·综述·

糖尿病性骨质疏松与脂肪干细胞成骨分化能力损害机制研究进展

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摘　要：糖尿病（DM）患者长期高血糖所致骨质疏松及骨愈合延迟等骨骼并发症已成为显著降低其生活质量的临床难题，其核心机制与脂肪干细胞（ADSCs）成骨分化能力受损密切相关。在骨组织工程中，ADSCs 因取材微创、增殖迅速及多向分化能力被视为骨缺损修复的种子细胞，但 DM 病理环境显著抑制了 ADSCs 的成骨潜能，进而影响了糖尿病骨病的治疗效率。因此，探索高糖环境下 ADSCs 成骨能力障碍的深层机制对优化糖尿病骨病的治疗策略具有重要意义。本文系统回顾并总结了高糖环境中 ADSCs 迁移能力下降、增殖活性降低、衰老凋亡加速及成骨分化障碍的潜在机制。高糖环境可通过激活氧化应激、晚期糖基化终产物积聚以及扰乱 Wnt/β-catenin、PI3K/Akt/mTOR、Notch 等关键信号通路，从而抑制成骨相关基因的表达。此外，表观遗传修饰中 DNA 甲基化及非编码 RNA 网络可共同沉默成骨基因。深入阐明上述机制不仅有助于理解糖尿病骨病的发病机理，更为制定干预策略提供了方向。本综述旨在推动 ADSCs 再生医学在 DM 中的应用，并为进一步开发 DM 患者自体 ADSCs 修复和治疗骨缺损的策略提供理论依据。

关键词：脂肪干细胞；成骨分化；糖尿病性骨质疏松；糖尿病；骨组织工程
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Research Progress on the Mechanism of Diabetic Osteoporosis and Impaired Osteogenic Differentiation Ability of Adipose-derived Stem Cells

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Abstract: Bone complications such as osteoporosis and delayed bone healing caused by long-term hyperglycemia in patients with diabetes mellitus (DM) have become clinical problems that significantly reduce their quality of life. The core mechanism is closely related to the impaired osteogenic differentiation ability of adipose-derived stem cells (ADSCs). In bone tissue engineering, ADSCs are considered as seed cells for bone defect repair due to their minimal invasiveness, rapid proliferation and multi-directional differentiation ability. However, the pathological environment of DM significantly inhibits the osteogenic potential of ADSCs, which affects the treatment efficiency of diabetic bone diseases. Therefore, it is of great significance to explore the underlying mechanism of impaired osteogenic ability of ADSCs in hyperglycemic environment for optimizing the treatment strategy of diabetic bone diseases. This article systematically reviewed and summarized the potential mechanisms of decreased migration ability, reduced proliferation activity, accelerated senescence and apoptosis, and impaired osteogenic differentiation of ADSCs in high glucose environment. High glucose environment can inhibit the expression of osteogenesis-related genes by activating oxidative stress, accumulation of

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advanced glycation end products, and disrupting Wnt/β-catenin, PI3K/Akt/mTOR, Notch and other key signaling pathways. In addition, DNA methylation in epigenetic modification and non-coding RNA network can jointly silence osteogenic genes. Further elucidation of the above mechanisms not only helps to understand the pathogenesis of diabetic bone diseases, but also provides a direction for the development of intervention strategies. This review aims to promote the application of ADSCs in regenerative medicine for DM management and provide a theoretical basis for further development of strategies for autologous ADSCs repair and treatment of bone defects in DM patients.

Key words: adipose-derived stem cells; osteogenic differentiation; diabetic osteoporosis; diabetes mellitus; bone tissue engineering

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糖尿病(diabetes mellitus, DM)是以胰岛素绝对或相对缺乏并伴生物利用障碍为病理特征的代谢性疾病,临床中常以持续性高血糖为主要表现。流行病学数据显示,2021年全球DM患者已有5.29亿例,预计至2050年将增至13亿例,为重大公共卫生挑战之一[1]。DM患者的骨骼系统常受高糖毒性影响而出现特征性变化,表现为成骨细胞活性降低与破骨细胞活性增强,进而引发骨密度的降低与骨微结构的损伤,即糖尿病性骨质疏松(diabetic osteoporosis, DOP)[2]。相关临床调查显示DM患者骨质疏松发生率高达60%,显著高于非DM人群[3-4]。在骨缺损修复领域中,基于种子细胞的骨组织工程技术为再生医学提供了新路径。其中,脂肪干细胞(adipose derived stem cells, ADSCs)凭借其强大的增殖能力、多向分化潜能及易获取性,在绝经后骨质疏松等代谢性骨病的成骨调控研究中已取得一定进展[5-6]。然而,近年研究发现DM病理环境可通过表观遗传修饰、信号通路失调等机制显著降低ADSCs的成骨效应,这可能是导致DM骨修复障碍的重要诱因。因此,本文聚焦DM微环境对ADSCs成骨分化的调控机制,旨在为开发针对DM的临床靶向治疗策略提供理论依据。

