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·综述·

力学负荷调控甲状旁腺激素促进下颌骨髁突骨折愈合的机制综述

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【摘要】 下颌骨髁突骨折是口腔颌面外科常见损伤，其解剖结构和力学环境的特殊性使得髁突的骨折愈合过程区别于长骨。甲状旁腺激素（PTH）的活性片段PTH（1-34）（如药物特立帕肽）是目前临床上少数具有促骨形成作用的药物之一，在骨折修复中展现出良好应用前景。但是，髁突与长骨在解剖结构和力学环境上的差异，使得长骨中PTH的疗效证据能否直接推广至髁突骨折尚存疑问。而力学负荷如何影响PTH在下颌骨髁突这一特殊力学环境中的骨改建调控效应，正是解析这一问题的关键切入点。本文从髁突骨折愈合的力学敏感性、PTH调控骨改建的分子机制以及力学-药物协同作用三个层面，综述力学负荷影响PTH促进下颌骨髁突骨折愈合的相关研究进展，旨在梳理现有长骨及体外模型中力学-PTH协同的分子证据，并辨析其向髁突骨折外推的可行性与局限性。基于长骨骨折及体外力学加载模型的研究表明，力学负荷通过调控核因子κB受体活化因子配体/骨保护素（RANKL/OPG）轴和磷脂酰肌醇3-激酶/蛋白激酶B/糖原合酶激酶3β/活化T细胞核因子c1（PI3K/Akt/GSK3β/NFATc1）通路影响PTH对骨改建的调控方向，这一效应呈现显著的力学强度依赖性和时间依赖性。但目前该领域仍存在关键问题待解决，包括力学负荷的定量标准化、髁突特异性骨折模型的直接证据积累以及力学-药物协同调控机制的深入阐明。未来研究应整合有限元分析、标准化力学加载与单细胞组学技术，建立力学参数—细胞响应—PTH效应的定量关系，为优化髁突骨折术后咀嚼负荷管理及PTH用药策略提供依据。

【关键词】 力学负荷；　下颌骨髁突骨折；　甲状旁腺激素；　破骨细胞；　骨改建；　PI3K/Akt/GSK3β/NFATc1信号通路；　力学依赖性；　咀嚼应力
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Mechanical loading modulates parathyroid hormone-promoted healing of mandibular condylar fractures: a mechanistic review

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【Abstract】 Mandibular condylar fractures are common injuries in oral and maxillofacial surgery. The unique anatomical structure and mechanical environment of the condyle render its fracture healing process distinct from that of long bones. Parathyroid hormone (PTH) and its active fragment PTH(1-34) (such as the drug teriparatide) are among the few clinically available agents with bone-anabolic properties, and have shown promise in fracture repair. However, the anatomical and mechanical discrepancies between the condyle and long bones raise doubts as to whether the efficacy of PTH observed in long bones can be directly extrapolated to condylar fractures. Elucidating how mechanical loading modulates the bone remodeling effects of PTH within the specific mechanical environment of the mandibular condyle thus constitutes a critical entry point for addressing this question. This review summarizes recent advances regarding

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how mechanical loading influences PTH-promoted healing of mandibular condylar fractures from three perspectives: the mechanical sensitivity of condylar fracture healing, the molecular mechanisms by which PTH regulates bone remodeling, and the synergy between mechanical and pharmacological interventions, with the aim of clarifying the existing molecular evidence for mechanical-PTH synergy derived from long-bone and in vitro models, and critically evaluating the feasibility and limitations of extrapolating these findings to condylar fractures. Evidence from long-bone fracture models and in vitro mechanical loading systems indicates that mechanical loading modulates the direction of PTH-mediated bone remodeling through the receptor activator of the nuclear factor-κB ligand (RANKL)/osteoprotegerin (OPG) axis and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/glycogen synthase kinase-3β (GSK3β)/nuclear factor of the activated T-cells c1 (NFATc1) pathway, an effect that exhibits marked intensity- and time-dependent characteristics. Nevertheless, critical challenges remain in this field, including the standardization of quantitative mechanical loading parameters, the accumulation of direct evidence from condyle-specific fracture models, and the in-depth elucidation of the regulatory mechanisms governing mechanical-drug synergy. Future research should integrate finite element analysis, standardized mechanical loading techniques, and single-cell omics to establish a quantitative relationship between mechanical parameters, cellular responses, and PTH effects, thereby providing a theoretical basis for optimizing postoperative masticatory load management and PTH administration strategies in condylar fractures.

