DOI: 10.13376/j.cbls/2020033
文章编号：1004-0374(2020)03-0239-06

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成纤维细胞生长因子信号在骨损伤修复中的作用

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摘　要：骨损伤是常见的骨外科疾病。许多复杂的骨缺损，如创伤性大块骨缺损等常导致骨折延迟愈合及骨不连，是临床治疗中的难题。组织工程方法的运用为骨不连等的治疗提供了新的契机。成纤维细胞生长因子 (fibroblast growth factor, FGF) 信号在骨骼发育过程中发挥重要作用。基于其家族成员在骨折愈合过程中的时空表达及相关基因工程小鼠的表型，FGF 信号相关分子被认为是骨再生修复的重要调节分子。该文将对 FGF 信号在骨损伤修复中的作用及应用方面的研究进展做综述，以期为其临床应用提供借鉴与参考。

关键词：骨骼；骨损伤；修复；成纤维细胞生长因子信号
中图分类号：Q819；R683　　**文献标志码：**A

Role of fibroblast growth factor signaling in bone injury repair

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Abstract: Bone injury is a common bone surgery disease. Many complex skeletal defects such as large traumatic bone defects may cause delayed bone healing and fracture nonunion, which remains a challenge in clinical practice. The application of tissue engineering therapy provides a new opportunity for the treatment of nonunion. Fibroblast

收稿日期：2019-12-19
基金项目：国家自然科学基金项目(81772359)；军事医学创新工程重点项目(16CXZ016)
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growth factor signaling plays an important role in bone development. Based on the their spatio-temporal expression during fracture healing and the phenotypes of genetically modified mice, FGF signaling-related molecules are considered as important regulatory molecules for bone regeneration and repair. This review will summarize the current understanding of FGF signaling-related molecules in bone injury repair, providing reference for its clinical application.

Key words: bone; injury; repair; fibroblast growth factor signaling

骨骼是一种特殊的结缔组织，处于不断的重塑过程中。骨损伤修复是一个多种细胞、因子参与精细调控的病理生理过程。虽然大多数骨损伤能够正常愈合不留瘢痕，但仍有 5%~10% 将发生骨延迟愈合或骨不连。骨组织工程技术的发展为骨损伤修复提供了新的治疗方式。生物活性因子作为组织工程技术所需的三个因素之一在促进损伤修复中广泛应用。成纤维细胞生长因子 (FGF) 信号是骨 / 软骨发育及稳态的重要调节分子，参与软骨细胞、成骨细胞及破骨细胞等相关骨骼细胞功能的维持。近年来研究发现，其在骨损伤修复过程中发挥至关重要的作用。本文对近年来 FGF 信号在骨损伤修复中的作用与应用相关研究作一综述。

1 骨损伤修复过程简介

骨骼组织修复与骨骼发育过程类似，主要通过软骨内成骨与膜内成骨两种方式完成 [1]。大部分骨损伤修复包括以下连续发生而又互相重叠的过程。首先，炎性反应后，骨骼及血管相关的干细胞在临近骨折线区域聚集并分化，逐渐形成软骨性骨痂组织。在这个中心区域的外围，在新的软骨组织的边缘，新生血管形成，骨膜膨胀，初始骨形成过程开始。随着软骨细胞的进一步分化，软骨细胞最终发生凋亡，软骨细胞外基质发生矿化。伴随着软骨组织的逐渐减少，继发性骨形成开始，形成骨性骨痂。随后，进入骨重塑阶段，致密骨逐渐替代小梁骨，骨髓空间被重建，原始骨髓结构再生，增多的血管逐渐减少恢复至正常 [2]。在骨折断端稳定且活动较少时，不形成骨痂组织，直接通过成骨细胞的骨形成与破骨细胞的骨吸收作用完成修复。骨损伤修复是由再生组织中不断变化的细胞集群和信号传递组成的连续过程 [3-6]，其中 FGF 信号发挥重要调节作用。

