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·综述·

颞下颌关节盘破坏的病因及基础研究进展

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【摘要】 颞下颌关节是口腔颌面部唯一的滑膜关节，其关节盘是一种重要的纤维软骨结构，能够分散应力并维持关节运动的稳定。多种因素可导致关节盘破坏，进而引起关节功能障碍甚至面部畸形。近年来，关节盘疾病已成为口腔医学领域的研究前沿。以往研究及文献综述主要围绕诊断与治疗展开，缺乏关节盘破坏的基础研究进展的文献综述。本文综述了颞下颌关节盘破坏的病因、病理特征、分子机制、组织工程修复材料的最新研究进展，为颞下颌关节盘破坏的基础研究与临床防治提供参考。研究表明：关节盘破坏的原因包括机械刺激(例如关节盘前移位、咬合异常、创伤等)、慢性炎症(例如骨关节炎、类风湿性关节炎等)、年龄和性别等易感因素以及心理社会因素；主要表现为胶原纤维的超微结构和力学性能改变；病变分子机制包括血管异常生成、机械刺激或炎症刺激下纤维软骨细胞稳态失衡、干细胞异常分化。组织工程研究主要从细胞来源、支架材料和生长因子等方面推进组织工程材料的开发与优化。未来应重点关注关节盘破坏的分子机制，胚胎及出生后关节盘发育调控，新型生物材料研发与转化，以及人工智能在材料设计、分子靶点筛选、临床决策中的应用等方面。

【关键词】 颞下颌关节盘；　颞下颌关节盘破坏；　病理特征；　分子机制；　组织工程材料；　修复再生；　人工智能

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Etiology and basic research progress on temporomandibular joint disc destruction

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【Abstract】 Temporomandibular joint (TMJ) is the only synovial joint in the oral and maxillofacial region, with its disc being a critical fibrocartilaginous structure that distributes stress and maintains the stability of joint movement. Various factors can lead to TMJ disc destruction, resulting in TMJ dysfunction and facial deformities. In recent years, research on TMJ disc destruction has become a frontier in the field of oral and maxillofacial surgery. Previous research and literature reviews have mainly focused on diagnosis and treatment, with a lack of reviews on the progress of basic research related to disc destruction. This review summarizes current progress in the etiology, pathological features, mo-

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lecular mechanisms, and tissue-engineered repair materials of TMJ disc destruction, providing reference for basic research and clinical prevention and treatment. Studies have shown that the causes of TMJ disc destruction include mechanical damage (*e.g.* anterior disc displacement, malocclusion, trauma), chronic inflammation (*e.g.* TMJ osteoarthritis, rheumatoid arthritis), and susceptibility factors such as age and sex, as well as psychosocial factors. Its main manifestations are alterations in the ultrastructure and mechanical properties of collagen fibers. Its molecular mechanisms include abnormal angiogenesis, imbalanced fibrocartilage cell homeostasis under mechanical or inflammatory stimulation, and abnormal stem cell differentiation. The present study focuses on the development and optimization of tissue engineered biomaterials through cell sources, scaffold materials, and growth factors. Future studies should focus on the molecular mechanisms of TMJ disc destruction, regulation of disc development during embryonic and postnatal stages, development and translation of novel biomaterials, as well as the application of artificial intelligence in material design, molecular target screening, and clinical decision-making.

【Key words】 temporomandibular joint disc;　temporomandibular joint disc degeneration;　pathological characteristics;　molecular mechanisms;　tissue engineering;　repair and regeneration;　artificial intelligence

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颞下颌关节(temporomandibular joint,TMJ)是口腔颌面部唯一的滑膜关节,由下颌窝、关节结节及下颌骨髁突组成,参与维持颌面部重要生理功能。颞下颌关节盘(以下简称"关节盘")位于髁突和关节结节之间,为薄层纤维软骨,其细胞外基质(extracellular matrix,ECM)主要由胶原纤维和蛋白聚糖组成。胶原纤维以Ⅰ型胶原(collagen type Ⅰ,COL1)为主,COL1在维持形状和拉伸强度方面起重要作用。蛋白聚糖则与抗压能力及粘弹性密切相关。其他类型的ECM也在关节盘功能维持中发挥重要作用,如Ⅵ型胶原(collagen type Ⅵ,COL6)与关节盘应对咬合力密切相关[1],Ⅴ型胶原(collagen type Ⅴ,COL5)在关节盘发育及力学稳定性中起到重要调控作用[2]。因此,关节盘的正常解剖和组织结构赋予其出色的多向承载能力,能够有效分散负荷、缓冲震荡并稳定关节运动。临床上,关节盘前移位、颞下颌关节骨关节炎(temporomandibular joint osteoarthritis,TMJOA)、外伤等因素可引起关节盘破坏(如穿孔、撕裂、退行性变)。破坏后的关节盘丧失分散负荷和缓冲震荡的功能,进一步导致患者功能障碍甚至面部畸形。因此及时干预关节盘破坏对防止病情恶化非常重要。近年来,TMJ关节盘疾病已成为口腔医学领域的研究热点与前沿。以往研究及文献梳理主要围绕诊断与治疗展开,对关节盘破坏的基础研究进展的文献梳理相对不足。本文将综述关节盘破坏的病因、病理及结构特征、分子机制、组织工程修复材料等方面的最新进展,并提出未来研究建议,旨在为TMJ关节盘破坏的基础研究与临床防治提供思路。