【Key words】 mechanical loading; mandibular condylar fractures; parathyroid hormone; osteoclast; bone remodeling; PI3K/Akt/GSK3β/NFATc1 signal pathway; mechanical dependence; masticatory stress
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下颌骨髁突是颞下颌关节的关键组成部分,参与咀嚼、吞咽及言语等重要生理功能[1]。系统综述与Meta分析(PROSPERO注册号:CRD42023488662)显示,下颌骨髁突骨折约占下颌骨骨折的29.3%[2]。由于解剖位置特殊、血供单一,下颌骨髁突骨折后常面临愈合缓慢、骨质吸收、关节强直等并发症[3],其治疗决策需综合考虑骨折类型与患者个体条件(PROSPERO注册号:CRD42017052346)[4]。而无论选择何种治疗方式,促进下颌骨髁突骨折的快速、高质量愈合始终是研究重点。临床回顾性研究已证实稳定的力学环境是骨折愈合的重要保障[5]。

甲状旁腺激素(parathyroid hormone, PTH)的活性片段PTH(1-34)(特立帕肽)可显著促进骨形成、加速骨折愈合,已在骨质疏松及骨折修复中广泛研究应用[6-7]。但其效应一定程度上受局部力学微环境的影响,力学负荷可增强PTH的骨合成代谢效应,而缺乏力学刺激则削弱该作用[8-9]。Wolff定律指出骨骼会根据力学需求调整其结构与质量[10],而下颌骨髁突在咀嚼过程中承受复杂的压应力,这种力学刺激如何与PTH的药理作用交互成为当前研究前沿[11]。多中心随机对照试验(ClinicalTrials.gov注册号:NCT00190944)已证实了PTH在长骨骨折治疗中的疗效[12]。

PTH给药时机与力学负荷的时序组合对骨愈合结局存在显著的剂量-时间依赖性[13]。宿主因素(年龄、骨质量)也调节着PTH与力学刺激的交互效应[14]。荟萃分析(PROSPERO注册号:CRD558868)比较了多种骨形成促进剂在骨折愈合中的效果,发现PTH1受体激动剂(特立帕肽和阿巴洛肽)均可有效降低骨折风险,其中阿巴洛肽在降低非椎体骨折和髋部骨折方面优于特立帕肽[15];关于下颌骨髁突骨折治疗方式的系统综述进一步评估了不同手术入路的疗效差异,结果显示开放手术在减少术后咬合紊乱和疼痛方面优于保守治疗,但保守治疗在无移位骨折中仍可获得良好效果,治疗选择应个体化[16]。药物与力学环境的联合干预策略日益受到关注[9],一项随机对照试验(Clinical Trial Registry of India注册号:CTRI/2019/07/020148)比较了PTH与植物提取物促进颌面骨折愈合的效果,发现两者均可加速骨折愈合、改善咬合力恢复,但特立帕肽在增加血清骨形成标志物和早期影像学愈合方面表现更优[17]。骨折愈合的力学生物学基础研究揭示了力学信号调控骨改建的核心机制[18],PTH与Wnt/β-catenin信号通路的交互作用为力学-药物协同提供了分子层面的理论支撑[19]。

本文综述力学负荷影响PTH促进下颌骨髁突骨折愈合的研究进展,重点梳理破骨细胞介导的骨改建及核因子κB受体活化因子配体/骨保护素

(receptor activator of nuclear factor-κB ligand/osteoprotegerin, RANKL/OPG)轴和磷脂酰肌醇3-激酶/蛋白激酶B/糖原合酶激酶3β/活化T细胞核因子c1(phosphatidylinositol 3-kinase/protein kinase B/glycogen synthase kinase-3 beta/nuclear factor of activated T-cells c1, PI3K/Akt/GSK3β/NFATc1)通路的调控机制。在此基础上,辨析长骨及体外模型证据向下颌骨髁突骨折外推的可行性与局限性,并明确当前亟待解决的关键科学问题。

1　下颌骨髁突骨折愈合的力学敏感性

1.1　下颌骨髁突的解剖结构与力学环境

下颌骨髁突表面覆盖纤维软骨,下方为软骨下骨,主要承受压应力和剪切力[20]。咀嚼产生的压应力是维持髁突形态与功能完整性的必要条件[21]。力学负荷缺失可导致局部骨量丢失和骨改建异常[22-23],而保守治疗正是依赖力学平衡与自身改建来实现愈合[24]。