1 脂肪干细胞的成骨分化调控机制

ADSCs作为存在于脂肪基质血管组分中的多能干细胞,具有成骨、成软骨及成脂三系分化潜能,其高效的自我更新能力与特异性分化特征为骨缺损修复提供了理想的细胞来源[7]。而高糖环境会引发骨微环境的改变,包括炎症因子的释放和活性氧的增加。这些变化可能导致骨组织中趋化因子的表达增加,从而吸引ADSCs向骨缺损部位迁移,并在该部位大量增殖以进行成骨分化[8-9]。ADSCs的成骨分化可分为3个关键阶段(图1)。启动阶段:骨形态发生蛋白(bone morphogenetic protein, BMP)信号激活Smad1/5/8磷酸化,驱动关键转录因子Runx相关转录因子2(Runt-related transcription factor 2, Runx2)的核转位,同时抑制过氧化物酶体增殖物激活受体γ的表达以消除成脂分化的竞争性抑制。此阶段伴随碱性磷酸酶活性的快速上调,标志着成骨表型的初步确立[10-11];分化中期:经典Wnt/β-catenin信号通路的激活使β-catenin蛋白在胞内稳定累积,并与核内Runx2形成转录复合体,协同诱导下游调控因子Osterix的表达上调,导致成骨特异性基因群(*COL1A1*、*OPN*等)的转录激活,促进细胞外基质的早期矿化[12-13];成熟矿化期:成骨分化终末标志物骨钙素的表达显著增强,通过钙磷酸盐结晶沉积形成矿化结节。此过程受PI3K/Akt信号通路的正向调控,并与细胞外基质中羟基磷灰石的定向排列相关[14]。

2 糖尿病环境对脂肪干细胞成骨能力的影响

ADSCs成骨是一个复杂的过程,包括靶向迁移、快速增殖、定向分化等生物学过程。高糖环境可对该过程的每一个环节造成干扰,导致ADSCs向骨细胞分化的进程受到抑制,进而影响其成骨效应。

2.1 抑制脂肪干细胞的迁移能力

ADSCs向骨缺损部位的定向迁移能力是其参与骨修复的关键前提,该过程主要受CXCL12/CXCR4信号轴调控,并通过整合素α5β1与细胞外基质中的纤连蛋白结合实现空间定位[15-16]。这一过程受多重因素调节,包括化学趋化因子(如SDF-

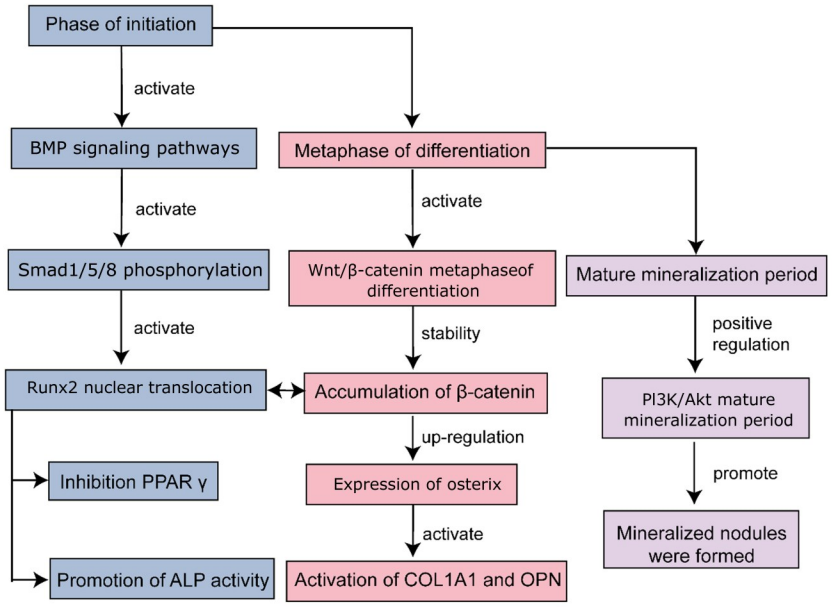


图1　ADSCs成骨分化的3个关键阶段示意图

Fig. 1　Schematic diagram of the three key stages of osteogenic differentiation of ADSCs

