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在线全文

软骨-骨交互作用的病理机制：动物实验研究骨关节炎的新视角*

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【摘要】 骨关节炎（osteoarthritis, OA）是一种以关节及其周围组织的退行性病变为特征的老年性慢性疾病。传统上，OA研究主要集中于关节软骨本身的病理变化及其修复，但随着近年来动物疾病模型的发展，尤其是时空特异性转基因小鼠模型的广泛应用，学者们逐渐意识到软骨下骨在OA发生发展中同样扮演着重要角色，即关节软骨与骨病变相互影响、相互促进，共同推动OA的进程，涉及血管侵入、异位钙化、神经生长及疼痛发生等病理过程。由于软骨-骨交互作用病理关系的复杂性，临床样本难以深入到软骨下骨病变，而体外细胞实验无法模拟OA过程，故动物模型在OA病理机制研究及临床药物开发中占据不可替代的地位。本文在梳理OA动物模型的基础上，综述了近年来关于OA的最新动物实验研究进展，强调了软骨-骨交互作用病理关系在OA进程中的主动作用。这些新发现为今后深入研究提供参考，也为实现OA根本性防治策略提供理论依据。

【关键词】 骨关节炎 关节软骨 软骨下骨 动物模型

Pathology of Cartilage-to-Bone Crosstalk: A New Angle for Animal Experimental Studies on Osteoarthritis

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[Abstract] Osteoarthritis (OA), a common age-related chronic disease, is characterized by degenerative changes in the joints and surrounding tissues. Traditionally, research on OA has primarily focused on the pathological changes in articular cartilage and its repair. However, with the advancements in animal disease modeling in recent years, especially the widespread use of spatiotemporally specific transgenic mouse models, scholars have gradually come to realize that the subchondral bone also plays an important role in the occurrence and development of OA. That is, the pathological changes in articular cartilage and bone mutually affect and promote each other, jointly driving the progression of OA, involving such pathological processes as vascular invasion, ectopic calcification, nerve growth, and the occurrence of pain. Given the complexity of cartilage-bone pathological relationship, it is difficult to conduct in-depth research on subchondral bone pathology using clinical human samples, or to simulate the pathological processes of OA through *in vitro* cell experiments. Therefore, animal models play an irreplaceable role in investigating the pathological mechanisms of OA and developing clinical drugs. This review, in addition to providing an overview of OA animal models, synthesizes the latest progress in animal experimental research on OA, highlighting the active role of the cartilage-bone pathological relationship in OA progression. These new findings provide references for future in-depth investigations and also provide a theoretical basis for developing fundamental strategies for OA prevention and treatment.

[Key words] Osteoarthritis Articular cartilage Subchondral bone Animal models

骨关节炎（osteoarthritis, OA）是一种常见的慢性退行性关节疾病，以关节软骨退化、软骨下骨重建、骨赘形成和滑膜炎症为特征。OA的临床表现具有多样性，常伴有如骨质疏松、肌肉萎缩、关节畸形和残疾等并发症[1-4]。根据全球疾病负担（Global Burden of Disease, GBD）数据库，2021年全球约有6.07亿人患OA。到2050年，全球范围内预计将有6.42亿人患有膝关节OA，2.79亿人患有手部OA，6 260万人患有髋关节OA，以及1.18亿人患有其他类型的OA[5]。OA为患者及社会带来沉重的负担，阐明OA的病因和发病机制以及开发相关治疗策略的重要性愈发凸显。

关节软骨与软骨下骨关系密切，二者共同构成一个功能复合体。在关节运动期间，软骨下骨为关节软骨提供力学支持，并通过骨重建不断适应力学环境的变化[6-8]。长期以来，关节软骨是OA研究的焦点，但近年来的大量研究表明软骨下骨同样参与OA的发生发展，其病理改变甚至可能先

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于关节软骨损伤,且与关节软骨损伤的严重程度相关;与此同时,关节软骨病变也可影响软骨下骨的骨重建过程[6, 9-11]。因此,单纯的关节软骨研究无法实现标本兼治的目标[8, 12-14]。

目前,软骨-骨的信号交流及其在OA中的作用尚未完全阐明,而相关研究的推进离不开有效动物模型的构建。动物模型不仅能够模拟人类的生理和病理过程,还提供更为便利、可控的条件,对疾病研究和药物研发具有不可或缺的价值。本文综述了近年来在动物实验研究中关于OA的最新进展,除指出了软骨与软骨下骨之间可通过信号分子进行互作外,还纳入了软骨下骨中血管侵入和神经异位长入对软骨的影响,进一步强调了软骨-骨相互作用的病理机制在OA发展中的主动作用,以期为后续深入研究提供参考。