不同方向的力学负荷对软骨下骨的影响存在差异[25]。有限元分析可定量评估不同固定方式[26]及咬合力经关节盘向髁突传递的应力分布[27]。压缩载荷下PTH增加骨量的效果优于拉伸载荷[28],对髁突力学治疗策略具有指导意义。此外,颌间牵引力值的大小与髁突应力分布呈正相关,过度牵引可能导致髁突吸收[29]。

本文所讨论的力学负荷主要包括:①咀嚼压应力——咬合传导至髁突骨折端的压缩载荷,是愈合中最主要的力学刺激形式,临床以食物硬度分级(普食、软食、流食)间接反映其强度;②咀嚼剪切力——下颌侧向运动时作用于髁突表面的剪切应力。需指出,长骨研究中常用的轴向拉伸载荷在髁突生理环境中较为少见,髁突以压应力和剪切应力为主。

1.2　下颌骨髁突骨折愈合过程中的力学调控

下颌骨髁突骨折愈合同样经历炎症、软骨痂、硬骨痂和骨改建四个阶段,但与长骨不同的是,其整个过程始终处于咀嚼压应力的动态调控之下。早期适当微动促进软骨痂形成,过度活动可致骨不连[30];中期需稳定的力学环境利于钙化;后期功能性力学刺激引导骨痂向力学需求方向改建[10]。间充质干细胞在力学刺激下的分化机制已得到系统阐述[31],动态力学加载的体外研究进一步揭示了力学参数与细胞分化命运的定量关系[32]。

骨细胞作为骨组织中最主要的力学感受细胞,通过初级纤毛、整合素及力学敏感离子通道感知力学刺激。瞬时受体电位香草酸亚型4(transient receptor potential vanilloid 4, TRPV4)和压电型机械敏感离子通道组件1/2(piezo-type mechanosensitive ion channel component 1/2, Piezo1/2)是骨细胞表面重要的力学信号转换器[33]。在髁突中,咀嚼产生的压应力经纤维软骨层传导至软骨下骨,骨细胞感知力学应变后,通过调节硬化蛋白和RANKL的表达将力学信号转化为骨改建信号。然而,该机制在髁突骨折愈合中的直接证据仍十分有限,现有结论主要源自长骨及体外模型的外推。骨膜单核转录组图谱鉴定了表达肽酶抑制剂16和干细胞抗原-1的骨骼干/祖细胞及其骨折后分化轨迹[34],为理解力学刺激下骨膜来源细胞的成骨分化提供了新的分子基础。

1.3　咀嚼应力对下颌骨髁突骨折愈合的影响

适当的力学刺激可通过促进血管化和成骨来加速骨痂形成与改建[35]。动物实验证实,食物硬度显著影响愈合质量:普食促进骨痂改建,软食改建缓慢,流食则改建停滞、骨质吸收风险增加[23]。咀嚼超负荷可使种植体周围骨应变增加3.6倍,同时增强骨形成与骨吸收,体现力学负荷的双向调控作用[23];不同模式的力学负荷(如间歇性与持续性)对骨痂改建的影响亦存在差异[25]。

研究表明,术后早期可控的低负荷咀嚼训练能加速下颌骨髁突骨折的功能恢复[36]。有限元分析证实,不同咀嚼压力条件下髁突骨折区域应力分布存在显著差异,骨痂形成与重塑过程受到咀嚼压力的直接作用[37]。然而,术后饮食指导的循证依据仍十分有限,临床决策多依赖经验[38]。现有研究多以食物硬度分级来间接反映咀嚼负荷,尚缺乏对骨折端实际力学刺激的直接量化手段。

目前"高""中""低"力学负荷的划分多以食物硬度的定性分级为基础,尚缺乏基于骨折端实际力学参数(如微应变、应力值)的定量标准——多数研究以普通饲料代表高负荷、软食或半流质代表中等负荷、流食代表低负荷。由于活体动物骨折端力学测量的技术瓶颈,食物硬度与力学刺激之间的定量换算关系尚未建立。未来研究需借助有限元分析结合体内应变测量,建立食物硬度-咀嚼力-髁突应力之间的定量关系。在此基础上,单侧咀嚼异常应力下的关键miRNAs可能成为评估力学环境的生物标志物[39],从分子层面为力学环境的评估提供了新思路。