1　颞下颌关节盘破坏的病因与病理特征

1.1　颞下颌关节盘破坏的病因

关节盘破坏可发生在关节盘的多个部位[3],其中以双板区和中带的破坏最常见[4],其破坏是多因素共同参与下的复杂病理过程,主要病因包括:机械刺激和慢性炎症等直接诱因,年龄和性别等易感因素以及抑郁和焦虑等心理社会因素。

1.1.1　异常机械刺激是TMJ关节盘破坏的首要因素　异常机械刺激主要包括关节盘移位、咬合异常以及创伤。关节盘移位尤其是不可复性前移位是关节盘破坏最常见的机械性原因。由于盘—髁关系长期异常,开闭口过程中髁突对关节盘双板区反复挤压,导致该区域应力集中,盘胶原纤维结构损伤,最终关节盘变薄、破坏[5-7]。关节盘前移位主要引起双板区的破坏。一项针对157例关节盘前移位和关节盘穿孔病例的研究,确认了关节盘前移位与破坏发生之间的高度相关性[8]。此外,咬合异常(长期咀嚼过硬食物、单侧咀嚼、夜磨牙等)和创伤(下颌骨外伤、咬合创伤等)等其他机械刺激也可能导致关节盘破坏。例如,长期夜磨牙患者通常出现关节盘形态异常[9]。单侧咀嚼增加了不可复性关节盘前移位和疼痛、关节杂音的风险,进而增加关节盘破坏的风险[10]。急性咬合变化亦可导致关节盘破坏[11]。

关于咬合异常与关节盘损伤的相互关系仍存在争议。一方面,长期咬合异常可能导致关节盘损伤。长期咬合异常会使某些区域牙齿承受过大压力,压力传递至关节,改变关节的力学环境,进而增加关节盘移位和破坏的风险[12-13]。然而,临床

及动物实验均显示，咬合异常仅是关节盘破坏的风险因素之一，在颞下颌关节紊乱（temporomandibular disorders，TMD）发生中的贡献度为4.8%～27.1%[14]。另一方面，关节盘破坏也可能导致咬合异常。关节盘破坏会引起髁突软骨和关节内压力增加，进而引发关节功能障碍和髁突结构破坏。对于单侧病变，可能出现咬合接触点改变和咬合平面倾斜；对于双侧病变，可能表现为前牙深覆盖、浅覆𬌗、开𬌗趋势，上颌牙弓宽度变小、下前牙外展等[15]。一项针对368例关节盘穿孔的患者的分析发现，40岁以下的穿孔患者约50%伴随咬合改变[16]。然而，临床上部分关节盘损伤患者并未出现咬合改变。总体上看，咬合异常和关节盘破坏可能相互促进，然而现有研究主要集中于临床现象的相关性观察，缺乏明确的因果关系研究。

1.1.2　慢性炎症是TMJ关节盘破坏的重要因素　慢性炎症主要包括TMJOA、类风湿性关节炎，它们导致关节腔内长期炎症，直接促进关节盘的破坏。TMJOA的慢性炎症导致关节盘破坏的机制可能有两方面：一方面，炎症因子在关节腔内的积累可能通过相关分子机制，加重关节盘细胞外基质降解，进而导致关节盘变薄甚至穿孔[17]；另一方面，炎症还可能导致关节腔内滑液分泌减少、滑液的黏度和成分变化，这导致润滑效果下降，使髁突在运动过程中施加在关节盘上的压缩、拉伸、剪切力和摩擦力增加，进而加速关节盘的磨损。关节盘破坏导致髁突受力急剧增加，髁突软骨退行性变加重，进而加重TMJOA，形成恶性循环。TMJOA主要引起关节盘中间带的破坏。

