的葡萄糖利用能力;mTORC2-AKT信号可促进Wnt、PTH等促成骨信号介导的有氧糖酵解;AMPK则在能量压力下作为代谢“校正器”,一方面促进葡萄糖利用和糖酵解恢复,另一方面在能量不足时限制过度mTORC1介导的蛋白合成消耗。因此,该网络的关键不在于单纯激活某一信号轴,而在于维持“糖酵解供能-合成代谢-成骨功能”之间的动态平衡^[44]。Ji等^[45]在1型糖尿病小鼠研究中发现,糖尿病会快速导致皮质骨和松质骨丢失,单细胞RNA测序显示糖尿病骨髓成骨谱系细胞代谢异常,体内稳定同位素示踪证实骨组织糖酵解通量下降。成骨细胞中过表达*Glut1*未改善骨量,反而加重1型糖尿病骨缺陷;而成骨细胞中过表达*Pfkfb3*可增加糖酵解通量,从而减轻1型糖尿病小鼠皮质骨和松质骨的骨量丢失。Esen等^[46]研究发现,*Lrp5*缺失小鼠骨细胞mTORC2活性及糖酵解酶表达水平下降,血清乳酸水平降低并伴随骨量下降,而高骨量*Lrp5*突变小鼠骨组织糖酵解活性增强。

综上,成骨细胞糖酵解适应障碍是骨质疏松骨形成不足的重要代谢机制。糖酵解通过提供ATP、代谢中间产物和乳酸信号,参与成骨分化、骨基质合成和矿化;HIF-1 α /GLUT1/HK2轴主要负责低氧和应激状态下的葡萄糖摄取及糖酵解启动,AMPK/mTOR轴则连接能量感知、代谢合成和成骨分化。应进一步明确不同骨质疏松类型中成骨细胞糖酵解障碍的具体模式,并探索如何在不促进破骨细胞糖酵解的前提下,选择性恢复成骨细胞代谢适应能力。

3 破骨细胞糖酵解增强与骨吸收增加

破骨细胞是介导骨吸收的核心效应细胞,其分化、融合、迁移、骨架重塑和骨基质降解均依赖持续能量供应。RANKL和M-CSF不仅启动破骨分化转录程序,还促使破骨前体细胞发生代谢重编程,表现

为葡萄糖摄取、糖酵解通量和乳酸生成增加^[47]。因此,破骨细胞糖酵解增强可被视为骨吸收功能获得的代谢基础;抑制PFKFB3、PKM2或LDHA等糖酵解相关节点,可减少破骨细胞形成,并减弱其骨吸收活性^[48]。

3.1 RANKL/NF- κ B/HIF-1 α 轴启动破骨代谢重编程

RANKL与核因子- κ B受体活化因子(receptor activator of nuclear factor- κ B, RANK)结合后经肿瘤坏死因子受体相关因子6(tumor necrosis factor receptor-associated factor 6, TRAF6)激活NF- κ B、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、PI3K/AKT和活化T细胞核因子胞质型1(nuclear factor of activated T cells, cytoplasmic 1, NFATc1),诱导*TRAP*、*Cathepsin K*、*DC-STAMP*和*OC-STAMP*等破骨基因表达。Indo等^[49]发现M-CSF/RANKL诱导的破骨分化伴随能量代谢重塑,提示转录程序和代谢程序同步启动。HIF-1 α 可上调GLUT1、LDHA和MCT4等蛋白表达。进一步研究发现破骨细胞HIF-1 α 稳定化可促进上述有氧糖酵解相关分子表达^[50]。因此,NF- κ B与HIF-1 α 通过交叉调控,促进炎症和低氧刺激下破骨前体细胞糖酵解相关基因的表达,进而增强葡萄糖利用及糖酵解活性。

3.2 PFKFB3、PKM2和LDHA构成糖酵解通量执行轴

PFKFB3提高糖酵解入口通量,PKM2调节丙酮酸生成并参与非代谢性信号,LDHA通过乳酸生成和NAD⁺再生维持持续糖酵解。在RANKL诱导的细胞模型及卵巢切除小鼠模型中,抑制PFKFB3可减少破骨细胞形成并减轻骨丢失,在RANKL诱导的体外细胞模型中,抑制LDHA可降低异常升高的糖酵解水平,并减少破骨细胞形成^[51]。上述证据主要来自细胞与动物实验,尚不足以直接推断临床疗效,但提示这些通量节点具有抗骨吸收研究价值。

PKM2的作用具有酶活性、磷酸化状态和亚细胞定位等多层级特征。Kim等^[52]发现,免疫球蛋白超家族成员11(immunoglobulin superfamily member 11, IgSF11)可激活肉瘤原癌基因酪氨酸蛋白激酶(sarcoma proto-oncogene tyrosine-protein kinase, Src)家族激酶并诱导PKM2酪氨酸磷酸化,降低其丙酮酸激酶活性,从而支持破骨细胞晚期成熟,在小鼠病理性骨丢失模型中,药理性激活PKM2可减轻骨丢失,且未观察到明显的骨形成抑制。近年来进一步分别从DC-STAMP/OC-STAMP介导的前体融合