2 FGF信号概述

FGFs 家族有 22 个成员，可分为内分泌 FGFs (FGF15/19、FGF21、FGF23)、胞内 FGFs (FGF11~14) 与经典的 FGFs[7]。其受体，成纤维细胞生长因子受体 (fibroblast growth factor receptors, FGFRs)，属于酪氨酸激酶型受体家族，有 FGFR1~4 四种类型。经典 FGFs 与其相对特异的 FGFRs 结合 (表 1)，并以硫酸肝素 (heparin sulfate, HS) 或硫酸乙酰肝素蛋白多糖 (heparan sulfate proteoglycan, HSPG) 作为共受体，形成 FGF-FGFR-HS 复合物。该复合物通过特定酪氨酸残基磷酸化激活 FGFR 细胞内酪氨酸激酶结构域，进一步激活包括 RAS-MAPK、PI3K-AKT、PLCγ 及 STAT 在内的细胞内信号通路，参与胚胎早期发育、器官发生、代谢维持及组织修复和再生的调节，在骨骼发育过程中发挥着尤为重要的作用 [8]。

3 FGFs/FGFRs在骨损伤修复过程中的表达

在动物模型中，多种 FGFs 与 FGFRs 被证实在骨折修复过程中有相对特异性表达。早期的研究通过定量 PCR 检测发现，在骨折后炎症期，FGF1、2、5 显著升高；软骨形成阶段，FGF16、18 表达达到峰值；而在硬骨痂形成及重塑阶段，FGF2、9、16 与 18 有较高表达，而 FGF1、17 表达达到峰值 [9]。免疫组化检测发现：FGF1 在骨折早期的成纤维细胞样间充质细胞中大量表达 [10]；FGF2 在纤维间充质细胞、未成熟成骨细胞及软骨样组织附近骨膜中表达 [11]；FGF18 在牵拉骨形成模型的骨修复全过程中均有较高表达 [12]；FGF23 在骨损伤修复过程中的成骨细胞和肉芽组织表达 [13]；FGFR1、2 在骨折后早期表达上调，在骨性骨痂形成阶段达到峰值，而 FGFR3 表达在软骨痂形成阶段达到峰值 [9,14]；FGFR1 在骨膜骨祖细胞、骨折愈合组织附近的炎性细胞中表达上调 [15]；FGFR1、2 均在增殖的骨膜间充质、软骨细胞及成骨细胞表达 [16]；FGFR1 在骨折修复组织中的破骨细胞中表达 [15]；FGFR3 表达升高较 FGFR1、2 晚，在骨折愈伤组织的间充质细胞、前肥大细胞和肥大软骨细胞表达 [16-18]。FGFs/FGFRs 在骨折愈合过程中的表达与发育阶段有一定的相似性，提示其可能参与在骨折愈合与骨再生。

4 FGFRs在骨损伤修复中的作用

FGFR1~3 均参与软骨形成与骨形成的调节，FGFR3 在软骨形成过程中发挥相对重要的作用。虽

表1　典型FGFs和内分泌FGFs的特异性受体[7]

FGF家族	FGF	共受体	相对特异性结合受体
FGF1亚家族	FGF1	HS/HSPG	所有FGFRs
	FGF2		FGFR 1c、3c、2c、1b、4Δ
FGF4亚家族	FGF4		FGFR 1c、2c、3c、4Δ
	FGF5		
	FGF6		
FGF7亚家族	FGF3		FGFR 2b、1b
	FGF7		
	FGF10		
	FGF22		
FGF8亚家族	FGF8		FGFR 3c、 4Δ、2c、1c、3b
	FGF17		
	FGF18		
FGF9亚家族	FGF9		FGFR 3c、2c、1c、3b、4Δ
	FGF16		
	FGF20		
FGF15/19亚家族	FGF15/19	βKlotho	FGFR 1c、2c、3c、4Δ
	FGF21		FGFR 1c、3c
	FGF23	αKlotho	FGFR 1c、3c、4

