软骨和软骨下骨与膝骨关节炎关系的研究进展

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摘　要　膝骨关节炎（knee osteoarthritis,KOA）的发生、发展涉及膝关节周围的多种组织病变,包括软骨的退变、软骨下骨的重建和二者构成的软骨-软骨下骨复合体间的异常分子交互。本文阐述了膝关节软骨、软骨下骨及软骨-软骨下骨复合体与 KOA 的关系,并介绍了目前检测软骨和软骨下骨早期损伤的新技术,以期为从膝关节软骨和软骨下骨角度防治 KOA 提供新的思路。

关键词　骨关节炎,膝;软骨;软骨下骨;软骨-软骨下骨复合体;综述

膝骨关节炎（knee osteoarthritis,KOA）是一种严重影响中老年人生活质量的慢性退行性疾病[1],会给患者、家庭和社会造成沉重负担[2-3]。越来越多的研究表明,KOA 的发生、发展与软骨和软骨下骨的变化关系密切[4-5]。因此,本文对软骨和软骨下骨与膝骨关节炎关系的研究进展进行了综述,以期为从膝关节软骨和软骨下骨角度防治 KOA 提供新的思路。

1　膝关节软骨与 KOA 的关系

正常关节软骨是一种无血管、无神经的组织,由软骨细胞和细胞外基质组成,后者主要由水分、胶原和蛋白多糖等构成[6-9]。软骨细胞在维持软骨微环境中发挥关键作用,几乎所有软骨成分的合成都有软骨细胞的参与[10]。在正常生理状态下,软骨细胞被基质包裹,并能通过调节基质成分和基质降解酶的方式帮助维持自身的分化和低周转状态,这种状态能使关节软骨具有承受机械负荷的能力[11]。另外,软骨细胞还能与滑膜细胞产生滑液并形成一层边界层,降低关节软骨表面的摩擦系数[12],而滑液在软骨中活动也能促进分子扩散到软骨中,进而为软骨提供营养[13]。关节软骨中 80% ~90% 的蛋白多糖形成大的聚合体,蛋白多糖聚合体由带强电荷的糖胺多糖链通过连接蛋白以非共价方式连接到透明质酸上,并与其他基质成分一起被包裹在交联型的Ⅱ型胶原纤维网络中[14]。这种胶原纤维网为关节软骨提供了形变和弹性强度,同样使关节软骨能够承受机械负荷[15-16]。在膝关节的正常活动中,关节软骨被挤压,亲水性的糖胺多糖链和大量带电溶质的水分子被挤出。当压力释放时,蛋白多糖因具有足够的固定电荷,能够重新吸收水和少量溶质进入基质,使软骨形态恢复。此外,软骨细胞表面分布有机械感受器,能通过承受的机械负荷调节软骨细胞的生化活动。在适度的关节活动中,感受器在适度压力下通过减少蛋白水解酶的合成,调节代谢平衡,防止软骨损伤的发生。

在 KOA 早期,最先出现的病理变化是软骨基质降解。为应对软骨基质降解,软骨细胞通过聚集和异常分化形成肥大软骨细胞来提高活性[8]。具有凝血酶反应蛋白基序的去整合素和金属蛋白酶（a disintegrin and metalloproteinase with thrombospondin motifs,ADAMTS）能够破坏蛋白多糖的聚集,导致软骨降解。基质金属蛋白酶（matrix metalloproteinase,MMP）能够裂解胶原纤维网络的三螺旋结构,使蛋白多糖降解,细胞外基质破坏,软骨细胞无法发挥正常作用,最终导致软骨降解[17]。目前已有多项研究证实,这 2 种酶在 KOA 的进展中表达水平升高。Wang 等[18]发现,骨关节炎小鼠的关节软骨中 ADAMTS1、ADAMTS2、ADAMTS5 的表达均增高,表明其与软骨的降解有关。Zhao 等[19]发现,KOA 的严重程度与 MMP-13 表达水平有关。软骨的降解能导致多种炎症介质的释放,而炎症介质的释放又能引发软骨降解[20]。Koh 等[21]发现,KOA 患者和非 KOA 患者的白细胞介素（interleukin,IL）-4、IL-8、IL-15、肿瘤坏死因子-α（tumor necrosis factor-α,TNF-α）、IL-1β 等炎症介质的血浆水平存在明显差异,并指出 IL-8 和 IL-18 血浆水平升高可能与 KOA 的发病有关。Ruan 等[22]发现,KOA 患者的血清 MMP-13 水平与血清 TNF-α、IL-8、IL-18 水平呈正相关。除上述因素外,微

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RNA[23]、血清 S100A8/S100A9 水平[24]也被发现与软骨降解有关。

2　膝关节软骨下骨与 KOA 的关系

软骨下骨位于关节软骨下方,并由钙化软骨分隔,其中钙化软骨和关节软骨的分界标志被称为潮汐线。软骨下骨又分为软骨下骨板和软骨下松质骨两部分。钙化软骨的下方为软骨下骨板,它主要由皮质骨构成,具有较低的孔隙率。而在深处支撑软骨下骨板的是软骨下松质骨,它具有较高的孔隙率,其中的骨小梁分布不均,在各个位置排列方向不同,由此构成一个独特的网状结构,以承受局部机械负荷[25]。