TMJOA的严重程度与关节盘破坏程度密切相关。一项针对238例不可复性关节盘前移位患者的研究中，根据是否伴有关节盘破坏将其分为两类，发现伴关节盘破坏组的髁突破坏更严重[18]；另一项研究显示，关节盘穿孔患者中，TMJOA临床Wilkes分期Ⅳ和Ⅴ占比较高，说明TMJOA晚期退变与盘穿孔密切相关[19]；TMJOA、摩擦音、症状出现时间与关节盘穿孔显著正相关：TMJOA使盘穿孔风险增加5倍；存在摩擦音患者的盘穿孔风险增加5倍；症状每增加1年，盘穿孔风险增加22%；而关节弹响与关节盘穿孔负相关[19]。

类风湿性关节炎亦可能累及TMJ导致关节盘破坏[20]。其机制可能与TMJOA中的慢性炎症相似。类风湿性关节炎的严重程度与关节盘破坏的程度可能密切相关。一项研究分析了不同结缔组织病患者的TMJ情况，包括类风湿性关节炎、强直性脊柱炎、脊柱关节炎、混合型结缔组织病，发现类风湿性关节炎患者的TMJ出现显著的疼痛、摩擦音和活动度降低症状[21]。另一项研究显示，在31例关节盘破坏的患者中，4例患有类风湿性关节炎，其中6例40岁以下的关节盘破坏患者中有2例患有类风湿性关节炎[22]。然而，关于类风湿性关节炎与关节盘破坏的关系，现有临床证据仍较为有限，尚需进一步探索。

1.1.3　年龄和性别是TMJ关节盘破坏的易感因素　随着年龄增长，关节盘ECM组成和结构发生改变[23-24]，这可能导致关节盘在受力后更容易发生结构性损伤；衰老还导致关节盘细胞功能下降，减弱其在损伤后的自我修复能力。性别差异对关节盘破坏有重要影响，女性的患病率更高[25]，这可能与雌激素通过调控关节盘ECM的合成分解代谢水平，从而影响其结构稳定性有关[26]。

1.1.4　焦虑和抑郁是TMJ关节盘破坏的心理社会因素　心理社会因素是指情绪、认知、社会支持和生活压力等因素。大量研究证实抑郁、焦虑等心理社会因素与TMD密切相关[27-28]。同样作为软骨病变，膝关节骨关节炎的疼痛和功能受限等症状与心理社会因素显著关联[29-30]。心理社会因素影响关节盘破坏的潜在机制可能有：①情绪压力可引起长期持续的咀嚼肌紧张和不良咀嚼行为，增加关节负荷；②激活下丘脑－垂体－肾上腺轴，促进皮质醇和儿茶酚胺分泌，导致全身炎症状态，从而加速关节退行性变[31-32]。然而，心理社会因素是否直接导致髁突软骨或关节盘病变，目前尚无确切因果证据。多数学者强调改善心理因素应作为TMD综合管理的组成部分。

1.2　*颞下颌关节盘破坏的病理及结构特征*

目前关节盘破坏的病理研究尚显不足，分类尚未统一，传统来看，大体可从形态上分为是否有关节盘变形、体积改变以及是否有关节盘磨损或破裂。从成分上分析是否有胶原沉积、是否有纤维变性、是否有炎性浸润、是否有血管新生以及是否钙化。一项针对22例颞下颌关节紊乱患者的研究，分析了30个手术切除的关节盘的病理变化。结果表明，所有关节盘均有变形，其中14个出现磨损和破裂。从病理学角度看，在30个关节盘中，25个表现出纤维黏液样变性和胶原沉积，表明关节盘退行性变处于早期阶段；25个表现出纤维玻璃样变和纤维组织增加、弹性丧失，提示病变的进一

步进展；18个表现出滑膜炎症、慢性炎症细胞浸润（淋巴细胞、组织细胞、浆细胞）和血管新生，表明组织经历了长期炎症；15个表现出散在钙化，标志着退行性变进入晚期[33]。这表明关节盘组织呈现多种退行性病理过程并存的状态。另一项针对晚期TMD手术切除的关节盘病理结果提示，胶原变性和微血管生成是其主要特征[34]。此外，对不可复性前移位患者的关节盘进行测量，发现其体积、表面积和最大横截面积均小于正常关节盘[35]。早期一篇文献观察到兔关节盘在2.5 mm直径穿孔后髁突软骨的退行性变和关节盘钙化[36]。另有研究通过关节腔注射弗氏完全佐剂诱导TMJOA，发现TMJOA引起了关节盘胶原纤维超微结构的显著改变[17]。