2　PTH促进骨折愈合的可能分子机制

2.1　PTH的双向调节作用

PTH对骨代谢的作用呈剂量和时间依赖性：持续高剂量促进骨吸收，间歇性低剂量则激活成骨细胞[6]，通过促进骨痂改建和矿化来增强新生骨的力学强度[40]。Jia等[41]在兔下颌骨髁突骨折模型中证实PTH可上调SRY盒转录因子9（SRY-box transcription factor 9，Sox9）、Ⅱ型胶原α1链（collagen type Ⅱ alpha 1 chain，Col2a1）并下调基质金属蛋白酶13（matrix metalloproteinase-13，MMP-13）、X型胶原（collagen type X，ColX），促进下颌骨髁突软骨愈合。黄志才等[42]进一步验证了PTH促进兔下颌骨髁突骨折骨愈合的效应。

此外，PTH可通过西罗莫司不敏感性mTOR伴侣（rapamycin-insensitive companion of mTOR，rictor）/哺乳动物西罗莫司靶蛋白复合物2（mechanistic target of rapamycin complex 2，mTORC2）通路促进骨髓间充质干细胞的迁移与黏附[43]，促进软骨内成骨的血管侵入[44]；印度刺猬蛋白（Indian hedgehog，Ihh）信号通路也参与了这一过程[45]。间歇性PTH治疗甚至可在老年萎缩性骨折模型中克服骨不连[46]。一项关于PTH治疗骨折延迟愈合和不愈合的系统综述为其临床应用提供了循证依据[47]。然而，上述机制在下颌骨髁突中的验证仍局限于少数兔模型，其在人类下颌骨髁突骨折中的适用性尚待证实。

2.2　RANKL/OPG轴在PTH调控骨改建中的枢纽作用

RANKL/OPG比值是评价骨吸收活性的核心指标[48]。PTH对其调控具有时间特异性和条件依赖性：骨折愈合早期上调OPG、下调RANKL，发挥保护性作用[42]；而在足够力学刺激下，PTH则促进RANKL表达、升高RANKL/OPG比值，驱动破骨细胞活化（详见第3节）。骨细胞源性RANKL在PTH促骨吸收中起主导作用[49]。

PTH在成骨细胞分化不同阶段对RANKL和OPG的调控方向存在差异[50]，多种激素和炎症因子亦可动态调节RANKL/OPG比值[51]。Wong等[52]系统梳理了GSK3β在RANK/RANKL/OPG信号网络中的核心调控作用。然而，上述RANKL/OPG调控模式主要来自长骨和基因敲除小鼠模型[49]，在下颌骨髁突特有的压应力环境下，PTH对RANKL/OPG的调控是否呈现相同的力学依赖性，尚无直接实验证据，这也是第3节重点探讨的问题。

2.3　PI3K/Akt/GSK3β/NFATc1通路在PTH诱导破骨细胞分化中的核心作用

NFATc1是破骨细胞分化的“主开关”[53]。Moon等[54]证明Akt/GSK3β/NFATc1级联是驱动破骨细胞分化的核心通路。PTH与成骨细胞、骨细胞表面的PTH1受体结合后上调RANKL表达，RANKL与破骨前体细胞表面RANK结合后激活肿瘤坏死因子受体相关因子6（tumor necrosis factor receptor-associated factor 6，TRAF6）信号，进而启动PI3K/Akt通路。活化的Akt磷酸化GSK3β并抑制其激酶活性，减弱对NFATc1的磷酸化，促进NFATc1核转位及破骨细胞分化基因的转录激活；反之，GSK3β活性增强则通过磷酸化NFATc1促使其出核，抑制破骨细胞活化[55]。

此外，O-N-乙酰葡糖胺（O-linked N-acetylglucosamine，O-GlcNAc）糖基化可促进NFATc1核转位驱动破骨细胞分化[56]。PTH还可通过盐诱导激酶-CREB调控转录共激活因子2（salt-inducible kinase-CREB-regulated transcription coactivator 2，SIK-CRTC2）信号轴调控RANKL转录[57]，Notch信号通路也参与了PTH促成骨效应[58]。PTH1受体信号在骨细胞中的调控机制日益受到关注[59]，但上述通路在下颌骨髁突骨折愈合中的具体作用尚无直接研究报道，有待进一步验证。

