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机械力在颅骨缺损修复中的机制和应用现状

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摘要 颅骨缺损修复是颅面外科领域的重要挑战之一,尤其在缺损口达到临界尺寸缺损(CSD)时,颅骨缺损无法自愈,需依赖外界干预。机械力在颅骨发育与修复中起到关键作用,包括压力、张力、剪切力等,通过激活Wnt/ β -连环蛋白信号通路(Wnt/ β -catenin)、压电机械敏感离子通道蛋白1(Piezo1)、Yes相关蛋白(YAP)、具有PDZ结合基序的转录共激活因子(TAZ)等信号通路,调控成骨细胞分化与骨再生。不同类型的力会特异性影响细胞行为与微环境,临床应用负压伤口治疗(NPWT),负压促进血管-成骨耦合,张力刺激硬脑膜分泌成骨因子等。人工骨膜等已初步验证适当力学刺激有促进骨修复的效果。该文对不同力及相关通路对成骨细胞及其微环境影响,以及当前应用技术进行综述。

关键词 机械力;颅骨缺损;骨再生;负压;流体剪切力

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骨组织作为人体重要的承重结构,其发育、重塑与修复过程高度依赖力学微环境的精确调控。从发育阶段的颅骨扩张^[1],到成年后的骨折愈合与骨缺损修复^[2],机械力始终是影响骨细胞命运、组织形态建成与功能重建的核心因素之一。近年来,随着生物力学、细胞信号转导与再生医学的交叉融合,机械力在骨发育与修复中的作用机制被逐步揭示,形成了“力学-生物学耦合”调控网络的多维度认知。机械力并非单一物理刺激,而是涵盖压力、张力、剪切力及流体剪切力等多种形式的动态力信号。这些力信号通过细胞表面的力学感受器被感知并转导为生化信号,进而激活关键通路,调控成骨细胞、破骨细胞及骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs)。此外,机械力还可通过表观遗传调控、代谢重编程及细胞间通讯等机制,协同促进骨组织的适应性重塑与再生。

1 机械力的分类

机械力在骨发育与修复中的作用可依据其作用方向及生物学效应分为压力、张力、剪切力以及流

体剪切力。

1.1 压力 压力是指作用于物体接触面并导致其体积或形态缩小的力。在颅骨系统中,颅内压(intracranial pressure, ICP)是主要的压力形式,其动态变化与颅脑发育密切相关^[1]。大脑容积在婴儿出生后两年内迅速增长,扩容所产生的压力提高了硬脑膜细胞中成骨分化标志物(如:骨桥蛋白, I型胶原蛋白等)的表达水平,这可能在协调新生儿颅骨的生长中发挥重要作用^[3]。以颅骨发育异常阿佩尔综合征(Apert syndrome)为例,Apert综合征表现为颅缝早闭进而导致ICP升高,Apert综合征患儿对慢性高颅压表现出明显的颅骨适应,综合征的特征是颅内容物增加和颅骨密度下降,高颅压导致颅骨密度降低,颅骨厚度增加^[4]。机械压力通过诱导Wnt配体表达来刺激成人骨形成^[5],同时,在部分骨膜增生颅骨筋膜炎患者中,检测出Wnt通路异常活化, β -连环蛋白(β -catenin)蛋白核染色^[6]。机械压力在骨细胞中通过激活Wnt/ β -catenin通路,对骨代谢进行调节^[7]。

1.2 张力 细胞外基质(extracellular matrix, ECM)在组织再生和疾病进展过程中经历动态重塑和渐进性硬化。实验设计^[8]采用了一种模仿天然ECM动态特性的自增强聚合物涂层。证明了自增强张力的反应依次激活 $\alpha 5\beta 1$ 整联蛋白(integrin alpha-5 beta-1, $\alpha 5\beta 1$)和 $\alpha v\beta 3$ 整联蛋白(integrin alpha-v