1 骨关节炎动物模型

OA建模方法主要包括手术诱导法、化学诱导法、力学诱导法、基因工程法以及自发性动物模型,各模型优缺点见表1。OA建模可选用解剖结构与人类相似的大型动

表 1 骨关节炎的动物模型

Table 1 Animal models of osteoarthritis

Methods			Characteristics
Surgical induction			High stability and success rate, requiring advanced surgical skills, and risk of infection and other complications
	Traditional Hulth method	Transection of the anterior cruciate ligament, posterior cruciate ligament, medial collateral ligament, and removal of the medial meniscus	Short modeling time and high reproducibility, complex procedure, significant trauma, difficulty in observing pathological changes at different stages due to rapid modeling
	Modified Hulth method	Based on the traditional Hulth method, but preserves the posterior cruciate ligament	Less traumatic, simpler procedure, and higher success rate compared to the traditional Hulth method
	Anterior cruciate ligament transection	Transection of the anterior cruciate ligament	Minimal trauma, simple procedure, and high stability; requiring high-load exercise post-surgery to induce OA
	Medial meniscus destabilization	Partial or complete removal of the meniscus	Minimal trauma and simple procedure; the method only induces local joint instability.
	Combined induction: anterior cruciate ligament transection and medial meniscus destabilization	Transection of the anterior cruciate ligament and removal/tearing of the anterior horn of the meniscus	No need for high-load exercise post-surgery to induce arthritis; meniscus tearing is easier than complete removal.
Chemical induction			Surgical trauma is avoided; difficulty in controlling drug concentration and dosage
	Intra-articular injection	Injection of papain, collagenase, iodoacetate, urokinase, TNF-α, etc., into the joint cavity	Rapidity, minimal invasiveness, simple procedure, and short modeling period; difficulty in controlling dosage; repeated injections may cause induration and ulceration.
	Botulinum toxin intramuscular injection	Injection of botulinum toxin at the midpoint of the right rectus femoris, vastus medialis, and vastus lateralis muscles	Simulation of muscle atrophy in knee OA pathogenesis; in combination with ovariectomy, the method can be used to model postmenopausal knee OA
Mechanical induction			Non-invasiveness, reduction of surgical trauma, and simple procedure
	Immobilization	Fixation with plaster or bandage and tail suspension	Simulation of OA progression, simple procedure, reduction of surgical trauma; prolonged fixation may cause local swelling, skin ulceration, and other complications
	Loading	In the cyclic compression model, the mouse's lower leg is placed horizontally (parallel to the body) between two loading platens and long-term cyclic pressure is applied. In the anterior cruciate ligament rupture model, the mouse's lower leg is placed vertically (perpendicular to the body) between two loading platens and pressure is applied until the anterior cruciate ligament ruptures.	Non-invasiveness, being easy to learn, high reproducibility, and low variability; the method is driven by mechanical factors, and OA progression speed cannot be regulated.
	Treadmill exercise	Exercise intensity is set at 70% of maximum oxygen uptake.	Non-invasive, low technical requirements; difficult to standardize due to numerous parameters
Genetic engineering	*Col2a1* knockout mice, *Col9a1* knockout mice, *Del* knockout mice, β-catenin conditional knockout mice, *SIRT1* conditional knockout mice, *EFNB2* conditional knockout mice, *DOT1L* conditional knockout mice, *Pten* conditional knockout mice, etc.		Avoids surgical trauma, allows study of gene expression effects on OA; long modeling period and high cost
Spontaneous models	SRT/ort mice, BCBC/Y mice, Dunkin-Hartley guinea pigs, etc.		Simulation of disease progression with minimal external interference; long modeling period and high cost

物，如恒河猴、狗、羊、马、猪等，但研究成本高，且受到伦理约束；而小鼠、大鼠、兔等动物操作相对简便，且价格低、易获取，应用更为广泛[15-16]。

膝关节OA模型的常用手术诱导法包括传统Hulth法与改良Hulth法、前交叉韧带切断法（anterior cruciate ligament transection，ACLT）和内侧半月板失稳法（destabilization of the medial meniscus，DMM）等。传统Hulth法操作难度高，建模不稳定、成功率低，且因建模太快不易观察到不同时期的病理变化；而改良Hulth法操作简单，目前更为常用[15, 17-18]。ACLT法创伤小、操作简单，可用于观察早期OA；但对关节所受的应力影响较小，术后需要高强度运动来诱发OA，与人类实际情况存在差异[19-20]。DMM法创伤小，但仅造成关节局部失稳状态。研究显示，在无高负荷运动下，DMM联合ACLT能取得良好的建模效果[20]。

药物诱导法包括关节腔药物注射法和肉毒素注射法。关节腔注射常用木瓜蛋白酶、碘乙酸钠、尿激酶、胶原酶和TNF-α等。该法操作简便、创伤小、建模时间短，但反复注射易出现硬结、溃烂，实验时需注意药物剂量[15-16]。肉毒素注射法能较好模拟膝关节OA发病中肌肉萎缩的病理基础，与双侧卵巢切除联合可用于建立绝经后女性膝关节OA模型[21]。

