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老龄化影响下骨质疏松性骨折的病理机制及其影响研究

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摘　要

随着全球老龄化进程的加快，骨质疏松性骨折(OPF)已成为严重威胁老年人健康的公共卫生问题，特别是在绝经后女性和老年男性中，骨折发生率显著上升。本文系统地分析了骨质疏松性骨折的病理机制，重点探讨了破骨细胞与成骨细胞在骨折发生及愈合过程中的关键作用。破骨细胞过度激活和成骨细胞功能受损是导致骨折愈合延迟和骨质量下降的主要原因。衰老、氧化应激、炎症反应以及雌激素缺乏等因素通过多条信号通路共同影响破骨细胞和成骨细胞的功能。为有效治疗骨质疏松性骨折，本文总结了近年来针对破骨细胞和成骨细胞的最新治疗策略，包括靶向RANKL/RANK信号通路抑制破骨细胞活性、应用甲状旁腺激素类药物促进成骨细胞功能、以及基因治疗和纳米技术在骨折治疗中的潜力。综上所述，精准治疗策略有望加速骨折愈合、改善骨质量，并显著减轻骨质疏松性骨折对患者生活质量和社会经济负担的影响。

关键词

骨质疏松性骨折，病理机制，破骨细胞，成骨细胞，治疗策略

Study on the Pathological Mechanisms and Impact of Osteoporotic Fractures under the Influence of Aging

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Abstract

With the acceleration of global aging, osteoporotic fractures (OPF) have become a significant public

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health issue threatening the health of the elderly, especially with a marked increase in fracture incidence among postmenopausal women and elderly men. This article systematically analyzes the pathological mechanisms of osteoporotic fractures, focusing on the key roles of osteoclasts and osteoblasts in fracture occurrence and healing. Overactivation of osteoclasts and dysfunction of osteoblasts are the main causes of delayed fracture healing and bone quality deterioration. Aging, oxidative stress, inflammatory responses, and estrogen deficiency, among other factors, influence osteoclast and osteoblast functions through various signaling pathways. To effectively treat osteoporotic fractures, this article summarizes the latest therapeutic strategies targeting osteoclasts and osteoblasts, including inhibition of osteoclast activity via the RANKL/RANK signaling pathway, promotion of osteoblast function with parathyroid hormone (PTH) analogs, and the potential application of gene therapy and nanotechnology in fracture treatment. In conclusion, precision treatment strategies are expected to accelerate fracture healing, improve bone quality, and significantly reduce the impact of osteoporotic fractures on patients' quality of life and the socioeconomic burden.

Keywords

Osteoporotic Fractures, Pathological Mechanisms, Osteoclasts, Osteoblasts, Treatment Strategies

1. 引言

随着全球老龄化进程的加快，骨质疏松性骨折已成为显著影响老年人健康的重大公共卫生问题[1] [2]。骨质疏松性骨折的高发生率和致残率不仅影响患者的生活质量，还对社会经济带来了沉重负担。其主要病理机制表现为骨吸收与骨生成失衡[3]，尤其是在破骨细胞和成骨细胞的调控过程中出现异常。据报道在全球范围内，骨质疏松症的患病率持续上升，特别在绝经后女性和老年男性中，骨折风险显著增加[4]。因此，深入理解骨质疏松性骨折的病理机制及其影响因素，对制定有效的治疗和预防策略至关重要。

2. 骨质疏松性骨折的病理机制

骨质疏松性骨折(OPF)是骨质疏松症最严重的并发症之一，全球约有 2 亿人受到其影响[5]。随着年龄的增长，骨质疏松性骨折的发生率显著增加，尤其在女性中，由于绝经后雌激素水平下降，骨密度丧失加剧，骨折风险显著提高[6] [7]。破骨细胞与成骨细胞功能失衡在骨折发生中发挥核心作用。正常情况下，破骨细胞通过骨吸收清除老化骨基质，成骨细胞则促进新骨生成并维持骨密度。然而，在骨质疏松症中，破骨细胞的过度活化与成骨细胞功能减退共同导致骨吸收超过骨生成，最终引发骨质疏松性骨折。