在正常生理活动中,骨的结构和组成都是通过骨细胞的介导来调节的,这个过程涉及成骨细胞和破骨细胞。成骨细胞合成新骨,而破骨细胞在局部生物力学因素、全身激素和局部可溶介质的作用下吸收旧骨[26-27]。二者相互协调作用,以动态的平衡维持正常骨骼的形态及功能。随着 KOA 的进展,骨细胞中核因子 κB(nuclear factor - κB,NF - κB)受体激活蛋白配体分泌增加,骨保护素分泌减少,使破骨细胞介导的骨吸收增强[28-29],进而导致软骨下骨骨质疏松。随着机械负荷增加,骨细胞分泌的硬化素减少,导致 Wnt 信号通路增强,使成骨细胞介导的骨形成增强[6]。在 KOA 晚期,膝关节软骨下骨板孔隙率减小,骨板增厚,骨松质网络破坏,至此新的骨结构形成,这种过程被称为软骨下骨的重建。但在这种快速骨重建的异常状态下,骨周转率加快导致骨质形成后期的矿物质积累中断,使膝关节软骨下骨出现相对矿化不足的状态,导致骨硬度降低,使其更易变形[25,30-31]。在 KOA 晚期,为应对过量的机械负荷和膝关节不稳定,转化生长因子-β(transforming growth factor-β,TGF-β)通过激活软骨下骨中的 Smad2/3 信号通路来促进成骨细胞介导的骨形成代谢,使软骨内骨化形成骨赘来维持膝关节的稳定性[32]。此外,晚期 KOA 影像学检查可出现“骨髓水肿”,其特征是脂肪坏死、局限性骨髓纤维化和骨小梁微骨折,这是由局部骨损伤相关的细胞活动产生的,与活跃的骨重建有关。这种骨髓损伤往往与软骨损伤区域有关,尤其好发于软骨下骨裸露的部位[33]。对于软骨下骨囊肿,有研究发现囊肿易出现在已发生过骨髓病变的部位,并因此产生了一种观点,即囊肿产生于软骨下骨中,而骨损伤和坏死启动了破骨细胞介导的骨吸收,从而导致了囊肿形成[8]。Fell 等[34]的研究表明,软骨下骨的厚度与软骨厚度呈线性关系,而软骨损伤量与骨密度和骨体积同样呈线性关系。因此,在异常的生物学和力学因素作用下,软骨发生缺损,软骨下骨失去保护,从而发生异常重建。同样,软骨下骨的骨质破坏也加大了对软骨的切割与磨损。二者相互作用,使整个关节陷入恶性循环,最终导致 KOA 病情不断恶化。

3　膝关节软骨-软骨下骨复合体与 KOA 的关系

随着对软骨和软骨下骨相互作用研究的深入,越来越多的研究者认为应将二者看作一个整体,并提出了“软骨-软骨下骨复合体”的概念。软骨-软骨下骨复合体由关节软骨深层、潮线、钙化软骨及下方软骨下骨板组成,是一个具有复杂生物功能的结构,其中各部分相互协同配合,对关节生理活动的调节和病理活动的发生起重要作用[8]。生物学和力学因素作用于软骨-软骨下骨复合体的任一结构,都可能导致其组成、结构和功能发生变化。既往认为钙化软骨是软骨与软骨下骨之间不可渗透的屏障的观点,目前已被推翻。从 1950 年有研究者发现软骨下骨内血管丛可能为软骨提供营养[35]开始,越来越多的研究发现软骨与软骨下骨之间允许各种大小的代谢物和调节分子扩散。Intema 等[36]在一项犬的动物实验中发现,在早期 KOA 中软骨下骨板变薄与软骨损伤有关。Aizah 等[37]的研究表明,KOA 早期软骨下骨的重建与软骨基质降解相互影响。此外,关节软骨和软骨下骨在结构上密切接触,它们之间的各种介质能够发生交互作用。目前已有多项研究证实了软骨与软骨下骨之间的生物化学变化和分子串扰能够跨越界面。Imhof 等[13]发现,软骨下骨区域的部分末端血管与深层软骨直接接触,软骨所需的葡萄糖、氧和水,50% 以上都由这些血管提供。Pouran 等[38]的研究发现,人和马的关节软骨与软骨下骨之间都存在中性溶质转运。Malinin 等[39]的研究也发现,软骨下骨能通过血管向软骨输送营养物质。上述研究表明,软骨-软骨下骨复合体将软骨与软骨下骨紧密连接,使其在维持关节稳态中发挥枢纽作用。

在 KOA 发展过程中,软骨表面微裂纹增加,软骨下骨板的孔隙率增大,使一系列血管生成因子分泌增加,扩大了软骨深层与软骨下骨之间的血管分布范围[40-41]。这种变化使软骨与软骨下骨之间物质的交