力学诱导法包括制动法、负荷法和高强度跑台运动法。制动法可通过石膏固定、绷带固定和悬吊等实现。GAN等[22]利用石膏固定小鼠的右后肢，建模4周后成功观察到膝关节OA病理改变。OZAWA等[23]对骨骼尚未成熟的雌性大鼠进行尾部悬吊，通过引发膝关节排列不良成功构建了髌股关节炎模型。需要指出的是，大鼠的关节成熟与人类存在差异，两足和四足运动中的力学环境也不尽相同，因此该模型呈现的病变过程不能与人类OA等同。制动法虽规避了手术创伤的影响，但长时间固定易造成局部肿胀、皮肤溃烂等并发症，应注意预防。负荷法的常用模型有循环压缩模型以及前交叉韧带断裂模型。该法简单易学、可重复性高、波动性小，良好的模拟性是其最突出的特点，目前使用的多数模型因采用手术和非生理性损伤方法，因而无法很好再现临床所见的实际情况[24]。高强度跑台运动法一般以70%最大摄氧量来设定强度，该法可用于构建OA早期模型，与手术或药物联用可加快或加重OA形成；但因运动方案涉及众多参数，较难统一标准[25]。此外，基因工程OA模型有*Col2a1*敲除小鼠、*Col9a1*敲除小鼠、*Del*基因敲除小鼠、β-catenin条件性敲除小鼠、*SIRT1*基因条件性敲除小鼠、*EFNB2*条件性敲除小鼠、*DOT1L*条件性敲除小鼠、*Pten*条件性敲除小鼠等，而SRT/ort小鼠、BCBC/Y小鼠、Dunkin-Hartley豚鼠等可自发产生OA[16, 26-28]。

2　软骨-软骨下骨相互作用机制

近年来，得益于动物模型尤其是转基因动物学技术，OA研究从单纯的软骨拓展到软骨下骨对OA病理进程的影响，对OA病理和防治的认知更为深入全面。在各类OA模型中均可见明显的软骨下骨和关节软骨病变，如软骨下骨的骨量下降、骨小梁结构破坏、骨髓病变、血管/神经侵入等；关节软骨的蛋白多糖减少、潮线向关节面靠近、血管/神经侵入等。软骨下骨和关节软骨在结构和功能上的密切联系决定了其病变并非完全独立的过程，二者相互影响、相互促进。

有学者提出了“破骨细胞-软骨细胞信号交流”机制来解释软骨下骨和关节软骨之间的相互作用：①破骨细胞和软骨细胞分泌的信号分子经微裂纹和血管到达目的地，进而介导相互作用；②骨髓单核细胞经侵入性血管进入软骨层，随后分化为破骨细胞，与处于不同分化阶段的软骨细胞直接接触；③破骨细胞通过降解骨-软骨交界（即软骨下骨板和钙化软骨）进入软骨层，与软骨细胞相互作用。④一方面，软骨下骨的骨重建异常导致其生物力学特性改变，将剪切力传递到软骨层，引发软骨细胞代谢异常；另一方面，软骨损伤降低其缓冲关节负荷的能力，诱导骨细胞和成骨细胞发出促破骨细胞信号，使软骨下骨的骨重建加速[6]。

3　软骨-骨重建的解耦联：成骨-破骨稳态失衡

在OA不同阶段，软骨下骨微结构呈现出不同的表型，且软骨下骨病变早于软骨损伤[6, 11, 29]。ACLT建模后的第2周，micro-CT分析显示小鼠胫骨软骨下骨的骨量减少，骨体积分数（BV/TV）介于34.3%～55.8%，软骨下骨板变薄，骨小梁变稀疏；而在第4周，骨量呈现回升趋势，BV/TV增加至56.6%～76.2%，软骨下骨板增厚，骨小梁间隙减小。相应地，软骨下骨中的破骨细胞在术后前2周快速增加，随后显著减少[13]。该现象同样见于DMM小鼠模型，术后第2周小鼠胫骨软骨下骨的微结构未发生显著变化；但自第4周起，软骨下骨骨量以及软骨下骨板厚度均增加，第6周更为显著[12]。

软骨下骨微结构的变化与骨重建解耦联有关，早期破骨细胞介导的骨吸收占主导地位，随后骨生成增强，最终超过骨吸收，导致软骨下骨硬化。这一过程受到破骨细胞、成骨细胞、骨细胞、软骨细胞以及内皮细胞的共同调控[7-8, 10-11, 30]（图1A）。