1）、炎症细胞因子（如TNF-α、IL-6）以及促生长因子（FGF-2、PDGF）等[17-20]。而DM诱导的糖毒性会显著抑制CXCR4的表达，导致ADSCs迁移能力显著下降，较正常ADSCs迁移细胞数减少约43%[21]。高糖环境不仅直接干扰趋化因子受体的功能，还会诱导活性氧（reactive oxygen species，ROS）的异常累积，促进晚期糖基化终产物的形成，进而破坏细胞迁移的微环境平衡[22]。因此，消除高糖环境对ADSCs定向迁移的负面影响是改善DM骨修复障碍的重要前提。ADSCs向骨缺损部位迁移仅是骨修复的初始步骤，迁移后的细胞需通过快速增殖形成足够密度的细胞群落，为后续分化提供基础。然而，高糖环境对增殖能力的抑制进一步削弱了骨修复的细胞储备。

2.2　降低脂肪干细胞的增殖活性

增殖阶段细胞通过激活mTORC1信号增强糖酵解水平，促进线粒体生物的合成及能量储备物质（ATP/NADPH）的积累以满足分化需求[23]。动物实验表明，在高糖环境下，DM小鼠ADSCs增殖速率降低，且伴有因ROS水平升高而引发的早衰现象；而将细胞置于低糖环境后，其增殖能力可部分恢复。这一现象在糖尿病人群的ADSCs中也得到了相同结果[24-25]。此外，DM环境中神经肽Y（neuropeptide Y，NPY）对ADSCs增殖呈现浓度依赖性调控，低浓度NPY通过激活ERK1信号使细胞增殖率提高，而高浓度则产生抑制作用。这提示精确调控DM微环境中NPY的浓度对维持干细胞的功能具有潜在意义[26-27]。值得注意的是，高糖对增殖的抑制常伴随细胞代偿性应激，即持续的能量代谢失衡与ROS累积将激活衰老程序，使ADSCs提前退出增殖周期，进入衰老阶段。

2.3　加速脂肪干细胞的衰老及凋亡

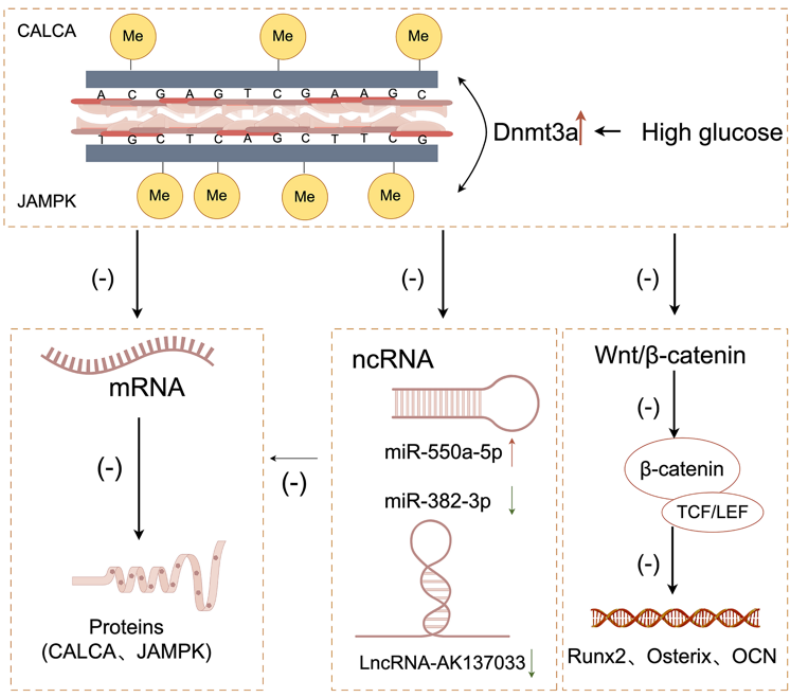
DM患者持续的代谢紊乱会加速ADSCs的衰老进程并促发程序性死亡。长期暴露于高糖环境会影响ADSCs的传代稳定性，至其第6代即出现增殖抑制、凋亡率升高的现象，至第8代时衰老标志物SA-β-gal阳性率较暴露于低糖的ADSCs显著增加[28]。这一过程中，TSC1蛋白表达增加，特异性阻断mTORC1复合物的募集与激活，导致mTOR-PI3K-Akt信号通路失衡，不仅干扰细胞自噬调控，而且可激活内质网应激加剧细胞代谢失衡[29-30]。同时，高糖环境导致线粒体膜电位持续下降，导致ATP合成减少和NAD^+/NADH动态失衡，共同形成衰老趋势[29]。据报道，miR-486-5p的高表达通过靶向抑制SIRT1介导的去乙酰化调控网络，以及过量ROS的产生也是造成ADSCs衰老及凋亡的潜在机制[31-32]。衰老的ADSCs不仅迁移、增殖能力减弱，其分化潜能也显著受损，进一步削弱其成骨能力。