然目前存在观点上的争议，但一般认为FGFR3抑制软骨细胞增殖和分化，促进软骨细胞凋亡，而FGFR1促进成骨细胞增殖和分化，FGFR2刺激成骨细胞增殖、分化和凋亡。FGFRs通过其下游信号通路调节骨骼相关细胞功能(图1)。目前，也有研究支持FGFRs在骨损伤修复中发挥重要作用。FGFR1的基因多态性与骨折骨不连相关[19]。利用FGFR2功能增强点突变(P253R)小鼠模型发现，FGFR2可经上调Wnt/β-catenin促进长骨骨髓机械消融后的骨形成[20]。利用FGFR3功能增强(G369C)及FGFR3全敲除小鼠胫骨骨折模型发现，FGFR3主要通过负向调节软骨内成骨，抑制软骨痂的形成，进而延迟骨损伤修复[14,18,21]。在小鼠破骨细胞系(Lysozyme-Cre)中，敲除FGFR3可通过破骨细胞的骨吸收功能抑制骨皮质损伤后的损伤组织重塑[22]。FGFRs在骨折愈合过程中广泛表达于多种类型的细胞，包括间充质细胞、软骨细胞、成骨细胞、破骨细胞以及炎症细胞等，提示FGFRs信号通过调节参与骨折愈合的多个细胞谱系参与骨损伤修复，其详细的作用与机制有待于进一步研究。

5　FGFs对骨损伤修复的可能调节作用

相关遗传修饰小鼠及体外干预研究发现，FGFs可能参与骨损伤修复的调节。Reiff等[23]发现FGF1处理可促进人成骨前体间质细胞的增殖，诱导成骨细胞特异性分化标志物的表达；而FGF1可能通过抑制成脂分化，增加炎症环境中的成骨细胞数量，在骨修复过程中协调骨形成和血管生成促进骨修复[24-25]。小鼠成骨前体细胞中过表达低分子量FGF2 (LMW FGF2)可经调节软骨细胞、成骨细胞分化与血管浸润等加速胫骨骨折愈合过程；经增强经典的Wnt信号转导与成骨活性，促进颅骨缺损愈合[26-27]。体外研究发现，FGF6处理可同时影响成骨细胞及破骨细胞功能，提示其可能参与骨损伤修复的调节[28]。FGF8通过引起Wnt信号失调导致颅骨相关前体细胞更易向软骨分化，提示FGF8信号通路为成骨命运的负调控因子[29-30]。FGF9在早期促进软骨细胞肥大，在骨骼发育的后期调控生长板的血管与成骨[31-32]；FGF9的表达足以将部分中胚层来源的间充质细胞的分化命运从膜内成骨转化为软骨内成骨[33]；成熟成骨细胞是FGF9的重要来源，其可能通过激活AKT信号通路维持成骨祖细胞功能[34]。体外实验发现，FGF2处理后再使用FGF9更有利于间充质细胞的扩增与成骨分化[35]，提示FGF9可能应用于促进骨损伤修复。FGF18通过促进细胞增殖与分化促进成骨，负性调节软骨形