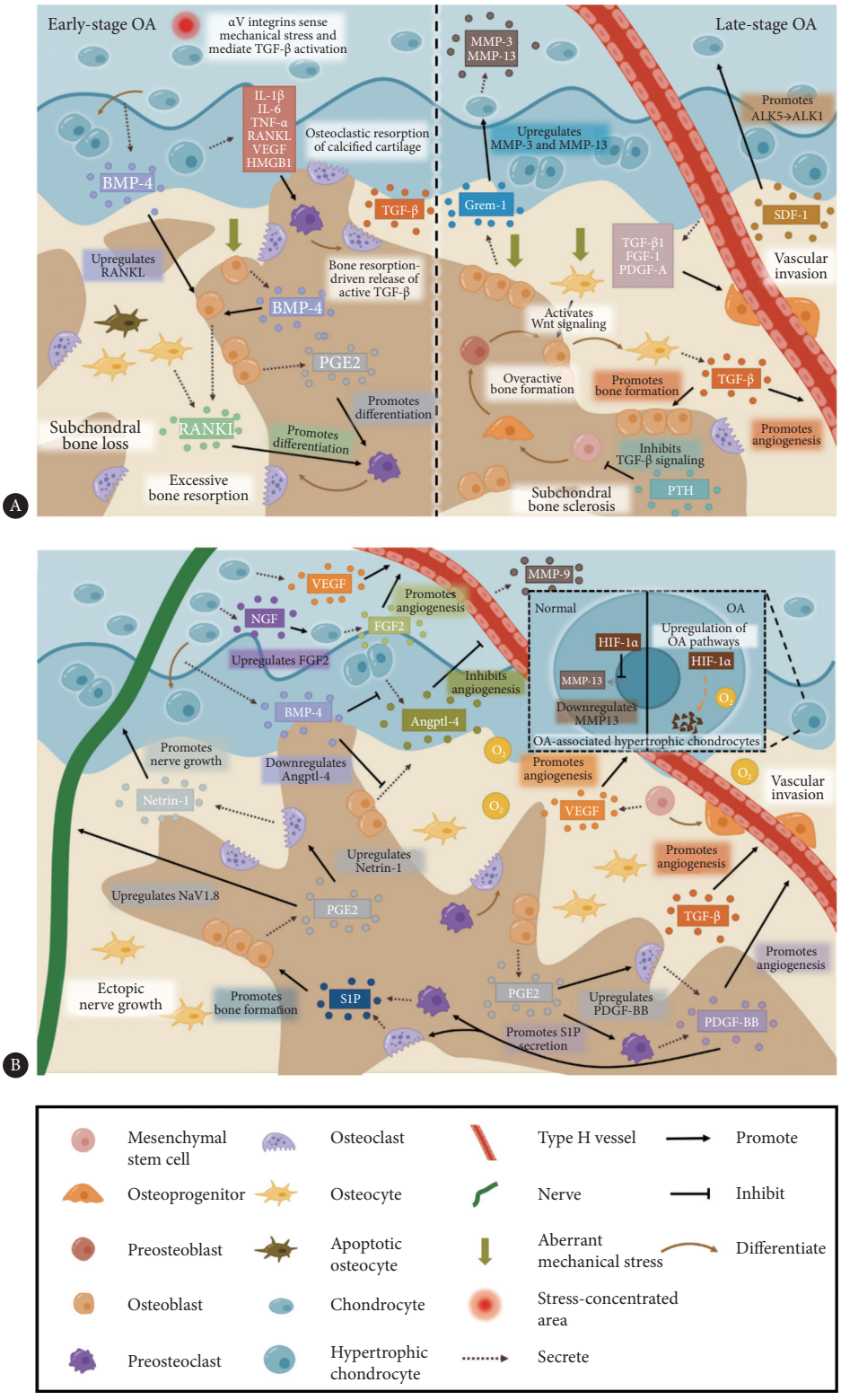

图 1 骨关节炎中软骨-骨相互作用的病理机制

Fig 1 Pathology of cartilage-to-bone crosstalk in osteoarthritis

IL: interleukin; TNF-α: tumor necrosis factor-α; RANKL: receptor activator of nuclear factor-κB ligand; VEGF: vascular endothelial growth factor; HMGB1: high-mobility group box 1; BMP-4: bone morphogenetic protein-4; TGF-β: transforming growth factor-beta; PGE2: prostaglandin E2; MMP: matrix metalloproteinase; Grem-1: gremlin-1; FGF-1: fibroblast growth factor-1; PDGF-A: platelet-derived growth factor subunit A; PTH: parathyroid hormone; ALK: anaplastic lymphoma kinase; SDF-1: stromal cell-derived factor-1; NGF: nerve growth factor; Angptl-4: angiopoietin-like protein-4; S1P: sphingosine-1-phosphate; HIF-1α: hypoxia-inducible factor-1α; PDGF-BB: platelet-derived growth factor-BB. A, Uncoupling of subchondral bone formation and absorption; B, vascular invasion and ectopic nerve growth.

3.1　OA早期: 软骨下骨吸收相对亢进

异常的力学刺激可影响核因子-κB活化体受体配体(receptor activator of nuclear factor κB ligand, RANKL)和骨保护素(osteoprotegerin, OPG)的表达比, 从而调控破骨细胞的分化和成熟[31]。CABAHUG-ZUCKERMAN等[32]采用尾悬法去除小鼠后肢负荷, 5 d后观察到股骨中的骨细胞凋亡增加, 伴骨细胞RANKL表达量上调; 14 d后则可见明显的骨吸收现象。骨吸收也与软骨下骨的微损伤有关, 在创伤性OA早期即可检测到软骨下骨的微损伤。已有研究证实, 紧邻微损伤部位的骨细胞发生凋亡, 并诱导其周围骨细胞的RANKL表达量增加[33-35]。异常的力学负荷同样能引发成骨细胞的代谢变化, 提高其骨形态发生蛋白-4 (bone morphogenetic protein 4, BMP-4)及其受体BMPR-1b的表达; BMP-4进一步刺激成骨细胞表达RANKL, 从而促进破骨细胞生成。此外, 软骨细胞在向肥大软骨细胞转变的过程中, BMP-4的表达量也增加。随着OA的进展, 软骨和软骨下骨中BMP-4水平均进一步升高[36]。