和信号转导与转录激活因子3(signal transducer and activator of transcription 3, STAT3)磷酸化角度证明PKM2参与破骨前体融合与炎症性破骨形成^[53]。因此, PKM2靶向策略需同时考虑其代谢酶活性、磷酸化修饰、亚细胞定位和信号转导功能。

3.3 乳酸生成与吸收陷窝酸化

成熟破骨细胞通过液泡型质子三磷酸腺苷酶(vacuolar-type proton adenosine triphosphatase, V-ATPase)、氯离子通道7(chloride channel 7, ClC-7)和碳酸酐酶II向相对封闭的吸收陷窝输送质子, 降低pH值并促进羟基磷灰石溶解, Cathepsin K和基质金属蛋白酶9(matrix metalloproteinase 9, MMP9)随后降解有机基质^[54], 这是吸收陷窝酸化的经典主轴。糖酵解来源乳酸并不替代质子泵, 而是通过维持NAD⁺再生和高通量糖酵解、经MCT协同转运乳酸/H⁺, 帮助形成有利于骨吸收的局部酸性微环境。Ahn等^[55]发现破骨分化过程中葡萄糖消耗、乳酸生成和细胞外酸化同步增加, 降低乳酸脱氢酶活性可减少乳酸积累、NFATc1表达量和多核破骨细胞形成。因此, 乳酸/H⁺升高应被视为破骨高糖酵解和酸化微环境的协同因素, 而不宜表述为吸收陷窝酸化的唯一来源。

3.4 代谢靶向兼顾破骨生理功能与旁路代谢

破骨细胞在正常骨更新、微损伤修复和钙稳态中不可或缺, 长期全身性抑制糖酵解可能影响免疫细胞和成骨细胞。与此同时, 破骨细胞可利用谷氨酰胺、脂肪酸和丝氨酸合成等旁路代谢维持分化^[56]。未来应进一步探索针对破骨细胞或骨表面的靶向干预策略, 重点评估PFKFB3、PKM2、LDHA/MCT及HIF-1 α 等关键分子作为干预靶点的可行性, 并关注干预过程中可能出现的代谢旁路代偿、骨转换过度抑制及免疫系统不良反应。

4 骨免疫炎症与乳酸代谢异常放大骨重建失衡

骨重建不仅受成骨细胞和破骨细胞直接调控, 也受到骨髓免疫微环境的深度影响。慢性低度炎症可通过改变巨噬细胞、T细胞及破骨前体细胞的代谢状态, 促进促炎因子释放和RANKL信号增强, 进而推动骨吸收增加。糖酵解重编程是炎症细胞获得促炎表型的重要代谢基础, 其中M1巨噬细胞糖酵解增强、辅助性T细胞17(T helper 17 cell, Th17)/调节性T细胞(regulatory T cell, Treg)失衡、NF- κ B/HIF-