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beta-3, $\alpha v\beta 3$) 以及 Rac 蛋白 (ras-related C3 botulinum toxin substrate, Rac)、RhoA 蛋白 (ras homolog gene family, member A, RhoA)、Rho 激酶 (rho-associated coiled-coil containing protein kinase, ROCK) 信号转导。整联蛋白活性的增强和 Rho 家族 GTP 酶 (Rho GTPases) 信号转导促进细胞机械转导和随后的 BMCSs 成骨分化^[8]。

1.3 剪切力与流体剪切力 在控制成骨的机械载荷 (流体剪切应力) 诱导的信号级联反应中, 小鼠胚胎头盖骨前成骨细胞系 (MC3T3-E1) 成骨细胞需要压电机械敏感离子通道蛋白 1 (piezo-type mechanosensitive ion channel component 1, Piezo1) 通道来适应外部机械流体剪切应力, 通过蛋白激酶 B (protein kinase B, AKT)/糖原合成酶激酶-3 β (glycogen synthase kinase-3 beta GSK-3 β) / β -catenin 途径诱导成骨细胞 runt 相关转录因子 2 (runt-related transcription factor 2, Runx-2) 基因表达^[9]。在含有骨样 ECM 的钛 (Ti) 纤维网支架上, 种植大鼠 BMSCs, 同一 TiECM 支架在灌流条件下的矿化量为静态培养的 5 倍。表明骨样 ECM 和流体剪切力之间具有协同效应^[10]。

2 机械力的生物力学效应与信号转导机制

2.1 ECM-整合素-细胞骨架力转导系统 整合素是细胞表面受体, 可将 ECM 成分连接到肌动蛋白细胞骨架, 并通过黏附复合物将化学和机械信号传递到细胞中^[11]。整合素介导的机械力感知具有“刚性依赖”特征, 当 ECM (1~30 kPa) 与细胞骨架张力达到力学平衡时, 触发 FAK/Src 磷酸化级联反应^[12], 同时有研究^[13]表明, 机械力通过改变 ECM 刚度, 影响细胞黏附和迁移, 基质刚度 (1~30 kPa) 通过 Yes 相关蛋白 (yes-associated protein, YAP)/PDZ 结合基序的转录共激活因子 (transcriptional co-activator with PDZ-binding motif, TAZ) 信号调控 BMSCs 向成骨或软骨分化^[14]。

2.2 机械电学信号转换 (离子通道) Piezo1 是机械激活的离子通道, 是多种细胞类型中机械感应功能所必需的^[15]。Piezo1 通道在成骨细胞^[16]中高表达, 生物力学和基质刚度上调了 Piezo1 通道的表达, 促进了钙调神经磷酸酶和活化 T 细胞核因子胞质型 1 (nuclear factor of activated t-cells, cytoplasmic 1, NFATc1) 的协同激活^[17], 激活钙调蛋白依赖的 NFATc1 通路, 抑制破骨细胞生成, 驱动骨基质矿

化^[18]。机械刺激瞬时受体电位香草酸亚型 4 (transient receptor potential vanilloid 4, TRPV4) 通道, 增强细胞内 Ca^{2+} 的激活水平, 促进成骨细胞特异性基因的表达并增加骨矿化。TRPV4 通道激活也会影响线粒体 Ca^{2+} 水平和线粒体代谢^[19]。Piezo1 通道作为一个关键的机械门控离子通道, 其与 TRPV4 通道之间的相互作用逐渐受到关注, 特别是在炎症反应方面, Piezo1 通道和 TRPV4 通道具有协同作用^[20]。有研究^[21]结果表明成骨细胞表达的 Piezo1 通道和 TRPV4 通道共同参与机械应力期间的机械感知过程。见图 1。