DMM小鼠模型实验表明, 软骨下骨中前列腺素E2 (prostaglandin E2, PGE2)及催化其生成的关键酶环氧化酶-2 (cyclooxygenase-2, Cox2)的表达水平在术后1周即上调, 早于软骨病变的发生; 且Cox2表达主要定位于成骨细胞, 提示成骨细胞是软骨下骨中PGE2的主要来源[37-38]。为探究PGE2对破骨细胞功能的影响, JIANG等[14]特异性敲除了小鼠髓系细胞的前列腺素E2受体*EP4*, 并采用ACLT诱导OA。术后2周, $EP4^{LysM}$小鼠软骨下骨和软骨病变得到缓解, 软骨下骨中破骨细胞前体数量减少, 破骨细胞活性显著降低。术后8周, $EP4^{LysM}$小鼠软骨下骨的组织学表现和形态计量学参数均明显优于$EP4^{fl/fl}$小鼠。随后研究人员向小鼠注射EP4拮抗剂HL-43, 观察到ACLT诱导的OA相关病变得到改善。进一步实验证实PGE2与EP4结合后, 通过Gαs/cAMP/PI3K/AKT/MAPK轴促进破骨细胞前体的迁移和分化。

此外, 肥大软骨细胞来源的IL-1β、IL-6、TNF-α、RANKL、VEGF、HMGB1等可直接或间接促进破骨细胞生成; 衰老软骨细胞分泌的多种降解酶、促炎因子, 以及坏死软骨细胞释放的损伤相关的分子模式(damage-associated molecular patterns, DAMPs)均能影响破骨细胞[6, 11, 39-43]。在多种细胞和因子的调控下, 破骨细胞活性和数量在OA早期显著提高, 导致软骨下骨的骨吸收过程增强。

3.2　OA晚期: 软骨下骨的异位骨生成过度活跃

随OA进展, 关节软骨发生进行性破坏, 关节所受的机械负荷增加。骨细胞感受机械刺激后, 激活成骨细胞中的Wnt信号通路, 促进骨生成[44-46]。在DMM小鼠模型中, 研究人员发现表达lncRNA H19的骨细胞增多, H19通过激活PI3K/AKT/GSK3信号通路抑制蛋白磷酸酶2A的表达, 介导骨细胞对流体剪切力刺激的力学转导, 从而抑制H19可以减轻软骨下骨硬化和软骨退化[47]。

转化生长因子-β1(transforming growth factor beta 1, TGF-β1)在软骨下骨的异位骨生成过程中具有重要作用。OA晚期, 骨细胞来源的TGF-β1可通过激活Smad2/3来增强成骨细胞介导的骨合成代谢[48]。与其他细胞因子不同, 分泌后的TGF-β以无活性形式沉积在细胞外基质。在骨吸收过程中, 由于骨基质的降解以及破骨细胞分泌的蛋白酶和盐酸的作用, TGF-β1被释放和激活[49-50]。OA早期, 骨吸收亢进, 大量活性TGF-β1被释放, 引发软骨下骨及血清中TGF-β1水平迅速升高[6, 50]。维持活性TGF-β处于适当水平对于骨稳态至关重要, 软骨下骨中TGF-β信号传导过度活跃则会引发骨重建过程异常。多项研究显示, ACLT和DMM小鼠软骨下骨骨髓内的间充质干细胞和骨祖细胞显著增多, 并出现成骨细胞和类骨质形成的小岛[12, 14, 38, 51]; 而向ACLT小鼠注射TGF-β1型受体阻断剂后, 间充质干细胞、骨祖细胞、成骨细胞以及类骨质小岛均明显减少, 提示TGF-β1通过招募间充质干细胞至软骨下骨, 促进骨髓中类骨质小岛形成, 从而在软骨下骨的异位骨生成中发挥重要作用[51]。这种由TGF-β1诱导的异常骨生成与骨吸收过程解耦联, 最终引发软骨下骨微结构的改变, 并进一步影响关节软骨的稳态。SUN等[38]自DMM术后第3天起, 每日向小鼠注射甲状旁腺激素(parathyroid hormone, PTH), 8周后通过micro-CT观测到软骨下骨微结构的多个形态学参数, 如小梁骨模式因子(Tb.pf)、结构模式指数(SMI)、孔隙空间总体积(Po.V)、软骨下骨板厚度(SBP.Th)等, 均明显改善。在细胞水平上, 软骨下骨骨髓内的间充质干细胞和骨祖细胞数量减少, 而破骨细胞数量增多。同时, 软骨下骨中TGF-β信号减弱, 伴间充质干细胞表面TGF-β2型受体减少。敲除间充质干细胞的*PTH1*型受体后, PTH的上述效应被削弱, 提示PTH可能通过与PTH1型受体结合, 诱导PTH1型受体与TGF-β2型受体形成的复合物发生内吞, 进而减弱间充质干细胞内TGF-β信号传导, 抑制骨生成, 并增强骨吸收功能, 从而恢复OA软骨下骨的骨重建平衡。另有研究发现, 在对关节施加负荷前向小鼠注射PTH, PTH可通过直接作用于骨和软骨, 减轻负荷诱导的OA[52]。ZHU等[53]利用TGF-β1型受体抑制剂开发了一种小分子药物, 该药物可被高效递送至骨表面并阻断TGF-β信号传导。注射