2.4　减弱脂肪干细胞的成骨分化

在高糖环境下，ADSCs表现出定向迁移受阻、增殖能力受损、衰老凋亡加速以及终末分化障碍特

点,这些变化共同导致了其成骨能力的显著下降。其中ADSCs成骨分化能力受损是DM骨缺损修复障碍的核心病理环节,这一过程涉及表观遗传调控、信号通路干扰、自噬失衡及氧化应激多种分子机制,形成高度整合的调控网络。

2.4.1 表观遗传学 作为表观遗传调控的核心机制,DNA甲基化在糖尿病性骨质疏松脂肪干细胞(diabetic osteoporosis-adipose derived stem cells, DOP-ADSCs)成骨分化障碍中显著增加。在DOP小鼠模型中,ADSCs的DNA甲基转移酶Dnmt3a表达显著增加,降低Dnmt3a表达在体内外实验中均证实可有效恢复ADSCs的成骨分化能力[33]。同时,成骨关键基因*Calca*同样因启动子区同发生高甲基化修饰,从而显著抑制其表达。*JKAMP*基因外显子3-7区域同样发生了特异性DNA高甲基化修饰,其表达恢复能有效改善DOP-ADSCs的成骨能力[34-35]。此外,非编码RNA网络失衡进一步加剧ADSCs表观调控紊乱。具体而言,miR-382-3p能显著增强DM患者ADSCs的成骨分化能力,而miR-550a-5p则发挥抑制作用,且2种miRNA均抑制ADSCs向脂肪组织分化[36]。LncRNA-AK137033的表达水平与DM环境中ADSCs成骨能力呈正相关[37]。这些研究结果表明,DM微环境显著破坏了ADSCs表观遗传调控网络的稳态平衡,详见图2。然而,目前的研究大多集中在单一调控层面,缺乏对表观遗传机制的系统性整合。未来研究需要进一步整合组蛋白修饰、染色质重构等多重表观遗传机制,以完善对DOP-ADSCs成骨分化障碍的调控网络的理解。值得注意的是,Dnmt3a的高表达不仅影响表观遗传调控,还通过抑制Wnt/β-catenin信号通路的活性,调节成骨相关基因(如*Runx2*、*Osterix*、*OCN*)的表达,进而影响ADSCs的成骨分化[35, 37]。因此,表观遗传调控与信号通路之间的交互作用可能是理解DOP发病机制的关键环节。



Me: methyl group; Dnmt3a: DNA methyltransferase 3A; TCF: T-cell Factor; LEF: lymphoid enhancing factor; Runx2: Runt-related transcription factor 2; Osterix: osterix transcription factor; OCN: osteocalcin. This figure was drawn by Figdraw.

图2 高糖环境下ADSCs成骨分化的表观遗传调控

Fig. 2 Epigenetic regulation of osteogenic differentiation of ADSCs under high glucose conditions

2.4.2 信号传导 高糖环境下ADSCs成骨分化主要由3条信号通路调控,分别为:Wnt/β-catenin、Notch以及PI3K/AKT/mTOR信号通路。①Wnt/β-catenin信号通路:Wnt信号通路是细胞进化中高度保守的信号通路之一,其异常变化在骨代谢疾病中有着至关重要的作用[38-39]。在高糖环境下,晚期糖基化终产物及其受体(receptor for advanced glycation end products, RAGE)的积累会抑制Wnt/β