2.4　PTH促成骨效应的细胞分子机制

PTH直接作用于成骨细胞和骨细胞，促进增殖分化、抑制凋亡，激活Wnt/β-catenin通路[60]，并通过抑制半胱氨酸天冬氨酸蛋白酶-3（caspase-3）延长成骨细胞寿命[61]；骨细胞亦通过PTH1受体响应PTH刺激[62]。

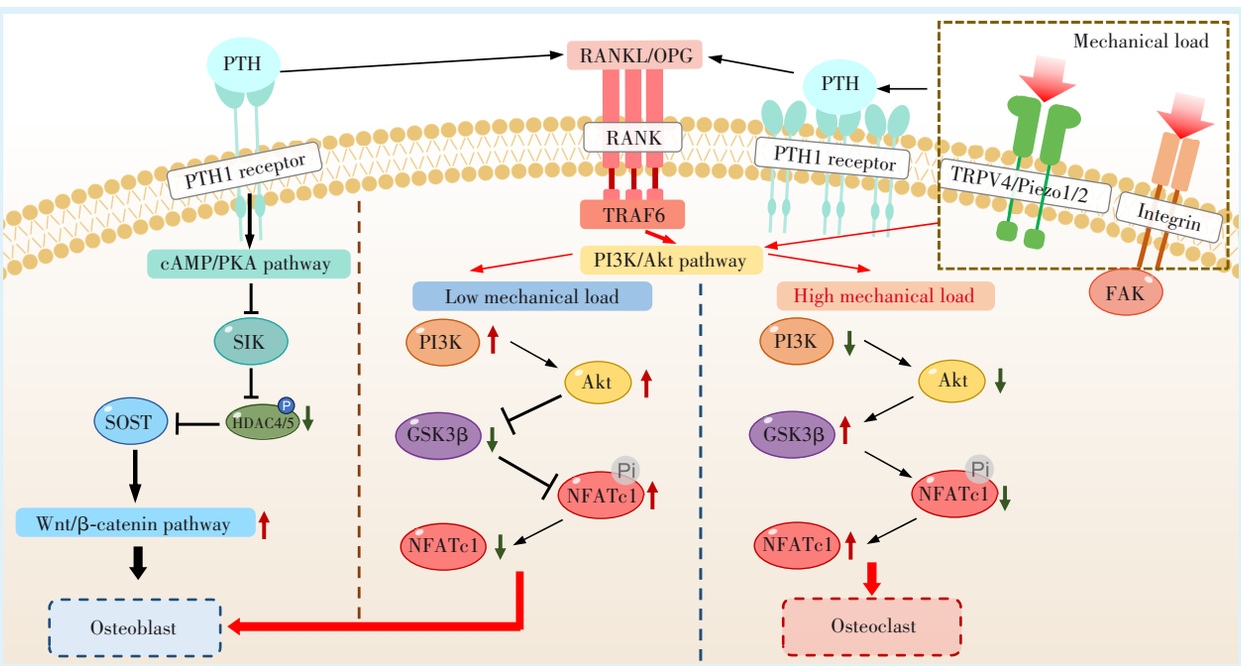
PTH通过抑制盐诱导激酶控制组蛋白去乙酰化酶4/5（histone deacetylase 4/5，HDAC4/5）和CRTC2的定位，分别调控硬化蛋白和RANKL表达[63]，将抑制Wnt和驱动破骨形成的双重效应统一于盐诱导激酶信号轴之下。PTH的生物活性形式可抑制硬化蛋白合成[64]，并可增强骨髓间充质干细胞来源外泌体的治疗效果[65]。Thomsen等[66]指出，间歇性PTH的细胞效应具有细胞类型和力学环境依赖性。单细胞转录组学进一步揭示了PTH促成骨效应的细胞层面异质性——PTH信号在成骨细胞谱系中的强度受基质金属蛋白酶14的精确调控，且PTH（1-34）促进的成骨过程中约50%由软骨细胞来源的成骨细胞贡献[67]。在下颌骨髁突中，由于软骨下骨上方覆盖纤维软骨层，PTH对