该药物后，ACLT小鼠的软骨OARSI分数下降，软骨下骨微结构改善，骨髓病变缓解，破骨细胞和成骨细胞前体数量均减少。以上结果提示软骨下骨的骨吸收与骨生成恢复耦联。除直接调控骨生成过程外，TGF-β还可促进COX-2表达和PGE2生成[54]。PGE2与成骨细胞上的EP4受体结合后，促进骨生成，并上调COX-2的表达，进一步放大上述反应[55]。SUN等[37]发现利用塞来昔布抑制PGE2合成后，DMM小鼠的软骨下骨BV/TV相比于对照组出现下降，且骨祖细胞数量减少超过50%。

3.3 OA进程：软骨下骨异常促进关节软骨破坏

软骨下骨骨重建的解耦联可通过多种机制影响关节软骨的稳态。

骨重建失衡所致的软骨下骨微结构异常会改变软骨下骨的生物力学特性，进而影响关节软骨的应力分布，最终诱发软骨损伤[38, 56-58]。ZHEN等[57]观察到，在OA患者关节软骨中，TGF-β活性与软骨下骨的微结构有关。为探究其背后机制，研究人员构建了ACLT小鼠模型，并利用有限元分析，模拟了软骨下骨传递给关节软骨的应力水平和分布。分析结果表明，最大主应变和Von Mises应力在胫骨内侧平台的前部和内部区域显著升高，而在中心区域略有降低。结合micro-CT的三维重建图像，研究人员证实了关节软骨的应力分布与软骨下骨微结构之间的关联性，并进一步发现承受较高应力的软骨区域展现出更高TGF-β活性。研究人员据此推断，软骨下骨的微结构可通过影响关节软骨的应力分布来改变TGF-β活性，进而调控软骨细胞的代谢状态。在此过程中，由αV整合素感受力学刺激并介导TGF-β的激活，而敲除软骨细胞的αV整合素可改善OA引起的关节软骨退化。

软骨下骨的异常骨重建可导致软骨下板孔隙增多和微裂纹形成，从而为软骨下骨中的血管和信号分子进入软骨层提供了通道[59]。钙化软骨层也同样受到破坏。WADA等[60]在DMM小鼠中发现软骨下骨中的破骨细胞也可吸收钙化软骨，且软骨下骨中破骨细胞的密度与钙化软骨损伤程度表现出正相关关系。在生理情况下，钙化软骨在关节软骨与软骨下骨之间起着屏障作用，阻止O_2进入软骨层，其半透膜效应允许小分子选择性交换；而在OA进展过程中，钙化软骨结构和功能破坏引发软骨-骨的异常信号交流，并进一步促进微裂纹形成和血管侵入[59]。软骨下骨中的多种分子可经微裂纹或血管进入软骨层，调控软骨细胞的代谢。ACLT小鼠软骨下骨中含量升高的SDF-1不仅能招募间充质干细胞、引发过度的骨吸收，还能进入软骨层，与软骨细胞上的CXCR4结合，诱导软骨细胞的TGF-β1型受体从促合成代谢的ALK5亚型转变为促分解代谢的ALK1亚型[61]。成骨细胞分泌的Grem-1可上调软骨细胞中MMP-3和MMP-13的表达来增强分解代谢[36]。同样，软骨细胞来源的RANKL、OPG、酶、炎症因子等也可由上述通道进入软骨下骨，影响骨重建过程[6, 11, 13]。

此外，骨重建异常也与软骨下骨中血管侵入和神经异位长入有关，而随后血管和神经对软骨层的侵入进一步加重了软骨损伤[62]。

4 软骨-骨信号交流与血管侵入

软骨下板的血管异位侵入是OA恶化的病理特征之一。在ACLT和DMM诱导的OA动物模型中，H型血管数量明显增加，这一发现提示异常的力学负荷可能是血管生成的始动因素[12, 14, 51]。H型血管是一种高表达CD31和内皮黏蛋白(endomucin, Emcn)的特殊血管亚型，因其血管周围有丰富的骨祖细胞而被认为与骨生成密切相关[63-65]。成骨细胞、破骨细胞与H型血管内皮细胞之间的相互作用可促进软骨下骨的血管生成，加重骨重建失衡[6]（图1B）。