2.1. 破骨细胞在骨质疏松性骨折中的作用

骨质疏松性骨折的愈合受多重因素影响，尤其是破骨细胞的过度激活，过度活化的破骨细胞不仅会加剧骨密度的下降，还可能导致骨结构的损伤和骨折风险的增加[8]。此外，由于骨质疏松患者骨量减少和骨重塑过程的失衡，破骨细胞功能的异常活跃常常导致骨折愈合的延迟和骨质的劣化。这种过度激活的现象通常受到多种因素的驱动，包括衰老、氧化应激、慢性炎症反应以及雌激素水平的下降等。衰老不仅通过促进破骨细胞前体细胞增殖和分化，还通过激活 p53 等衰老相关信号通路[9]，增加 RANKL 表达，激活破骨细胞，进一步加剧骨吸收和骨质丧失。雌激素缺乏是破骨细胞活性增加的重要因素，雌激

素通过雌激素受体(ER)信号通路抑制破骨细胞形成和活性，主要通过抑制 NF-κB、MAPK 等通路减少破骨细胞分化和功能[10]。然而，随着雌激素水平下降，破骨细胞的形成和活性显著增强，尤其是通过促进 RANKL 与其受体 RANK 结合，激活 NF-κB、PI3K/Akt 等信号通路，增加破骨细胞增殖和骨吸收[11]。氧化应激通过产生过量活性氧(ROS)激活多条信号通路(如 NF-κB、MAPK、PI3K/Akt 等) [12] [13]，不仅增强破骨细胞分化和骨吸收，还促进破骨细胞前体凋亡，导致骨量丧失[14]。慢性低级别炎症反应，尤其是 TNF-α、IL-1β 和 IL-6 等炎症因子的持续释放[15]，也通过激活 NF-κB、MAPK、JAK/STAT 等信号通路，促进破骨细胞形成与活性，进一步加重骨质疏松[16]。炎症介质不仅直接刺激破骨细胞前体分化，还通过增加 RANKL 表达，间接促进破骨细胞活化，增加骨吸收。总体而言，衰老、雌激素缺乏、氧化应激和慢性炎症等因素通过多条信号通路(如 NF-κB、MAPK、PI3K/Akt、JAK/STAT 等)协调作用，增强破骨细胞形成与活性，破坏骨重塑平衡，导致骨质疏松性骨折愈合延迟和骨质劣化[17]。因此，针对破骨细胞的调控，尤其是控制其过度激活，可能成为骨质疏松性骨折治疗的重要策略。

2.2. 成骨细胞在骨质疏松性骨折中的作用

成骨细胞是新骨生成的主要参与者，在骨质疏松模型中的成骨细胞显示分化能力下降、矿化能力降低，这些因素共同导致了骨量减少和骨结构脆弱。在骨质疏松性骨折中，成骨细胞功能障碍是导致骨折愈合延迟和骨质量下降的关键因素之一。成骨细胞的功能受 Wnt/β-catenin、BMP/Smad、Notch 等信号通路调控，且这些通路的紊乱会导致成骨细胞分化、增殖及功能受损。在 Wnt/β-catenin 通路中，Wnt 信号通过激活 β-catenin 的核转位促进成骨细胞分化和骨基质合成，Wnt 信号下调或抑制会直接导致成骨细胞功能减退，抑制骨形成。BMP/Smad 信号通路通过 BMP 与其受体结合，激活 Smad 蛋白转录因子，调节成骨细胞的分化和成熟。BMP 信号失调在骨质疏松性骨折中同样促进骨吸收，并抑制骨形成[18]。Notch 信号通路参与成骨细胞的增殖、分化和骨质形成，但其过度激活或抑制会导致成骨细胞功能障碍，进而影响骨重塑平衡。氧化应激和炎症反应是影响成骨细胞功能的关键因素之一[19]。氧化应激通过过量活性氧(ROS)刺激成骨细胞凋亡并抑制骨基质合成，炎症因子，如 TNF-α 和 IL-1β，通过激活 NF-κB 等通路，抑制成骨细胞分化及骨形成[19] [20]。同时，骨折愈合过程中的血管生成不足及局部缺氧进一步会加剧成骨细胞功能的衰退。低氧环境不仅诱导成骨细胞凋亡，还促进破骨细胞的过度活性，形成骨吸收过度的恶性循环。