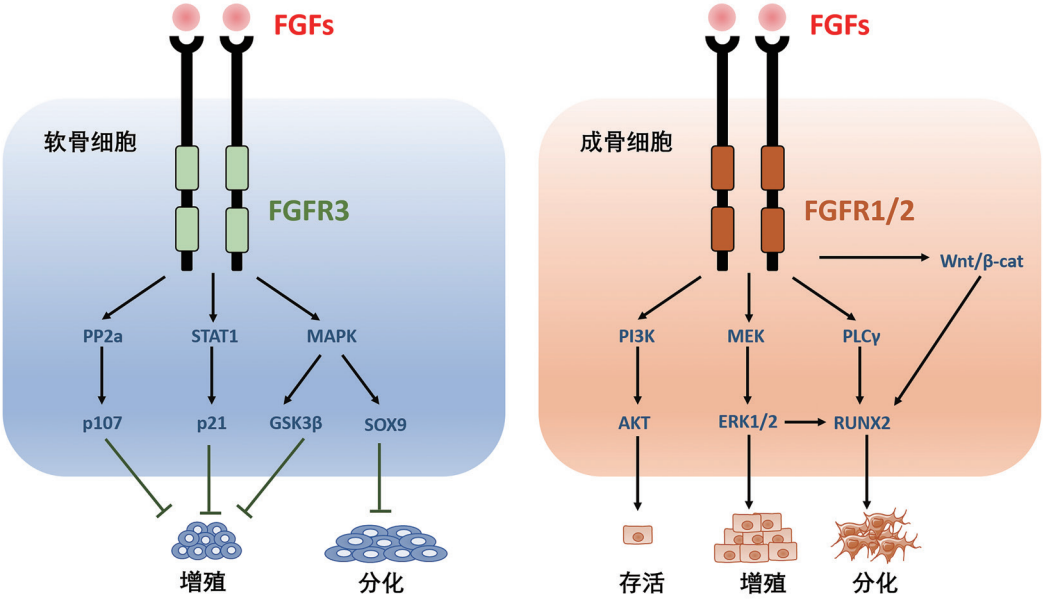

图1 FGF信号对成骨、软骨细胞的调节

成[36-37]；然而也有研究发现，FGF18可能经FGFR3促进软骨形成[38-39]。小鼠中增强FGF21可导致骨形成降低，骨吸收增加，进而导致骨量丢失[40]；然而，在人群中发现，健康女性血浆FGF21水平与骨密度显著正相关[41]，FGF21可通过上调依赖BMP2的Smad信号通路，增强BMP2的成骨活性[42]。FGF23是重要的钙磷调节分子，FGF23在体外抑制成骨细胞分化和基质矿化，血清中的FGF23水平可能作为小梁参数降低的预测因子及判断骨骼易于愈合或不愈合的指标[13,43-44]。

6 FGFs在骨再生中的应用

与直接干预FGFRs相比，通过配体实现FGF信号的调节更贴近临床应用实际，目前已有较多研究围绕外源性FGFs应用开展，尤其是损伤局部使用[45-46]。FGF1(2.6 μg)包埋于琼脂糖或与海绵蛋白载体复合均可促进大鼠顶骨的临界大小缺损修复过程中的骨桥形成[47-48]。FGF1(11.25 μg)与兔脱矿骨基质和纤维蛋白递送系统复合可促进兔桡骨临界缺损的修复[49]。Kawaguchi实验室发现，明胶水凝胶中FGF2可剂量依赖性地加速人截骨术后愈合[50-51]，并且对胫骨骨干新鲜骨折的愈合有促进作用[52]。单次200 μg的FGF2可通过增强骨痂形成及骨痂重塑促进狗胫骨横断及食蟹猴右尺骨中段稳定骨折的愈合[53]。在兔、大鼠的多种骨损伤模型中发现，不同剂量的FGF2局部应用均具有促进骨再生的潜力[54-56]。研究发现，FGF2主要通过诱导血管生成及增强成骨细胞谱系的增殖能力促进骨损伤修复。外源性FGF2的体内作用可能具有双向性。Sakano等[57]发现，注射1 μg FGF2可显著降低骨基质植入诱导的异位成骨，10 μg FGF2可完全抑制异位成骨的发生。高剂量FGF2抑制骨形成在胶原小颗粒骨膜下植入实验中也得到了证实[58]。在大鼠下颌骨缺损模型中，通过可吸收胶原蛋白海绵载体递送1 μg FGF2抑制骨形成，而10 ng与100 ng组则显示出一定的促骨形成作用[59]。可吸收胶原蛋白海绵下颌局部递送1 μg FGF7可增加间质细胞趋化及成骨，促进下颌骨缺损的骨形成[60]。FGF9单拷贝缺失小鼠表现为胫骨皮质损伤修复延迟，伴有新生血管受损，细胞增殖减少，Runx2、骨钙素、Vegf-a及PECAM-1表达下调；胶原蛋白海绵载体递送2 μg FGF9可缓解皮质损伤修复障碍[61]。FGF18半缺失导致成骨功能障碍，引起小鼠胫骨皮质损伤修复障碍，补充FGF18可改善其骨形成[62]。此外，体外实验证实，不同FGFs或FGFs与其他因子的联合/序贯使用可能有助于骨损伤修复。Kang等[63]发现利用研发的基于核-壳结构的多孔纳米微球实现FGF2与FGF18的有序释放，可促进骨损伤修复。

7 结语与展望

FGFs/FGFRs在骨愈合和再生中的重要作用提示可通过调节FGF信号促进骨折愈合。然而，我

们对 FGF 信号在骨折愈合中的复杂作用及其机制的认识非常有限。单个 FGF 和 FGFR 在骨折愈合和骨再生不同时期及细胞中的精确作用，FGFs 的应用剂量、时机和持续时间，以及与其他骨调节信号分子、新型载体和蛋白传递系统的联合应用等，仍需要进一步探讨，以有效地促进骨再生，实现临床转化应用。

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