1 α 轴激活、LDHA/MCT介导的乳酸生成与转运, 共同构成炎症性骨丢失的重要代谢网络。乳酸及其介导的乳酸化修饰进一步拓展了糖酵解参与骨免疫调控的机制内涵。

4.1 M1巨噬细胞糖酵解增强与炎症性破骨活化

巨噬细胞是骨免疫微环境中连接炎症反应与骨重建失衡的重要细胞。经典活化的M1巨噬细胞通常表现为葡萄糖摄取量增加、糖酵解通量提高、乳酸生成水平升高和氧化磷酸化相对受限, 其代谢特征有利于快速产生ATP, 并促进TNF- α 、IL-1 β 、IL-6、白细胞介素-12(interleukin-12, IL-12)等促炎细胞因子的产生和分泌, 同时增加NO及ROS等炎症相关介质的生成^[57]。M1样炎症巨噬细胞的三羧酸循环发生功能性断裂, 可导致琥珀酸积累。胞内琥珀酸可抑制脯氨酰羟化酶、稳定HIF-1 α 并促进IL-1 β 转录, 炎症性巨噬细胞还可将琥珀酸释放至胞外, 并同步上调SUCNR1/GPR91, 由此形成自分泌/旁分泌回路, 进一步促进HIF-1 α 依赖的IL-1 β 表达与分泌, 并加剧关节炎症反应^[58]。Guo等^[59]发现琥珀酸受体1(succinate receptor 1, SUCNR1)表达于破骨前体和成熟破骨细胞, 琥珀酸结合SUCNR1后促进经典核因子- κ B p65亚基(nuclear factor- κ B p65 subunit, NF- κ B p65)/核因子- κ B p50亚基(nuclear factor- κ B p50 subunit, NF- κ B p50)核转位, 上调RANKL诱导的NFATc1、TRAP和CTSK等破骨分化/成熟相关分子的表达, 进而促进破骨细胞分化、成熟和骨吸收, 而SUCNR1拮抗剂、小干扰RNA(small interfering RNA, siRNA)或基因敲除均可削弱该效应。现有研究已证明RANKL诱导的破骨分化伴随LDH活性、葡萄糖消耗、乳酸生成和细胞外酸化同步升高, 抑制乳酸脱氢酶(lactate dehydrogenase, LDH)可降低NFATc1表达水平, 并减少成熟破骨细胞形成^[60]。结合破骨细胞表达MCT1/2/4且不同亚型分别调节破骨分化、存活和骨吸收的研究, 可见LDHA/MCT轴能够把高糖酵解与乳酸/H⁺转运、NFATc1程序和吸收微环境耦联。然而, 尚缺乏谱系示踪直接证明M1来源乳酸被破骨前体摄取后必然促进分化, 且外源乳酸效应受浓度和pH影响^[61]。因此, 炎症性破骨取决于促破骨的“琥珀酸/SUCNR1-NF- κ B”和“乳酸/MCT-NFATc1”两条关键效应轴共同作用, 而非仅取决于M1细胞数量。

4.2 Th17/Treg失衡与骨免疫性骨丢失

Th17细胞与Treg细胞是骨免疫调控中具有相

反效应但又高度可塑的两类分化簇4阳性(cluster of differentiation 4-positive, CD4⁺) T细胞亚群。Th17细胞主要通过分泌IL-17、TNF- α 、IL-6等促炎因子,诱导成骨细胞、骨细胞、滑膜成纤维细胞及骨髓基质细胞表达RANKL,并增强破骨前体细胞对RANKL的反应性,从而促进破骨细胞分化和骨吸收^[62]。Treg细胞通常通过叉头框蛋白P3(forkhead box P3, Foxp3)、白细胞介素-10(interleukin-10, IL-10)、转化生长因子- β (transforming growth factor- β , TGF- β)、细胞毒性T淋巴细胞相关蛋白-4(cytotoxic T-lymphocyte-associated protein-4, CTLA-4)等途径抑制炎症反应和破骨细胞生成,维持骨免疫稳态。因而,当骨髓微环境由Treg优势转向Th17优势时,可形成“IL-17/TNF- α /RANKL升高-NF- κ B/NFATc1激活-破骨细胞生成增加-骨吸收增强”的病理链条^[63]。研究发现Th17/Treg平衡是类风湿关节炎、绝经后骨质疏松和牙周炎等炎症性骨丢失的重要免疫调控节点^[64]。Bhadricha等^[65]研究对比绝经前与绝经后女性外周血Th17、Treg及相关细胞因子水平,绝经后女性Th17细胞频率升高,Th17/Treg值高于绝经前女性,绝经后低骨密度人群中IL-17水平升高更明显,且Th17细胞频率及Th17/Treg值与腰椎和股骨颈T值呈负相关。该研究提示,雌激素不足不仅直接影响成骨与破骨细胞,还可能改变T细胞亚群平衡,使免疫微环境向促炎、促破骨方向偏移。

4.3 NF- κ B/HIF-1 α 轴连接炎症信号与糖酵解重编程

NF- κ B/HIF-1 α 轴是炎症信号转化为糖酵解重编程的重要枢纽。NF- κ B主要感知RANKL、TNF- α 、IL-1 β 、脂多糖(lipopolysaccharide, LPS)等炎症或破骨刺激,启动促炎因子和破骨相关基因表达;HIF-1 α 进一步调控GLUT1、HK2、PFKFB3、LDHA、MCT4等糖酵解相关分子,使破骨前体细胞、M1巨噬细胞和部分T细胞获得高葡萄糖摄取、高乳酸生成和高炎症输出状态^[66]。因此,在OP及炎症性骨丢失中,该轴可形成“炎症信号-糖酵解增强-破骨活化”的正反馈环路,是骨免疫代谢干预的重要候选节点^[67]。Rius等^[68]研究发现NF- κ B可通过转录水平调节HIF-1 α 表达,将先天免疫炎症反应与低氧适应联系起来,炎症刺激激活NF- κ B后促进HIF-1 α 表达,HIF-1 α 作为糖酵解基因核心转录因子,可增强细胞对低氧和炎症微环境的代谢适应,RANKL、TNF- α