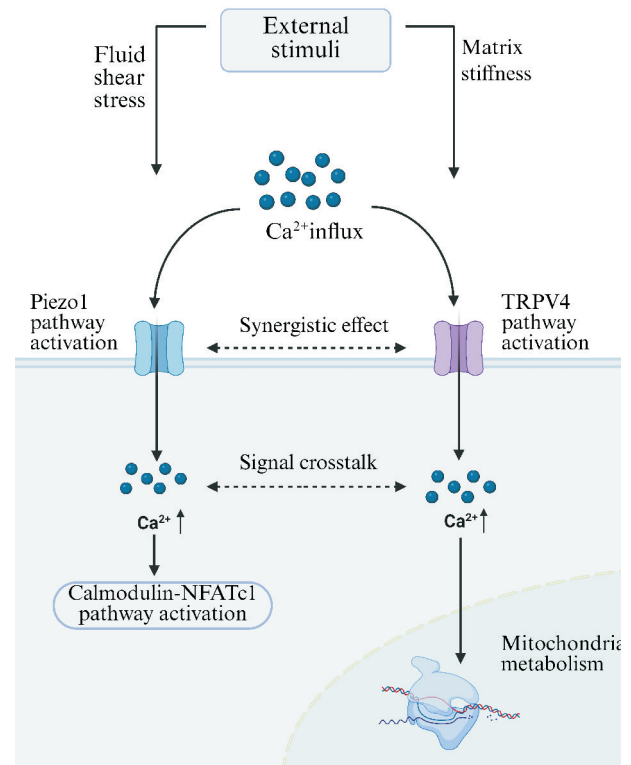


图 1 机械电学信号转换 (离子通道)

Fig. 1 Mechano-electrochemical signal transduction (ion channels)

2.3 表观遗传调控 由于组织刚度、细胞骨架重组和细胞物理环境的变化 (即使是细微的), 细胞内可能会产生机械力。这些变化在细胞内蛋白质网络 (胞质和细胞核) 内施加了机械张力^[22]。例如, F-肌动蛋白细胞骨架重组导致的细胞内压缩力降低进而影响细胞核的机械内和机械外环境, 这种变化可能影响成骨分化过程中的基因表达和 DNA 复制^[23]。持续静水压力通过一系列涉及 SRY 框转录因子 9 (SRY-box transcription factor 9, SOX9)、RUNX2 和多囊藻毒素-1、2 的分子事件刺激软骨细

胞分化^[24]。研究^[25]证实,机械张力通过驱动自噬介导的骨细胞生成因子成纤维细胞生长因子23(fibroblast growth factor 23, FGF23)促进成骨。垂直全身低幅度高频振(vertical whole-body low-magnitude high-frequency vibration, LMHFV)可能通过机械敏感 Wnt/ β -catenin 通路促进骨再生^[26];此外,周期性拉伸力增强骨形态发生蛋白2(bone morphogenetic protein 2, BMP2)表达,协同促进骨形成^[27]。细胞物理环境的改变会影响细胞蛋白调控及基因表达。

2.4 代谢通路力学调控 机械力会通过影响线粒体调控细胞的能量代谢^[28],流体剪切应力激活了三羧酸循环(tricarboxylic acid cycle, TAC),从而促进成骨细胞中线粒体能量的产生,使三磷酸腺苷(adenosine triphosphate, ATP)产量提升,为骨细胞增殖提供能量^[29]。在 BMSCs 中,30~90 nm、1 000 Hz 纳米振动促进成骨基因表达和成骨细胞生成。这种生物物理刺激增加了 Piezo2 通路和 TRPV1 通路的表达,并上调了线粒体代谢,包括糖酵解和 TAC 循环以及反应性氧种(reactive oxygen species, ROS)生成^[30]。见图2。