换更为活跃，并触发了生化信号通路在二者间的串扰。TGF-β/Smad 信号通路中的 TGF-β 在正常关节软骨中高表达，而在 KOA 关节软骨中几乎不表达；抑制转化 TGF-β/Smad 信号通路能加剧软骨退化，激活转化 TGF-β/Smad 信号通路可减轻软骨损伤；TGF-β1 除能激活 Smad2/3 介导骨形成外，还可通过增加软骨下骨板的孔隙率影响 Smad 的表达，最终加剧软骨退化[42-43]。Jia 等[44]在研究中通过抑制 Sirtuin1/NF-κB 信号通路改善了软骨细胞外基质的降解，并减少了软骨细胞凋亡。Yang 等[45]通过抑制 Toll 样受体 2/NF-κB 信号通路，延缓了软骨损伤的进展，并使关节骨赘形成和骨质吸收明显减少。Wu 等[46]的研究表明，通过下调 JAK3/STAT4 通路使 ADAMTS4 和 MMP-13 的表达减少，从而防止软骨受损。Zhang 等[47]的研究表明，通过抑制受体相互作用蛋白（receptor-interacting protein，RIP）1/RIP3/MLKL 信号通路促进软骨细胞与细胞外基质的合成代谢，并抑制破骨细胞分化，进而保护软骨及软骨下骨。Guo 等[48]在研究中通过 AMP 活化蛋白激酶（AMP-activated protein kinase，AMPK）/NF-κB/胞外信号调节激酶（extracellular signal-regulated kinase，ERK）信号通路同样抑制了破骨细胞的分化，改善了软骨下骨的异常重塑，延缓了 KOA 的进展。促分裂原活化的蛋白激酶信号通路通过磷酸化级联将胞外信号传递到细胞核，从而调节细胞的生物学变化。ERK 信号通路与软骨细胞中 ADAMTS4、ADAMTS5、MMP-3、MMP-9 和 MMP-13 表达密切相关[49]，也有研究指出它能调控骨调节素使软骨下骨发生病理变化[50]。Liu 等[51]的研究发现，通过刺激 α7-nAChRs/哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号通路可延缓软骨降解，并能减轻骨关节炎导致的关节疼痛。

此外，NOD 样受体蛋白 3（NOD-like receptor thermal protein domain associated protein 3，NLRP3）[52]、结节性硬化症复合体亚单位 2-RHBE-mTOR[53]、AMPK/叉头框转录因子 3[54]、磷脂酰肌醇 3 激酶/Akt/mTOR[55]、NF-κB/NLRP3[56]、miR-214-5p/PPARGC1B[57]、单核细胞趋化蛋白 2/细胞表面趋化因子受体 2[58]、胰岛素样生长因子 1/Akt/胰岛素受体底物 1[59]、缺氧诱导因子 1α/NLRP3[60]等信号通路也被证实参与到 KOA 的过程中。这使我们对软骨与软骨下骨交互作用的了解越来越清楚，有助于我们更加全面地了解 KOA 的发展过程。

4　检测软骨和软骨下骨早期损伤的新技术

目前已有许多新的 MRI 定量技术能够识别出软骨早期损伤。Kretzschmar 等[61]发现，与周围软骨相比，发生病变前的软骨 T2 弛豫时间明显延长。Madelin 等[62]通过钠 MRI 技术检测软骨中钠离子浓度来预测软骨退变。Jena 等[63]在研究中使用 PET-MRI 技术观察到软骨的动态变化。此外，T1rho 映射、弥散加权成像、糖胺多糖的化学饱和转移成像技术都可评估早期软骨损伤[64-65]。

通过 X 线、双能 X 线、CT 等检测软骨下骨来评估 KOA 是目前临床常用的方法，同时许多新的技术也在不断涌现。Shiraishi 等[66]采用高分辨率外周定量 CT 分析软骨下骨微观结构参数，发现软骨下骨微观结构参数与 Kellgren-Lawrence 分级有关。Turunen 等[67]使用造影剂增强锥束 CT 检测软骨下骨体积骨密度的变化，认为对其进行定量分析有助于诊断 KOA。Chang 等[68]在研究中用 7T MRI 检测到轻度 KOA 患者软骨下骨微结构的恶化。此外，软骨下密度 CT 地形图、动态对比增强 MRI 也能检测到软骨下骨的改变[69-70]。

5　小　结

KOA 是涉及多种组织结构的病变，软骨和软骨下骨作为膝关节的重要组成部分，相互作用、相互影响，共同维持膝关节的稳态，同时也在 KOA 的发生、发展中起重要作用。一方面，软骨的破坏会使软骨下骨表面失去保护，异常的应力将直接作用于软骨下骨，引起软骨下骨的异常重建；另一方面，软骨下骨的破坏也会使软骨失去足够的支撑，加剧异常机械负荷对软骨的剪切与破坏。随着对软骨和软骨下骨相互作用的深入探索，研究者提出了软骨-软骨下骨复合体的概念，并受到了广泛认可。在此基础上，研究者发现了多种生化信号通路介导了 KOA 的发生与发展，这使我们在分子层面对 KOA 有了新的认识。同时，目前许多新兴技术能够帮助我们更好地识别软骨和软骨下骨的早期损伤。

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