和IL-1 β 等炎症因子激活NF- κ B,通过HIF-1 α 稳定化或转录上调,使破骨前体细胞和巨噬细胞获得更强的糖酵解能力。

4.4 LDHA/MCT轴介导乳酸生成、转运与骨吸收微环境改变

LDHA/MCT轴是糖酵解重编程向骨吸收功能转化的关键执行环节。LDHA催化丙酮酸还原为乳酸并再生NAD⁺,MCT1、MCT2和MCT4等单羧酸转运蛋白则负责乳酸及相关代谢物跨膜转运^[69]。破骨细胞在RANKL刺激下乳酸生成和外排增加,既可维持细胞内糖酵解通量,也可与V-ATPase/ClC-7介导的质子转运共同塑造酸性吸收微环境^[70]。而不同MCT亚型在破骨前体细胞和成熟破骨细胞中的作用并不完全一致,提示乳酸转运可能具有阶段特异性和靶点选择性^[71]。Imai等^[72]系统研究MCT亚型在破骨细胞中的作用,发现巨噬细胞和破骨细胞表达Mct1、Mct2和Mct4,Mct1和Mct4在巨噬细胞中表达水平较高,Mct2在破骨细胞中表达水平较高;Mct1敲低促进RANKL诱导的破骨形成,Mct2敲低则抑制破骨形成;成熟破骨细胞中敲低Mct2可减少骨表面破骨细胞数量并降低骨吸收,LDHA负责乳酸生成,MCT决定乳酸和相关代谢物跨膜转运,MCT1、MCT2、MCT4在不同细胞阶段和微环境中可能分别影响破骨分化、细胞存活和骨吸收功能。

4.5 乳酸化修饰:糖酵解连接代谢与表观遗传的新机制

乳酸化修饰是近年来提出的一类由乳酸衍生的赖氨酸翻译后修饰形式,其中组蛋白乳酸化可将细胞糖酵解状态转化为染色质结构和基因转录变化。在骨组织中,内皮细胞来源乳酸可诱导BMSCs组蛋白H3K18乳酸化并促进成骨分化;内皮PKM2表达水平降低、乳酸不足或组蛋白H3第18位赖氨酸乳酸化(histone H3 lysine 18 lactylation, H3K18la)减弱则可能加重OP表型^[24]。Nian等^[25]发现成骨分化过程中LDHA、细胞内乳酸和组蛋白乳酸化水平同步升高,敲低LDHA可降低ALP水平、减少矿化结节形成,并伴随JunB表达水平下降,提示LDHA-乳酸-组蛋白乳酸化-JunB轴参与成骨成熟。Minami等^[73]进一步发现,低糖培养或抑制LDH可降低组蛋白乳酸化水平,并下调成骨相关标志物的表达;补充乳酸可部分逆转上述变化。敲低p300则可同时降低组蛋白乳酸化水平及Sp7、Tnap的表达水平,提示p300依赖的组蛋

白乳酸化可能参与早期成骨相关基因的转录调控。Wu等^[74]发现骨内血管及内皮PKM2下降会减少乳酸供给,继而削弱BMSC H3K18la和成骨分化,内皮细胞特异性*Pkm2*缺失加重OP,而内皮*PKM2*过表达、乳酸补充或运动可部分恢复骨表型,CUT&Tag联合RNA测序还定位了H3K18la相关成骨基因。该研究建立了“内皮糖酵解-乳酸旁分泌-BMSC H3K18la-成骨基因转录”的跨细胞代谢-表观遗传轴,是乳酸化参与OP最直接的体内研究之一。乳酸的促成骨作用并不完全依赖乳酸化,骨缺损早期局部乳酸水平升高可作为Olf1440配体触发BMSC Ca^{2+} 内流并促进成骨,Olf1440缺失延迟骨修复。该研究显示同一乳酸信号可并行激活“受体- Ca^{2+} ”快速通路和“p300/H3K18la-转录”慢速通路^[75]。后续研究应通过p300/HDAC、Olf1440及MCT的组合干预,区分两条通路对骨形成的相对贡献,避免将乳酸的全部效应归因于乳酸化。乳酸化还是解释乳酸的阶段“双刃剑”效应。研究发现炎症后期巨噬细胞组蛋白乳酸化可促进部分修复相关基因表达,但这一规律能否直接外推至骨髓M1巨噬细胞、破骨前体或成熟破骨细胞,尚无充分的细胞特异性体内研究。持续高糖酵解环境中的乳酸一方面可能诱导有利于炎症消退或成骨耦联的乳酸化,另一方面又可维持破骨细胞 NAD^+ 再生、MCT/ H^+ 外排和酸化^[76]。因此,评价乳酸化必须同时记录组织pH、乳酸通量、细胞来源和疾病阶段,不能仅用总乳酸或全组织泛赖氨酸乳酸化水平推断其功能方向。