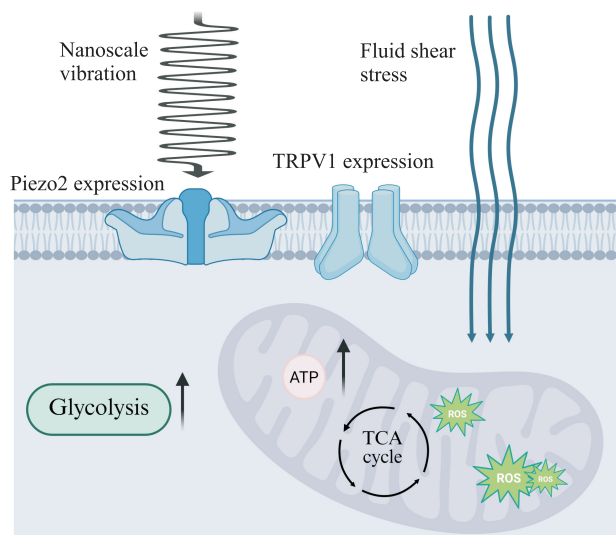


图2 代谢通路力学调控

Fig. 2 Mechanical regulation of metabolic pathways

2.5 力学调控的细胞互作网络 机械力在骨再生中的作用至关重要,通过协调骨组织内多种细胞的时空行为,实现精准调控。该过程涉及多个机制:①骨细胞层状小管形态和网络结构(骨细胞网络)^[31],作为力学信号的“中枢处理器”,骨细胞通过初级纤毛感知机械刺激^[32],通过 Piezo1 和靶向连接蛋白43等通道传递信号,协调成骨细胞的迁移并平

衡骨吸收与形成^[33];②机械刺激通过骨髓来源巨噬细胞分泌外泌体,促进 BMSCs 成骨^[34];③免疫-骨骼细胞协同调控,机械力通过影响巨噬细胞极化^[35-36]、T细胞活化^[37]和中性粒细胞招募^[38],促进骨修复与再生;④血管-成骨单元协同构建,巨噬细胞通过 Piezo1 通路调节机械负荷诱导的血管生成-成骨耦合,支持血管化骨组织的形成^[39]。这些机制相互协作,促进骨修复与再生,为骨组织工程和再生医学的临床应用提供了新的思路和策略。

3 机械力在颅骨缺损修复中的应用

3.1 负压的促进修复机制 负压技术通过局部力学刺激调控微环境,成为颅骨缺损修复的重要辅助手段,其作用机制主要包括改善血流、增强干细胞活性及调控成骨微环境。有研究^[40-41]表明负压诱导硬脑膜血管向缺损区迁移,通过激活血小板内皮细胞黏附分子-1(cluster of differentiation 31, CD31)/内皮黏蛋白(endomucin, EMCN)内皮细胞介导的“血管-成骨耦合”并显著增强支架孔隙内血管侵入能力;负压伤口治疗(negative pressure wound therapy, NPWT)通过 AMP 活化蛋白激酶(AMP-activated protein kinase, AMPK)-Unc-51 样激酶1(Unc-51 like kinase 1, ULK1)自噬轴促进 BMSCs 的成骨细胞分化和骨再生^[42]。见图3。

3.2 张力调控硬脑膜的成骨作用 硬脑膜作为距离颅骨缺损最近的组织之一,在颅骨缺损中扮演重要角色^[43]。硬脑膜细胞通过细胞外囊泡途径,对于成骨细胞分化有极强的促进作用^[44]。同时硬脑膜在机械张力刺激下释放成骨因子并调控干细胞行为。硬脑膜细胞在施加10%双轴应变后,增殖率提升5.8倍,同时 FGF-2 和 BMP-2 分泌量分别增加4.5倍和3.2倍,显著促进 BMSCs 成骨分化^[3]。见图4。