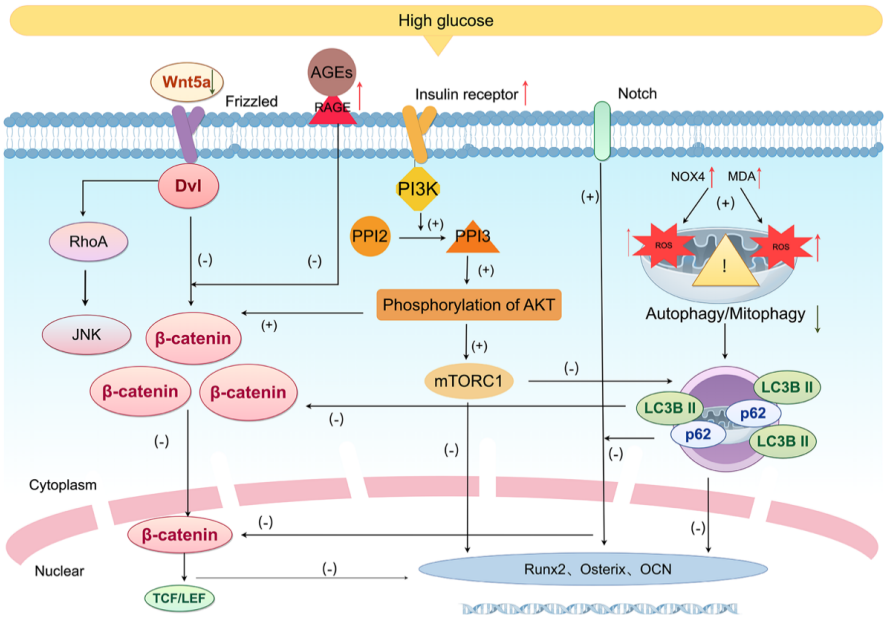
-catenin信号通路。研究发现，RAGE特异性抑制剂FPS-ZM1能够降低ADSCs中DNMT1和DNMT3a的表达，同时增加β-Catenin和LEF1的表达，通过减少DNA甲基化来激活Wnt信号通路，从而改善ADSCs的成骨分化能力[40]。同时，DNMT1/DNMT3a介导的DNA超甲基化可直接抑制Wnt/β-catenin信号通路。据报道，使用DNA甲基转移酶抑制剂5-aza-dC或调节Dnmt3a、JKAMP、LncRNA-AK137033的表达，可降低DNA甲基化水平，恢复Wnt/β-catenin信号通路的活性，进而促进ADSCs成骨[33, 35, 37, 41]。此外，胰高血糖素样肽-1可通过Wnt/GSK-3β/β-catenin途径促进人ADSCs的体外成骨分化，这一结论在DM小鼠体内试验中也得到了证实[42]。②Notch信号通路：在骨组织发育过程中，Notch信号通路对成骨和破骨细胞的形成具有双重作用。Notch信号激活后，可促进成骨细胞分化和矿化过程，而过度激活会促进破骨细胞前体分化为成熟破骨细胞，增强骨吸收[43]。Rao等[44]发现DOP-ADSCs的自噬能力和成骨分化能力均呈下降趋势，且自噬通过激活Notch信号通路促进成骨分化，而抑制Notch信号可阻断自噬对成骨的正向作用，这为DM骨代谢紊乱中细胞自噬与经典信号通路的相互作用提供了直接证据。③PI3K/AKT/mTOR信号通路：为经典响应胰岛素信号的通路。RNA-seq分析表明，糖尿病脂肪干细胞（diabetes mellitus-adipose derived stem cells，DM-ADSCs）中PTEN mRNA高表达可抑制AKT/mTOR/HIF-1α通路从而阻碍成骨基因转录，而*PTEN*基因敲除可显著改善这一过程，这对DM动物模型中植入物的骨融合起着重要作用[45]。此外，高糖环境中，PI3K/AKT/mTOR信号通路的过度激活可抑制自噬，而Torin1激活自噬后ADSCs的成骨能力可部分恢复[46]。这与之前ADSCs成骨分化障碍与自噬通量衰减相关的结论一致[44, 47]。