5 小结与展望

综上所述,糖酵解重编程为理解OP骨重建失衡提供了重要代谢维度,将成骨细胞、破骨细胞、骨免疫炎症和乳酸化修饰纳入同一机制框架,强调糖酵解在不同细胞中的效应并不相同:成骨细胞适度糖酵解有利于骨形成,而破骨细胞及促炎免疫细胞糖酵解过度增强则可促进骨吸收。与传统“激素-钙磷-炎症”解释相比,这一视角更有助于揭示衰老、雌激素缺乏、糖尿病和慢性炎症等多因素如何通过代谢适应失败共同导致骨质疏松。而糖酵解相关靶点具有显著细胞特异性和疾病阶段依赖性,对于骨形成不足占优势的老年性、糖尿病性或糖皮质激素相关OP,通过增强成骨谱系细胞HIF-1 α /GLUT/HK2、PFKFB3或AMPK/mTOR相关代谢适应来改善成骨

功能;而在绝经后OP、炎症性骨丢失或破骨活跃状态下,则应重点限制破骨细胞和促炎髓系细胞中过度激活的PFKFB3、PKM2、LDHA/MCT、HIF-1 α 和NF- κ B轴。

传统观点多将乳酸视为糖酵解终末产物和酸化因素,但近年研究提示乳酸还可作为代谢信号分子和表观遗传底物,参与BMSC成骨分化、成骨细胞成熟及血管-成骨耦联。然而,乳酸的骨效应具有“双刃剑”属性:在组织修复和成骨微环境中,适度乳酸可能通过组蛋白乳酸化促进成骨;在破骨优势或慢性炎症微环境中,乳酸积累又可能通过酸化、MCT转运和免疫代谢重塑促进骨吸收。目前关于糖酵解重编程与OP的研究仍以细胞实验和动物模型为主,人源骨组织证据、纵向队列证据和临床转化研究相对不足。课题组将结合单细胞RNA测序、空间转录组、空间代谢组、稳定同位素示踪、条件性基因敲除、谱系追踪以及临床骨活检样本,系统解析不同OP亚型中糖酵解通量、乳酸转运和乳酸化谱的动态改变。同时,可进一步研究血清或骨髓乳酸水平、LDH同工酶谱、MCT及糖酵解关键酶的表达水平、外泌体代谢相关标志物以及免疫细胞糖酵解特征,评估这些指标作为反映骨重建状态和监测治疗反应的候选生物标志物的潜在价值。综上,糖酵解重编程通过“成骨细胞代谢适应障碍-破骨细胞糖酵解增强-骨免疫炎症放大-乳酸/乳酸化表观遗传调控”共同参与OP发生发展。

参考文献 (References)

- [1] Morin S N, Leslie W D, Schousboe J T. Osteoporosis: a review [J]. The Journal of the American Medical Association, 2025, 334(10): 894-907.
- [2] Bolamperti S, Villa I, Rubinacci A. Bone remodeling: an operational process ensuring survival and bone mechanical competence [J]. Bone Research, 2022, 10(1): 48.
- [3] Bertels J C, He G X, Long F X. Metabolic reprogramming in skeletal cell differentiation [J]. Bone Research, 2024, 12(1): 57.
- [4] Zhang Z W, Tian S, Li Q, et al. Regulating glucose metabolism enzymes for osteoporosis therapy: current and future approaches [J]. International Journal of Molecular Sciences, 2026, 27(10): 4536.
- [5] Peng S Y, Yao Z, Guo J Z, et al. Glucose metabolism in osteoporosis: a potential therapeutic target (review) [J]. International Journal of Molecular Medicine, 2026, 58(4): 288.
- [6] Ledesma-Colunga M G, Passin V, Lademann F, et al. Novel insights into osteoclast energy metabolism [J]. Current Osteoporosis Reports, 2023, 21(6): 660-669.
- [7] Da W, Tao L, Zhu Y. The role of osteoclast energy metabolism in