3. 破骨细胞和成骨细胞的治疗策略

3.1. 破骨细胞的治疗策略

破骨细胞过度活化是骨质疏松性骨折的主要病理机制之一[21]，因此，抑制破骨细胞的活性是治疗的关键策略。近年来，针对破骨细胞功能的精准调控已成为治疗骨质疏松的新趋势[22]。例如，靶向 RANKL/RANK/OPG 信号通路的 Denosumab (一种抗 RANKL 单克隆抗体)通过阻断 RANKL 与 RANK 的结合，抑制破骨细胞的分化和活性，从而减少骨吸收[23]。但在长期使用的副作用方面研究还比较少。因此，未来的研究应着重对不同治疗药物的疗效、治疗期限及其副作用进行系统评估和比较，以为临床实践提供更全面的证据支持。此外研究表明，骨质疏松症的发生与发展常伴随慢性低度炎症，免疫系统的过度激活与破骨细胞过度活化密切相关，研究表明，抗炎治疗(如非甾体抗炎药(NSAIDs)和免疫抑制剂)[24]通过减少促炎因子的释放(如 TNF-α 和 IL-1)在一定程度上抑制了破骨细胞活性，进而有助于骨折愈合[25]。关于免疫调节在骨质疏松治疗中的长效性和安全性的系统性文献仍较为匮乏，尚需更多高质量的临床研究来证实其疗效与安全性。纳米技术的快速发展为破骨细胞治疗提供了新的方向。通过纳米载体将抗破骨细胞药物(如 Denosumab、双膦酸盐)精确递送至骨折部位，可提高局部治疗效果并减少全身副作

用[26] [27]。尤其是纳米药物递送系统，能够通过调节药物释放速度，提供长效治疗，有望在临床中为骨折治疗带来更好的效果[28]。尽管如此，关于不同纳米递送系统的比较研究和临床应用数据仍然不足，未来的研究应聚焦于评估纳米技术在骨质疏松性骨折治疗中的疗效、靶向性及其潜在的副作用。

3.2. 成骨细胞的治疗策略

成骨细胞功能减弱是骨质疏松性骨折愈合延迟的原因之一，因此，促进成骨细胞功能已成为治疗的关键。近年来，甲状旁腺激素(PTH)类药物[29]，特别是其合成类似物 Teriparatide，在促进骨生成方面发挥了重要作用。PTH 通过激活 Wnt/β-catenin 和 MAPK 通路，增强成骨细胞活性，进而促进骨生成[30]，但其对骨折长期愈合效果的影响尚无统一结论，且高成本及长期使用的副作用问题仍需进一步解决。此外，骨形态发生蛋白(BMP)尤其是 BMP-2 和 BMP-7，在促进成骨细胞分化及骨生成方面起着至关重要的作用。BMP 通过激活 Smad 信号通路及 Wnt/β-catenin 通路，增强成骨细胞的分化、增殖和矿化功能[31]，随着生物材料技术的发展，BMP 在局部递送和组织工程中的应用已获得广泛关注[32]。基因治疗在促进骨生成方面展示了较大的潜力。通过基因转导与骨生成相关的基因(如 BMP、OPG、Wnt 等)至骨组织中，可以显著促进成骨细胞的分化、增殖和功能，从而加速骨折愈合[33] [34]。基因治疗的优势在于其长期、持续的治疗效果[35]，但目前的研究仍局限于动物模型和小规模临床试验，尚需大规模、多中心的临床研究验证其疗效与安全性。

4. 总结与展望

骨质疏松性骨折(OPF)随着老龄化加剧而成为全球日益严重的公共卫生问题。破骨细胞与成骨细胞功能失衡是骨质疏松性骨折发生和愈合延迟的主要原因。近年来，治疗策略在破骨细胞和成骨细胞的调控方面取得了显著进展，靶向 RANKL/RANK/OPG 信号通路、免疫调节、纳米技术和基因治疗等方法正在成为新的治疗方向。未来，随着精准医学和纳米技术的进一步发展，骨质疏松性骨折的治疗将趋向个性化和精准化，为患者提供更加有效的治疗方案。

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