2.4.3　氧化应激　除信号通路调控外，ADSCs的成骨分化障碍也被证实与高糖环境引发的氧化应激有着密切关联。研究表明，DM-ADSCs内ROS蓄积，伴谷胱甘肽过氧化物酶和超氧化物歧化酶活性显著降低，这提示氧化-抗氧化系统稳态失衡是高糖环境引发ADSCs成骨障碍的核心特征[48]。在体外实验中，高糖处理后ADSCs的ROS水平和NADPH氧化酶4（NADPH oxidase 4，NOX4）表达增加，同时氧化应激标志物丙二醛升高，利用NOX1/4双重抑制剂GKT137831可显著减少ROS产生，同时下调丙二醛水平从而恢复ADSCs成骨能力[31]。此外，有学者认为，适度的自噬可以清除受损的线粒体和过量的ROS，减轻氧化应激对细胞的损伤，从而保护胰岛β细胞的功能。然而，过度的氧化应激可能导致自噬过度激活，进一步损伤细胞[49]。因此，调节氧化应激与自噬之间的平衡以及调控相关信号通路的活性可能是治疗2型DM的重要策略，详见图3。

3　总结与展望

DOP是DM的一种慢性并发症，主要由于DM患者长期碳水化合物、脂肪和蛋白质代谢紊乱，导致骨吸收超过骨形成，更易发生骨折。高糖环境下患者的骨修复障碍ADSCs成骨功能受损密切相关。一方面，DM抑制CXCL12/CXCR4信号轴并诱导ROS异常积累，导致ADSCs向骨缺损部位的迁移能力显著下降，同时mTORC1信号失调和NPY的浓度依赖性调控进一步削弱细胞增殖活性，加速早衰现象。另一方面，长期高糖暴露引发线粒体功能障碍和内质网应激，促使ADSCs衰老标志物SA-β-gal阳性率升高，并通过miR-486-5p/SIRT1轴加剧凋亡进程。更重要的是，DM微环境通过表观遗传修饰、信号通路抑制以及氧化应激与自噬稳态破坏的相互影响，形成复杂的调控网络，最终导致ADSCs成骨能力丧失。需指出的是，本研究结论主要基于体外实验及部分动物模型，临床样本数据仍显不足，未来需扩大临床队列，深入探究DM骨微环境中代谢-表观遗传-信号通路的交互网络，以推动ADSCs的临床转化。研究者可以着眼于此，以表观遗传修饰为核心，深入探讨DM骨微环境中代谢状态如何影响ADSCs的表观遗传图谱，如DNA甲基化、组蛋白修饰等，进而揭示其对成骨相关基因表达调控的机制。

再生医学领域中自体移植ADSCs已成为精准修复骨缺损的重要手段。因此，恢复DM患者自体ADSCs的正常生理功能，是实现骨再生的关键[50-51]。药物联合治疗中，维生素D3和二甲双胍的协同应用可清除ROS蓄积；恩格列净可调控溶酶体-自噬体偶联效率，进而部分逆转高糖对成骨能力的抑制[48,52-53]。非药物干预手段中的运动疗法已证实可改善高糖环境，但是否可以改变ADSCs分化特性仍有待研究[54]。鉴于此，未来研究可深入探索



Wnt5a: wingless-type MMTV integration site family, member 5A; Dvl: dishevelled; RhoA: Ras homolog gene family member A; JNK: c-Jun N-terminal kinase; TCF: T-cell factor; LEF: lymphoid enhancing factor; AGE: advanced glycation end products; RAGE: receptor for advanced glycation end products; PI3K: phosphatidylinositol 3-Kinase; mTORC1: mammalian target of rapamycin complex 1; NOX4: NADPH oxidase 4; MDA: malondialdehyde; p62: sequestosome-1; LC3B: microtubule-associated protein 1 light chain 3B; Runx2: Runt-related transcription factor 2; Osterix: osterix transcription factor; OCN: osteocalcin. This figure was drawn by Figdraw.

图3 高糖环境下ADSCs成骨分化的自噬、氧化应激与信号通路调控

Fig. 3 Regulation of autophagy, oxidative stress and signaling pathways in osteogenic differentiation of ADSCs under high glucose environment

运动对DM高糖环境下ADSCs成骨能力增强的具体作用机制,从而为优化非药物干预策略提供科学依据,推动自体移植ADSCs在DM相关骨缺损精准修复中的临床应用。

近年来,随着DM患者骨折发生率的不断攀升,骨组织工程作为骨缺损重建的潜在手段备受关注。深入探寻提升DM患者ADSCs成骨分化效应的治疗策略,已成为再生医学领域亟待突破的新热点。本文总结了高糖环境对ADSCs特性影响的潜在机制,以期为解决DM患者自体ADSCs骨修复效率低下这一难题提供临床治疗策略的理论依据。

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