- the occurrence and development of osteoporosis [J]. *Frontiers in Endocrinology*, 2021, 12: 675385.
- [8] Jin Z R, Liu L S, Wang H R, et al. Advances in the study of the role of bone immunity in physiological and pathological processes related to bone metabolism [J]. *International Immunopharmacology*, 2026, 187: 117219.
 - [9] Sun J H, Ge M, Gao P, et al. Lactate and lactylation in osteoporosis: pathogenesis, regulation, and future perspectives [J]. *Journal of Bone and Mineral Metabolism*, 2026, 44(3): 277-287.
 - [10] Delaisse J M, Andersen T L, Kristensen H B, et al. Re-thinking the bone remodeling cycle mechanism and the origin of bone loss [J]. *Bone*, 2020, 141: 115628.
 - [11] Choi I A, Umemoto A, Mizuno M, et al. Bone metabolism: an underappreciated player [J]. *NPJ Metabolic Health and Disease*, 2024, 2(1): 12.
 - [12] Shen L Y, Hu G L, Karner C M. Bioenergetic metabolism in osteoblast differentiation [J]. *Current Osteoporosis Reports*, 2022, 20(1): 53-64.
 - [13] Arponen M, Jalava N, Widjaja N, et al. Glucose transporters GLUT1, GLUT3, and GLUT4 have different effects on osteoblast proliferation and metabolism [J]. *Frontiers in Physiology*, 2022, 13: 1035516.
 - [14] Wei J W, Shimazu J, Makinistoglu M P, et al. Glucose uptake and Runx2 synergize to orchestrate osteoblast differentiation and bone formation [J]. *Cell*, 2015, 161(7): 1576-1591.
 - [15] Karner C M, Long F X. Wnt signaling and cellular metabolism in osteoblasts [J]. *Cellular and Molecular Life Sciences*, 2017, 74(9): 1649-1657.
 - [16] Esen E, Lee S Y, Wice B M, et al. PTH promotes bone anabolism by stimulating aerobic glycolysis via IGF signaling [J]. *Journal of Bone and Mineral Research*, 2015, 30(11): 1959-1968.
 - [17] Li Y Y, Li Q L, Zhang K H, et al. Metabolic rewiring and post-translational modifications: unlocking the mechanisms of bone turnover in osteoporosis [J]. *Aging and Disease*, 2026, 17(2): 849-876.
 - [18] Ma J L, Li X, Li Q Y, et al. Niacin regulates glucose metabolism and osteogenic differentiation via the SIRT2-C/EBP β -AREG signaling axis [J]. *Biomedicine & Pharmacotherapy*, 2024, 180: 117447.
 - [19] Cao X K, Liu K X, Rong K W, et al. Txnip regulates glycolysis and tricarboxylic acid cycle balance to maintain bone homeostasis [J]. *Journal of Orthopaedic Translation*, 2026, 58: 101095.
 - [20] Regan J N, Lim J, Shi Y, et al. Up-regulation of glycolytic metabolism is required for HIF1 α -driven bone formation [J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2014, 111(23): 8673-8678.
 - [21] Donat A, Knapstein P R, Jiang S, et al. Glucose metabolism in osteoblasts in healthy and pathophysiological conditions [J]. *International Journal of Molecular Sciences*, 2021, 22(8): 4120.
 - [22] D'Ignazio L, Bandarra D, Rocha S. NF- κ B and HIF crosstalk in immune responses [J]. *The FEBS Journal*, 2016, 283(3): 413-424.
 - [23] Smith C O, Eliseev R A. Energy metabolism during osteogenic differentiation: the role of Akt [J]. *Stem Cells and Development*, 2021, 30(3): 149-162.
 - [24] Zhang D, Tang Z Y, Huang H, et al. Metabolic regulation of gene expression by histone lactylation [J]. *Nature*, 2019, 574(7779): 575-580.
 - [25] Nian F G, Qian Y Z, Xu F Y, et al. LDHA promotes osteoblast differentiation through histone lactylation [J]. *Biochemical and Biophysical Research Communications*, 2022, 615: 31-35.
 - [26] Ye Z Y, Chen X Y, Zou J Y, et al. Lactylation's role in bone health and disease: mechanistic insights and therapeutic potential [J]. *PeerJ*, 2025, 13: e19534.
 - [27] Dirckx N, Moorer M C, Clemens T L, et al. The role of osteoblasts in energy homeostasis [J]. *Nature Reviews Endocrinology*, 2019, 15(11): 651-665.
 - [28] Lee W C, Ji X, Nissim I, et al. Malic enzyme couples mitochondria with aerobic glycolysis in osteoblasts [J]. *Cell Reports*, 2020, 32(10): 108108.
 - [29] Salhotra A, Shah H N, Levi B, et al. Mechanisms of bone development and repair [J]. *Nature Reviews Molecular Cell Biology*, 2020, 21(11): 696-711.
 - [30] Karner C M, Long F X. Glucose metabolism in bone [J]. *Bone*, 2018, 115: 2-7.
 - [31] Lee W C, Guntur A R, Long F X, et al. Energy metabolism of the osteoblast: implications for osteoporosis [J]. *Endocrine Reviews*, 2017, 38(3): 255-266.
 - [32] Lee S Y, Long F X. Notch signaling suppresses glucose metabolism in mesenchymal progenitors to restrict osteoblast differentiation [J]. *The Journal of Clinical Investigation*, 2018, 128(12): 5573-5586.
 - [33] Zhivodernikov I V, Kirichenko T V, Markina Y V, et al. Molecular and cellular mechanisms of osteoporosis [J]. *International Journal of Molecular Sciences*, 2023, 24(21): 15772.
 - [34] Liu C G, Feng N B, Wang Z M, et al. Foxk1 promotes bone formation through inducing aerobic glycolysis [J]. *Cell Death & Differentiation*, 2024, 31(12): 1650-1663.
 - [35] Lin P I, Tai Y T, Chan W P, et al. Estrogen/ER α signaling axis participates in osteoblast maturation via upregulating chromosomal and mitochondrial complex gene expressions [J]. *Oncotarget*, 2018, 9(1): 1169-1186.
 - [36] Min H, Li Y X, Chen G, et al. 17 β -estradiol maintains mitochondrial homeostasis in osteoblasts by inhibiting MMP-8 and activating the ras signaling pathway in postmenopausal osteoporosis [J]. *The FASEB Journal*, 2026, 40(14): e72139.
 - [37] Xu W N, Zheng H L, Yang R Z, et al. HIF-1 α regulates glucocorticoid-induced osteoporosis through PDK1/AKT/mTOR signaling pathway [J]. *Frontiers in Endocrinology*, 2020, 10: 922.
 - [38] Li X, Liang T Z, Dai B Y, et al. Excess glucocorticoids inhibit murine bone turnover via modulating the immunometabolism of the skeletal microenvironment [J]. *The Journal of Clinical Investigation*, 2024, 134(10): e166795.
 - [39] Song F F, Lee W D, Marmo T, et al. Osteoblast-intrinsic defect in glucose metabolism impairs bone formation in type II diabetic male mice [J]. *eLife*, 2023, 12: e85714.
 - [40] Pang C Y, Chen L R, Chen K H. Osteoporosis in patients with pre-existing diabetes mellitus and in women with estrogen deficiency: a molecular and cellular perspective [J]. *International Journal of Molecular Sciences*, 2026, 27(3): 1453.
 - [41] Hao Y S, Wu M T, Wang J M. Fibroblast growth factor-2 ameliorates tumor necrosis factor-alpha-induced osteogenic damage of human bone mesenchymal stem cells by improving oxidative phosphorylation [J]. *Molecular and Cellular Probes*, 2020, 52: 101538.