3.3 骨膜与机械力的协同修复作用 骨膜对力的反应刺激皮质骨迁移^[45]。机械负荷通过 Piezo1 通路的信号传导诱导骨膜 CD68 F4/80 髓系细胞分化为 CD68 F4/80 巨噬细胞以分泌转化生长因子(transforming growth factor, TGF)- β 1, TGF- β 1 进而募集骨祖细胞^[46]。研究^[47]显示,在骨表面和骨膜之间人工创造空间,无需皮质切开术即可产生新骨。目前已经有团队^[48]研发用于骨修复的具有磁响应特性的人工骨膜,这种人工骨膜通过响应施加的磁场产生的拉伸变形模仿了天然骨膜,复制了体内所经历的机械力,促进细胞增殖和成骨分化。身体的不同部

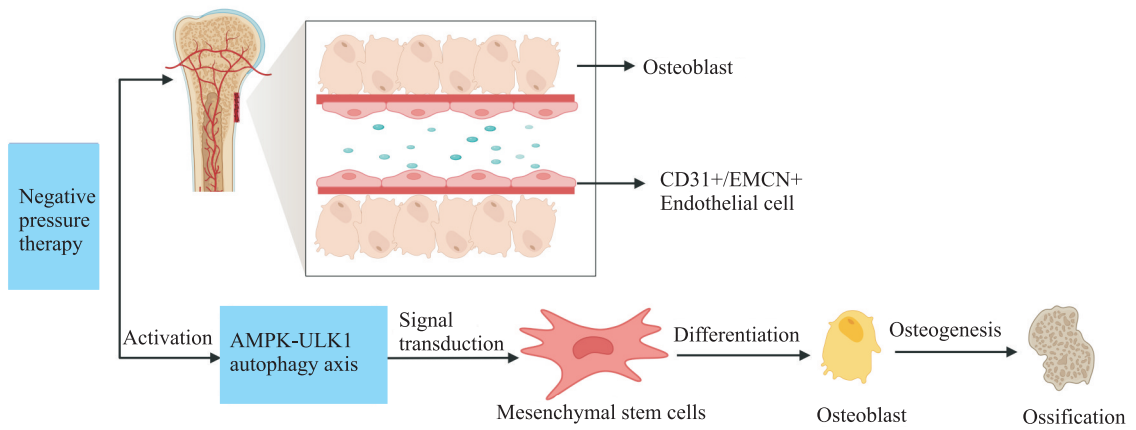


图3 负压的促进修复机制

Fig. 3 Mechanism of negative pressure-promoted tissue repair

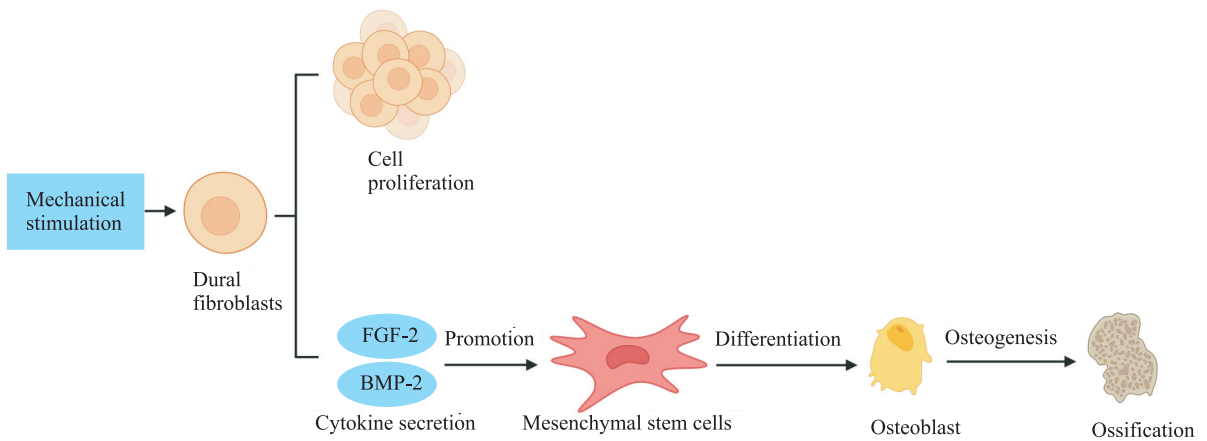


图4 张力调控硬脑膜的成骨作用

Fig. 4 Tension-mediated osteogenic effect on the dura mater

位骨膜具有不同的成骨类型和能力,例如胫骨骨膜可以通过膜内骨化和内软骨增生两种机制形成新骨,而颅骨骨膜只能通过膜内骨化形成新骨^[49]。此外,胫骨骨膜的成骨能力远强于颅骨骨膜^[50]。骨膜对力刺激的反应,可为临床骨修复提供新靶点。

4 讨论

机械力在颅骨缺损修复中的作用机制及其应用潜力近年来受到广泛关注。本文系统总结了压力、张力、剪切力及流体剪切力等不同类型机械力通过调控细胞行为、信号通路及微环境促进骨再生的机制。研究发现,机械力通过整合素介导的力传导系统^[10]、离子通道(如Piezo1和TRPV4)^[22]、表观遗传修饰及代谢重编程等多层级网络协调骨修复。例如,压力通过激活Wnt/ β -catenin通路使成骨细胞分化及上调活性相关基因,促进骨形成,而张力通

过RhoA/ROCK信号这个连续过程增强了细胞机械转导以及BMSCs的成骨分化^[7],凸显了机械力类型与其生物效应的特异性关联。在临床应用方面,负压技术通过改善局部血流、以及增强血管-成骨耦合,显著提升颅骨缺损的修复效率^[42],但其长期安全性及对不同缺损形态的适应性仍需验证。硬脑膜在机械张力刺激下,FGF-2和BMP-2分泌量增加促进成骨分化^[3]。骨膜会对力的刺激做出反应,同时在骨再生中担任极其重要的角色,提示靶向骨膜力学信号是临床转化的关键方向。但是,当前研究仍存在局限性。首先,多数实验基于动物模型,人体内复杂微环境(如炎症、衰老)对机械力响应的影响尚未明确;其次,机械力参数(如频率、强度、作用时间)的优化缺乏统一标准,可能影响治疗的可重复性。未来研究应聚焦于开发智能化力学调控设备(如可调式生物反应器),结合多组学技术解析力

学信号的时空动态变化,并探索机械力与生物材料等技术的交叉融合,以实现颅骨缺损修复的精准化和个性化治疗。

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Mechanisms and current applications of mechanical forces in cranial bone defect repair