软骨细胞和成骨细胞的交互调控可能较长骨更为复杂，但相关机制研究极为有限。

2.5　力学-PTH协同调控骨改建方向的信号整合网络

综合上述机制，力学负荷与PTH在下颌骨髁突骨折愈合中的协同调控可归纳为一个信号整合网络（图1）。PTH激活成骨细胞和骨细胞表面PTH1受体后，一方面通过环磷酸腺苷（cyclic AMP，cAMP）/蛋白激酶A（protein kinase A，PKA）途径抑制盐诱导激酶，降低组蛋白去乙酰化酶4/5磷酸化，抑制硬化蛋白表达，解除对Wnt/β-catenin通路的抑制，促进成骨[63]；另一方面通过上调RANKL、下调OPG，提高RANKL/OPG比值，激活破骨前体细胞表面RANK，启动TRAF6/NFATc1信号级联，驱动破骨细胞分化与活化[52,54]。力学信号经整合素和力学敏感离子通道（TRPV4、Piezo1/2）转导后，上调PTH1受体表达并促进其向初级纤毛转运[68]；同时可激活PI3K/Akt和丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）等与PTH信号共享的下游通路，增强PTH的调控效应[69]。非编码RNA（non-coding RNA，ncRNA）网络通过长链非编码RNA（long non-coding RNA，lncRNA）/环状RNA（circular RNA，circRNA）/微小RNA（microRNA，miRNA）/信使RNA（messenger RNA，mRNA）调控轴在骨再生中发挥关键作用，circRNA/miRNA网络对PTH下游信号通路的转录后调控可能成为骨折愈合干预的新方向[70-71]。

该网络的核心在于：力学负荷强度通过影响骨细胞硬化蛋白表达和成骨细胞PTH1受体表达，决定PTH信号优先驱动成骨还是破骨通路，从而动态调控骨改建方向。



Upon PTH binding to PTH1R, the cAMP/PKA axis modulates salt-inducible kinase (SIK) activity, thereby regulating sclerostin (SOST) expression and the RANKL/OPG ratio. Mechanical signals, transduced via TRPV4/Piezo1/2 channels and integrins, converge on shared downstream cascades, including the PI3K/Akt/GSK3β pathway. The intensity of mechanical loading dictates whether PTH signaling is biased toward the osteogenic (Wnt/β-catenin) or osteoclastogenic (NFATc1) direction. The arrows indicate the following: →, promotion/activation; —| ,inhibition/suppression. PTH: parathyroid hormone; PTH1R: parathyroid hormone type 1 receptor; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; SIK: saltinducible kinase; SOST: sclerostin; RANKL: receptor activator of nuclear factorκB ligand; OPG: osteoprotegerin; RANK: receptor activator of nuclear factorκB; TRAF6: TNF receptorassociated factor 6; NFATc1: nuclear factor of activated Tcells c1; TRPV4: transient receptor potential vanilloid 4; Piezo1/2: piezotype mechanosensitive ion channel component 1/2; Wnt/βcatenin pathway: Wingless-related integration site/β-catenin signaling pathway; PI3K: phosphatidylinositol 3kinase; Akt: protein kinase B; GSK3β: glycogen synthase kinase 3 beta; FAK: focal adhesion kinase; HDAC4/5: histone deacetylase 4/5. This figure is an original work by the authors, created using Microsoft PowerPoint 2021, and was not processed with any generative artificial intelligence tools

Figure 1　Core signaling pathways through which mechanical loading influences PTH-promoted healing of mandibular condylar fractures

图1　力学负荷影响PTH促进下颌骨髁突骨折愈合的核心信号通路

3　力学负荷与PTH的协同作用

目前直接针对下颌骨髁突骨折、同时干预力学负荷与PTH给药的原始研究极为有限。本节所综述的力学-PTH协同效应的分子机制与调控规律，主要来源于长骨骨折模型（小鼠胫骨、大鼠股骨）、体外细胞力学加载实验（流体剪切力、周期性拉伸）以及骨质疏松动物模型。这些研究为理解力学-药物交互提供了重要的理论框架，但由于髁突在解剖结构（纤维软骨覆盖、薄层软骨下骨）、力学环境（以压应力和剪切力为主，而非长骨的弯曲/扭转应力）及血供特点上的显著差异，上述结论向髁突骨折的外推需谨慎对待。