- [42] Kok S H, Hou K L, Hong C Y, et al. Sirtuin 6 modulates hypoxia-induced apoptosis in osteoblasts via inhibition of glycolysis: implication for pathogenesis of periapical lesions [J]. *Journal of Endodontics*, 2015, 41(10): 1631-1637.
- [43] Stegen S, van Gastel N, Eelen G, et al. HIF-1 α promotes glutamine-mediated redox homeostasis and glycogen-dependent bioenergetics to support postimplantation bone cell survival [J]. *Cell Metabolism*, 2016, 23(2): 265-279.
- [44] Chen J Q, Holguin N, Shi Y, et al. mTORC2 signaling promotes skeletal growth and bone formation in mice [J]. *Journal of Bone and Mineral Research*, 2015, 30(2): 369-378.
- [45] Ji X, Seeley R, Li K, et al. Genetic activation of glycolysis in osteoblasts preserves bone mass in type I diabetes [J]. *Cell Chemical Biology*, 2023, 30(9): 1053-1063.e5.
- [46] Esen E, Chen J Q, Karner C M, et al. WNT-LRP5 signaling induces Warburg effect through mTORC2 activation during osteoblast differentiation [J]. *Cell Metabolism*, 2013, 17(5): 745-755.
- [47] Park-Min K H. Metabolic reprogramming in osteoclasts [J]. *Seminars in Immunopathology*, 2019, 41(5): 565-572.
- [48] Taubmann J, Krishnacoumar B, Böhm C, et al. Metabolic reprogramming of osteoclasts represents a therapeutic target during the treatment of osteoporosis [J]. *Scientific Reports*, 2020, 10(1): 21020.
- [49] Indo Y, Takeshita S, Ishii K A, et al. Metabolic regulation of osteoclast differentiation and function [J]. *Journal of Bone and Mineral Research*, 2013, 28(11): 2392-2399.
- [50] Nishioku T, Nakao S, Anzai R, et al. HIF-1 α stabilization in osteoclasts induces the expression of aerobic glycolysis-related proteins GLUT1, LDHA, and MCT4 [J]. *Journal of Pharmacological Sciences*, 2025, 158(4): 336-342.
- [51] Wang J, Guan H F, Liu H, et al. Inhibition of PFKFB3 suppresses osteoclastogenesis and prevents ovariectomy-induced bone loss [J]. *Journal of Cellular and Molecular Medicine*, 2020, 24(3): 2294-2307.
- [52] Kim H, Takegahara N, Choi Y. IgSF11-mediated phosphorylation of pyruvate kinase M2 regulates osteoclast differentiation and prevents pathological bone loss [J]. *Bone Research*, 2023, 11(1): 17.
- [53] Cai C, Jiang J W, Li S, et al. PKM2 regulates osteoclastogenesis by affecting osteoclast precursor cell fusion via downregulation of OC-STAMP and DC-STAMP [J]. *Journal of Biological Chemistry*, 2025, 301(5): 108439.
- [54] Veis D J, O'Brien C A. Osteoclasts, master sculptors of bone [J]. *Annual Review of Pathology: Mechanisms of Disease*, 2023, 18: 257-281.
- [55] Ahn H, Lee K, Kim J M, et al. Accelerated lactate dehydrogenase activity potentiates osteoclastogenesis via NFATc1 signaling [J]. *PLoS One*, 2016, 11(4): e0153886.
- [56] Arnett T R, Orriss I R. Metabolic properties of the osteoclast [J]. *Bone*, 2018, 115: 25-30.
- [57] Wang C Y, Wu Q H, Zhuang L Y, et al. Immunometabolism of macrophages in the bone microenvironment: a new perspective for bone healing therapy [J]. *Journal of Advanced Research*, 2026, 82: 485-506.
- [58] Fan Y, Wang N D, Zhao C X, et al. Succinate-mediated metabolic alterations and signaling in RA: mechanisms and therapeutic implications [J]. *Frontiers in Immunology*, 2026, 17: 1842560.