DMM建模后，小鼠软骨下骨中破骨细胞前体的数量和活性均增加，破骨细胞前体大量分泌血小板源性生长因子BB(platelet-derived growth factor-BB, PDGF-BB)，后者通过激活血管细胞和周细胞的PDGFR-β信号通路，诱导新生血管形成[12]。JIANG等[14]发现敲除小鼠破骨细胞的*EP4*可抑制ACLT诱导的H型血管生成，并进一步证实了PGE2通过结合EP4激活NF-κB通路，促进破骨细胞和破骨细胞前体分泌PDGF-BB。TGF-β信号通路也被认为软骨下骨中的H型血管生成有关。miR-210-3p可通过抑制TGF-β1型受体的翻译和诱导DNA结合抑制因子4(DNA-binding inhibitor 4, ID4)mRNA的降解，进而干扰内皮细胞内的TGF-β信号传导，降低其血管生成能力。相较于对照组，ACLT小鼠软骨下骨中的miR-210-3p表达减少；而利用腺相关病毒(adeno-associated virus, AAV)在内皮细胞中过表达miR-210-3p不仅能抑制血管生成、改善软骨下骨微结构，还能减轻软骨损伤[63, 66]。此外，软骨下骨的血管生成也受到软骨细胞的调控，软骨细胞内激活的mTORC1可上调血管内皮生长因子(vascular endothelial growth factor A, VEGFA)的表达，随后VEGFA作用于内皮细胞促进血管生成[67]。在肥大分化过程中，软骨细胞分泌的BMP-4增加，BMP-4可下调成骨细胞、肥大前软骨细胞和肥大软骨细胞中血管抑制因子Angptl-4的表达，从而调控血管生成[36]。OA软骨细胞中神经生长因子(nerve growth factor, NGF)及其受体TrkA的表达升高，NGF与TrkA结合后，激活PI3K/Akt和ERK/MAPK信号通路，促进软骨细胞表达FGF2，进而诱导血管生成[68]。

H型血管生成通常被认为与骨生成耦联，因此可进一步干扰软骨下骨骨重建过程[6]。HU等[69]利用ACLT小鼠证实H型血管与间充质干细胞之间存在正反馈循环，即H型血管提供间充质干细胞，参与软骨下骨的异常骨生成；而间充质干细胞中增强的FAK-Grb2-MAPK通路上调VEGF表达，促进血管生成。同时，研究人员发现利用FAK抑制剂defactinib干扰H型血管生成后，软骨病变得到缓解，表明H型血管也是软骨下骨与软骨相互作用的媒介。H型血管内皮细胞还可分泌TGF-β1、FGF-1、PDGF-A等多种因子进一步诱导其周围的骨祖细胞增殖、分化[6,63-65,70]。破骨细胞前体来源的PDGF-BB不仅具有促血管生成的效应，还可诱导破骨细胞前体和破骨细胞分泌S1P，S1P可促进成骨细胞分化，增强骨生成功能[71]。

随OA进展，软骨下骨中的新生血管可侵入关节软骨。相较于滑膜起源的血管侵入，软骨下骨起源的血管侵入被认为对软骨的损害更为严重[62]。血管侵入不仅引发软骨-骨的异常信号交流，更为重要的是，还会破坏软骨组织特殊的低氧环境，而低氧是维持软骨稳态的前提条件。已有研究证实，OA患者软骨细胞中的转录因子HIF-1α随软骨损伤程度加重而显著下降。HIF-1α在维持软骨完整性中发挥着关键作用：在生理情况下，HIF-1α通过下调MMP-13的表达而抑制软骨基质降解；而在OA病理状态下，HIF-1α通过促进线粒体自噬而减少软骨细胞的死亡[9, 13]。L-plastin（LPL）主要表达于髓系细胞，与破骨细胞融合和成熟有关。ZHANG等[13]发现在敲除*Lcp1*后，ACLT小鼠的血管生成受到抑制，软骨下骨和关节软骨的低氧环境未发生显著变化，同时软骨下骨吸收减弱，关节软骨退化减轻。该结果不仅表明破骨细胞与血管生成相关，还证实了血管生成的确会影响软骨下骨和关节软骨内的氧分压。敲降软骨细胞中的*Hif1a*可部分抵消*Lcp1*敲除所带来的保护效应，提示HIF-1α在延缓OA进展中发挥着一定的作用。研究人员进一步通过单细胞测序分析鉴定出了一类与OA相关的肥大软骨细胞，这些细胞主要位于严重受损的软骨区域，参与软骨基质降解和软骨内骨化；其内的HIF-1信号通路显著下调，而与OA相关的信号通路被激活。值得注意的是，维持软骨细胞中的HIF-1α水平可抑制ACLT引起的软骨损伤，但对软骨下骨病变并未表现出明显的改善作用。此外，血管内皮细胞还可直接分泌蛋白酶，降解软骨基质，其中MMP-9发挥着关键作用[72]。