3.1　力学信号与PTH信号的交互

力学刺激与PTH信号在信号转导和转录调控层面存在交互[72]。力学负荷可上调PTH1受体表达[68]，并可通过整合素/黏着斑激酶等通路激活共享下游分子；力学信号经整合素及TRPV4/Piezo1/2转导后，上调PTH1R并促进其向初级纤毛转运，进而通过C-X-C基序趋化因子配体5（C-X-C motif chemokine ligand 5，CXCL5）和白细胞介素-6（interleukin-6，IL-6）抑制破骨细胞形成[69]。

间歇性PTH与周期性力学负荷联合应用可协同增加骨形成速率，该效应依赖PTH1R信号通路的完整性[73]。Castoldi等[74]通过逆向工程Frost力学稳态模型进一步揭示了PTH联合力学加载降低骨形成阈值的剂量依赖性和部位特异性机制。Sugiyama等[75]在小鼠胫骨模型中证实，轴向力学加载可增强间歇性PTH（1-34）对松质骨和皮质骨的合成代谢效应。Sato等[76]发现流体剪切力通过黏着斑激酶/组蛋白去乙酰化酶5轴抑制硬化蛋白转录，解除对Wnt的抑制，增强PTH促成骨效应。上述理论主要基于长骨和体外流体剪切力实验，其在以压应力为主的髁突咀嚼负荷环境中的适用性有待进一步研究。

3.2　不同力学环境下PTH效应的差异

PTH对骨改建的调控呈力学依赖性——力学负荷强度通过影响信号转导效率及下游效应分子表达来调节PTH效应方向。目前直接针对下颌骨髁突骨折不同力学负荷下PTH效应的研究有限，以下结论主要整合自长骨、颅面骨模型及体外实验的间接证据。

高力学负荷环境（普食）：PTH通过上调RANKL/OPG比值激活PI3K/Akt/GSK3β/NFATc1级联，启动力学适应性破骨，促进骨痂快速塑形，形成力学性能优良的新生骨[77-79]。

中等力学负荷环境（软食）：PTH作用温和，破骨细胞数量和RANKL/OPG比值介于高、低负荷之间，骨痂改建缓慢但有序，仍能显著改善骨痂力学强度[21,80]。

低力学负荷环境（流食）：PTH的促改建效应明显减弱，骨痂改建停滞，骨质吸收风险增加，PTH延续骨折早期的保护性作用，抑制非特异性骨吸收，但无法启动力学适应性改建[42]。PTH（1-34）可通过调控铁代谢促进失负荷状态下的骨形成[81]，提示即使在低负荷条件下PTH仍具有一定的成骨调节能力。力学环境显著影响骨改建的方向与速率[82]。目前关于低力学负荷的研究证据主要源自肢体骨模型，其在咀嚼负荷主导的下颌骨髁突骨折中的适用性仍有待验证。

目前尚缺乏直接比较不同力学负荷梯度下PTH效应的前瞻性研究，现有结论多从间接比较中推断；且活体动物骨折端直接测力技术尚未成熟，现有实验多以食物硬度间接反映咀嚼负荷。未来需采用标准化力学加载装置直接控制骨折端力学参数，以更准确评价力学-PTH协同效应。

3.3　力学负荷强度对PTH效应的条件依赖性调控

综合上述证据，力学负荷强度对PTH的骨改建效应具有显著的条件依赖性：高负荷条件下PTH更倾向于启动改建性骨吸收，引导骨痂向功能性结构塑形；而在无负荷或极低负荷状态下，PTH的促改建效应明显减弱，骨痂塑形受到抑制[9]。Gould等[83]进一步揭示了这一条件依赖性的分子基础：力学负荷与PTH通过共同的终极通路——溶酶体对硬化蛋白的快速降解来激活骨形成；抑制上游力学信号通路或溶酶体降解会损害加载诱导的骨形成，表明力学刺激是PTH充分发挥骨形成效应的前提。这一调控规律为临床个体化治疗提供了重要启示。Rowshan等[84]在大鼠下颌骨骨折模型中证实，间歇性PTH（1-34）可促进骨折早期骨痂形成，但长期给药后影像学密度与对照组无显著差异。

目前力学负荷影响PTH效应的精确量化仍是领域空白。现有证据尚不足以确定从保护性抑制状态转向改建性骨吸收状态的具体力学临界值（如骨应变量或咀嚼力，单位为N）。未来研究需借助有限元分析结合体内应变测量，建立咀嚼应力与PTH效应之间的定量关系，为上述调控规律的临床转化提供可操作标准。