- [59] Guo Y Q, Xie C Z, Li X Y, et al. Succinate and its G-protein-coupled receptor stimulates osteoclastogenesis [J]. *Nature Communications*, 2017, 8: 15621.
- [60] Nishioku T, Anzai R, Hiramatsu S, et al. Lactate dehydrogenase A inhibition prevents RANKL-induced osteoclastogenesis by reducing enhanced glycolysis [J]. *Journal of Pharmacological Sciences*, 2023, 153(4): 197-207.
- [61] Zong B Y, Yu F Z, Li S C, et al. The emerging role of lactate in skeletal homeostasis and disorders: integrated mechanisms and translational opportunities [J]. *Journal of Orthopaedic Translation*, 2026, 59: 101144.
- [62] Sato K, Suematsu A, Okamoto K, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction [J]. *The Journal of Experimental Medicine*, 2006, 203(12): 2673-2682.
- [63] Zhu L, Hua F, Ding W, et al. The correlation between the Th17/Treg cell balance and bone health [J]. *Immunity & Ageing*, 2020, 17: 30.
- [64] Qi Z Q, Luo J Y, Xiao Z, et al. Functional roles of immune cells in osteoporosis [J]. *Frontiers in Immunology*, 2025, 16: 1698283.
- [65] Bhadrachia H, Patel V, Singh A K, et al. Increased frequency of Th17 cells and IL-17 levels are associated with low bone mineral density in postmenopausal women [J]. *Scientific Reports*, 2021, 11(1): 16155.
- [66] Palazon A, Goldrath A W, Nizet V, et al. HIF transcription factors, inflammation, and immunity [J]. *Immunity*, 2014, 41(4): 518-528.
- [67] Wang Y H, Zhou L, Zhang L. The role of metabolic reprogramming in inflammatory bone diseases [J]. *Biochemical Pharmacology*, 2026, 243(Pt 2): 117541.
- [68] Rius J, Guma M, Schachtrup C, et al. NF- κ B links innate immunity to the hypoxic response through transcriptional regulation of HIF-1 α [J]. *Nature*, 2008, 453(7196): 807-811.
- [69] Li X L, Yang Y Y, Zhang B, et al. Lactate metabolism in human health and disease [J]. *Signal Transduction and Targeted Therapy*, 2022, 7(1): 305.
- [70] Ribet A B P, Ng P Y, Pavlos N J. Membrane transport proteins in osteoclasts: the ins and outs [J]. *Frontiers in Cell and Developmental Biology*, 2021, 9: 644986.
- [71] Halestrap A P. The monocarboxylate transporter family: structure and functional characterization [J]. *IUBMB Life*, 2012, 64(1): 1-9.
- [72] Imai H, Yoshimura K, Miyamoto Y, et al. Roles of monocarboxylate transporter subtypes in promotion and suppression of osteoclast differentiation and survival on bone [J]. *Scientific Reports*, 2019, 9(1): 15608.
- [73] Minami E, Sasa K, Yamada A, et al. Lactate-induced histone lactylation by p300 promotes osteoblast differentiation [J]. *PLoS One*, 2023, 18(12): e0293676.
- [74] Wu J H, Hu M, Jiang H, et al. Endothelial cell-derived lactate triggers bone mesenchymal stem cell histone lactylation to attenuate osteoporosis [J]. *Advanced Science*, 2023, 10(31): e2301300.
- [75] Wei T, Ma D N, Liu L L, et al. Lactate promotes bone healing by regulating the osteogenesis of bone marrow mesenchymal stem cells through activating Olfr1440 [J]. *Translational Research*, 2024, 273: 78-89.
- [76] Bao C C, Ma Q, Ying X H, et al. Histone lactylation in macrophage biology and disease: from plasticity regulation to therapeutic implications [J]. *EBioMedicine*, 2025, 111: 105502.