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Abstract Cranial bone defect repair remains a significant challenge in craniomaxillofacial surgery, particularly when defects exceed the critical size defect (CSD) threshold, rendering them incapable of spontaneous healing without external intervention. Mechanical forces—including compression, tension, and shear stress—play a pivotal role in cranial development and regeneration. These forces regulate osteoblast differentiation and bone regeneration by activating key mechanotransduction pathways, such as the Wnt/ β -catenin signaling pathway, the piezoelectric mechanosensitive ion channel Piezo1, and the transcriptional co-activators Yes-associated protein (Yes-Associated Protein, YAP) and Transcriptional co-activator with PDZ-binding motif (Transcriptional co-activator with PDZ-binding motif, TAZ). Distinct types of mechanical forces exert specific effects on cellular behavior and the microenvironment. Clinically, applications such as Negative Pressure Wound Therapy (NPWT) have demonstrated efficacy in promoting angiogenesis-osteogenesis coupling, while tensile forces stimulate the dura mater to secrete osteogenic factors. Preliminary studies using artificial periosteum and other biomaterials have further validated that appropriate mechanical stimulation enhances bone repair. This review summarizes the effects of various mechanical forces and their associated signaling pathways on osteoblasts and their microenvironment, alongside an overview of current technological applications in this field.

Key words mechanical force; skull defect; bone regeneration; negative pressure; fluid shear stress

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