3.4　时间维度的调控

PTH与力学刺激的协同作用随骨折愈合进程动态变化[40,73]。PTH与力学刺激的协同效应具有时序依赖性，PTH预处理可增强后续力学加载的骨合成代谢效果[73]。系统综述表明（PROSPERO注册号：CRD42019131967），PTH治疗可改善多种骨折类型的功能结局，但对骨折愈合率的提升作用有限[85]。

Zweifler等[86]在小鼠应力骨折模型中证实，PTH治疗可增加骨痂部位的巨噬细胞数量并增强骨痂骨体积，提示PTH在骨折愈合后期可通过免疫调节途径促进骨修复；Bun等[87]进一步发现，PTH的骨效应受年龄调节：高频PTH在老年小鼠中可能引起皮质骨微结构退化和骨丢失。老年骨折患者可能需要延长PTH给药或调整力学负荷方案。

4　总结与展望

4.1　核心机制总结与待验证问题

第一，下颌骨髁突具有高度力学敏感性，咀嚼应力的大小和模式是调控其骨折愈合进程的关键外部因素。

第二，基于长骨及体外模型，PTH通过RANKL/OPG轴和PI3K/Akt/GSK3β/NFATc1通路双向调控破骨细胞活性，其效应方向取决于局部力学负荷强度，高负荷下更倾向于启动改建性骨吸收，低负荷下则延续保护性抑制。上述规律在髁突骨折中是否成立、力学阈值如何、骨细胞与成骨细胞的相对贡献尚不明确。这一知识缺口限制了PTH从经验性用药向精准化力学-药物联合干预的转化，是该领域需要优先解答的关键问题。

第三，力学信号与PTH信号在受体、信号通路和转录层面存在多层次交互，且协同效应具有显著时间依赖性——骨折早期以药物主导，中后期以力学主导。但现有研究以描述性观察为主，对髁突骨折愈合中两信号的精确交互机制认识有限，尚不足以支撑临床指南修订。

4.2　临床启示与研究局限

术后饮食指导应根据骨折类型、固定方式和愈合阶段个体化制定。现有结论主要来自动物实验，且以骨折块稳定固定为前提。基于现有动物实验证据，可提出以下初步临床考量：①PTH的促骨折愈合效应可能依赖于局部力学刺激，严格制动条件下PTH效应可能被削弱[9,81]；②PTH治疗应与功能锻炼时序配合——早期以药物启动骨痂形成，中后期逐步引入负荷引导塑形[73,84]。然而，上述建议尚缺乏髁突骨折的前瞻性临床研究支持。临床决策仍应以骨折稳定固定和咬合关系恢复为首要原则[37,88]。骨形成促进剂的临床选择需个体化：罗莫索单抗与PTH受体激动剂的用药时机存在差异，需个体化权衡[89]；一项Meta分析（PROSPERO注册号：CRD42020152205）对PTH在不同部位骨折中的疗效进行了系统评价[90]；相关综述亦强调PTH用药需根据骨折部位和类型个体化[91-92]。

4.3　未来待解决的科学问题

此领域仍存在三个核心问题：①髁突骨折端实际力学参数（微应变、应力值）与食物硬度分级间的定量换算[27,37]；②髁突骨折愈合不同阶段PTH所需的最适力学刺激窗口（强度×频率×时长）[14,25]；③骨细胞与成骨细胞在压应力环境下对PTH的差异性响应，是决定PTH促成骨还是促吸收效应的关键节点。此外，小窝蛋白-1与PTH1R及初级纤毛的协同作用为理解压应力环境下细胞间差异性响应提供了新的分子线索[93]。

未来研究应借助细胞特异性PTH1R敲除模型验证上述机制，并整合如成簇规律间隔短回文重复序列基因编辑治疗、组织工程与药物递送等多学科技术[94-96]，基于机器学习与多组学数据的骨折愈合预测模型亦具良好前景[97]。个性化颞下颌关节假体置换已在粉碎性髁突骨折治疗中初步应用[98]，基于可穿戴传感器的咀嚼肌活动监测技术有望实现术后咀嚼负荷的实时监测[99-100]。

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study.

【Generative AI statement】 The authors declared that generative AI was not used in the creation of this manuscript.

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