5　软骨-骨相互作用与神经异位长入

关节疼痛是OA常见的临床症状之一。由于关节软骨缺乏神经分布，疼痛的产生主要与软骨下骨有关[53]（图1B）。基于ACLT小鼠模型的研究证实，软骨下骨中感觉神经的异位生长是关节疼痛的来源，而神经生长受破骨细胞分泌的Netrin-1的调控。敲除ACLT小鼠破骨细胞的*Netrin-1*可减轻OA疼痛。研究人员进一步发现OA患者的膝关节软骨下骨中表达Netrin-1的破骨细胞数量显著增加[73]。另一项采用ACLT小鼠模型的研究同样显示软骨下骨内Netrin-1水平升高伴感觉神经纤维增多；而敲除*Lcp1*以阻碍破骨细胞分化后，神经纤维数量明显减少，小鼠的疼痛敏感性下降[13]。为深入探究OA疼痛的分子机制，ZHU等[53]构建了ACLT小鼠模型。相较于对照组，ACLT模型小鼠背根神经节（dorsal root ganglia, DRG）神经元的电压门控钠通道$Na_V1.8$的表达显著上调，且这些神经元的轴突侵入了软骨下骨。鉴于OA软骨下骨中PGE2水平明显升高，研究人员探究了PGE2是否参与调控$Na_V1.8$的表达。特异性敲除成骨细胞的*Cox2*可减少$Na_V1.8^+$ DRG神经元的数量；而特异性敲除DRG神经元的*Ptger4*（编码EP4的基因）则降低神经元的兴奋性，并缓解OA疼痛。基于以上结果，研究人员进一步发现PGE2在结合DRG神经元的EP4后，通过PKA-Creb1信号通路上调$Na_V1.8$的表达，进而提高神经元的敏感性。此外，该项研究还显示抑制软骨下骨的异常骨重建不仅可以减轻OA疼痛，还能改善软骨下骨微结构和关节软骨病变，因而比单纯阻断疼痛传导通路具有更好的治疗效果。另一项研究对ACLT小鼠模型敲除了破骨细胞中的*EP4*，发现Netrin-1分泌量和软骨下骨中感觉神经元数量均发生下降，该结果提示PGE2也能激活EP4促进破骨细胞分泌Netrin-1，从而调控神经生长[14]。在DMM模型中，间歇性甲状旁腺激素（intermittent parathyroid hormone, iPTH）被发现能减轻OA疼痛并降低软骨下骨PGE2水平，但敲除$Nestin^+$间充质基质细胞的PTH1型受体后，iPTH的疼痛缓解效应减弱。研究人员据此推测，iPTH通过作用于PTH1型受体，降低软骨下骨中PGE2的合成，进而抑制神经生长，缓解疼痛[38]。此外，敲除小鼠的破骨细胞前体细胞的PDGF-BB几乎消除了软骨下骨中异位生长的神经纤维，提示PDGF-BB也可能与神经生长有关[12]。

软骨下骨中的神经异位长入同样会影响骨重建平衡。使用辣椒素抑制DMM小鼠软骨下骨中感觉神经的侵入后，除疼痛缓解外，软骨下骨微结构也得到改善，骨祖细胞数量显著下降[37]。随神经生长，关节内神经生长因子水平升高，敲除DMM小鼠关节中的神经生长因子受体*Ngfr*后，内侧软骨下骨BV/TV减少21%[74]。在正常骨组织中，交感神经和副交感神经活性处于平衡状态，但当

OA进展到晚期阶段时，交感神经活性增强[75]。研究显示，在施加干预措施8周后，自然衰老的小鼠、DMM小鼠以及接受机械负荷的小鼠体内去甲肾上腺素水平升高，伴软骨下骨硬化倾向；研究人员随后证实交感神经的激活可促进软骨细胞外泌体中的miR-125向成骨细胞转移，进而干扰软骨下骨稳态[76]。PGE2的促骨生成效应也被发现与感觉神经有关，PGE2通过作用于感觉神经上的EP4，促进间充质干细胞的成骨分化，而敲除成骨细胞的*COX-2*或敲除感觉神经上的*EP4*可有效延缓OA的进展，包括软骨退化、软骨下骨硬化和疼痛等[37, 77-79]。在OA进展过程中，软骨下骨中的神经纤维常与血管共同侵入软骨下板，加剧了软骨异位骨化和疼痛。

6 结语

软骨-骨相互作用的病理机制在OA的发生发展中发挥着关键作用。关节软骨可影响软骨下骨的生物力学环境，而异常力学负荷所致的软骨下骨骨重建解耦联是OA重要的病理机制；反之，软骨下骨微结构的变化也会影响关节软骨的应力分布，进而引发或加重软骨损伤。此外，在软骨下骨骨重建过程中释放的多种物质可调控关节软骨的代谢；而软骨下骨中新生血管和感觉神经纤维对软骨层的侵入会引发一系列病理过程，如破坏低氧环境、引发软骨内骨化、加重关节疼痛等。

历经近十年的研究，软骨-软骨下骨相互作用的病理机制逐渐成了解读OA的新发现和新视角。而在这个发展历程中，构建特异、稳定的动物模型在研究OA的病因、病理改变、发病机制以及开发相关治疗策略中占有不可替代的地位。构建动物模型的方法多样，包括手术、药物以及各种物理化学手段等。随着基因工程技术的不断发展，转基因动物模型在疾病研究中的应用也越来越广泛。目前，软骨-骨信号交流及相关机制尚未完全阐明，其在关节炎中的作用有待进一步探索，而相关研究的开展依赖于稳定可靠的动物模型构建方法的持续创新与改进。

* * *

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Author Contribution WU Jianing is responsible for methodology, writing--original draft, and writing--review and editing. ZHOU Yumeng is responsible for methodology and writing--review and editing. LIU Yijin and LIU Xiaoheng are responsible for writing--review and editing. ZHANG Ping is responsible for conceptualization and supervision. ZHANG Demao is responsible for conceptualization, writing--original draft, and writing--review and editing. All authors have agreed to submit the article to this journal, have approved the final version to be published, and agree to be accountable for all aspects of the work.

利益冲突 本文作者刘肖珩是本刊编委会编委。该文在编辑评审过程中所有流程严格按照期刊政策进行，且未经其本人经手处理。除此之外，所有作者均声明不存在利益冲突。

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