除传统的病理学研究外，近年来微纳米形貌和力学特征也越来越多地用于关节盘研究中。运用扫描电镜、透射电镜、双光子显微镜、原子力显微镜等技术，研究者比较了猪颞下颌关节盘在正常、穿孔、撕裂以及不可复性关节盘前移位状态下的微观结构和机械性能，结果表明，在上述情况下，关节盘会出现胶原纤维排列紊乱、变细，杨氏模量（即材料刚度）下降等现象[37]。与不可复性盘前移位相比，可复性盘前移位的关节盘在胶原纤维直径、排列的变化发生更早，且刚度的降低发生更早，长期观察发现两者都表现出严重的关节盘退变。关节盘内侧纤维连接区是关节盘前后向和环向排列纤维的过渡区域，研究表明该区域是盘病变发生的初始部位[6,38]。另一项针对人类TMJOA伴颞下颌关节盘破坏切除样本进行透射电镜分析发现，病变关节盘表面覆盖了大量成纤维细胞和组织细胞；胶原纤维束更加密集，富集在毛细血管周围；滑膜表面出现活化的巨噬细胞特征，并出现液泡形成。以上研究均提示在颞下颌关节紊乱疾病患者中，关节盘损伤与修复并存[39]。

2　颞下颌关节盘破坏的分子机制及靶向干预策略

2.1　异常血管生成

正常情况下关节盘无血管，但在关节盘破坏样本中常出现高密度血管，提示血管新生可能在关节盘破坏中发挥关键作用。临床样本显示关节盘破坏后高迁移率族蛋白B1（high mobility group protein B1，HMGB1）表达升高。HMGB1通过与受体结合，激活细胞外信号调节蛋白激酶（extracellular signal-related kinases，ERK）/c-Jun氨基末端激酶（c-Jun N-terminal kinase，JNK）信号通路，促进低氧诱导因子-1α（hypoxia inducible factor-1α，HIF-1α）和血管内皮生长因子（vascular endothelial growth factor，VEGF）的表达，推动血管生成过程。因此HMGB1、HIF-1α、VEGF及相关信号通路可能成为关节盘破坏的潜在治疗靶点[40]。

2.2　异常机械刺激下纤维软骨细胞稳态失衡

有研究通过前牙反𬌗模型验证了咬合干扰促进了大鼠关节盘炎症的发生发展；体外对关节盘细胞加力，验证了机械刺激上调与炎症和ECM分解代谢相关的基因；机械刺激通过激活Ca^{2+}通道瞬时受体电位香草酸受体4（transient receptor potential vanilloid 4，TRPV4），促进Ca^{2+}内流，引起关节盘细胞的炎症和分解代谢增加；TRPV4是治疗关节盘破坏的一个靶点[41]。

适度的机械刺激有助于关节盘形态的维持。研究发现，喂软食的大鼠关节盘厚度降低，糖胺聚糖和多种蛋白多糖表达下降，说明生物力学环境与关节盘ECM代谢密切相关[42]。

2.3　炎症刺激下纤维软骨细胞稳态失衡

一项对不可复性盘前移位伴穿孔患者的关节盘样本进行免疫组化分析发现，COL1排列无序，基质金属蛋白酶-3（matrix metallo proteinase-3，MMP-3）、基质金属蛋白酶-9（matrix metallo proteinase-9，MMP-9）表达增加，巨噬细胞数量增加，这表明炎症在关节盘ECM重塑中的重要作用[43]。炎症是导致关节盘退行性变和前移位的关键因素，持续的白细胞介素-1β（interleukin-1β，IL-1β）通过激活核因子κB（nuclear factor kappa-B，NF-κB），诱导关节盘胶原纤维重塑，表现出新生胶原纤维数量增加，但排列松散紊乱，进而引起力学性能下降，这加重了关节盘退行性变和前移位；阻断NF-κB可减轻关节盘退行性变和前移位[44]。有研究认为营养不足是关节盘退变的重要原因。低氧和低糖抑制关节盘纤维软骨细胞生长；低糖条件下，聚集蛋白聚糖（aggrecan，ACAN）、Ⅱ型胶原（collagen typeⅡ，COL2）等软骨ECM的合成被抑制；低氧条件下，线粒体数量代偿性增加，但无糖使线粒体变形肿胀[45]。间充质干细胞（mesenchymal stem cells，MSC）来源的外泌体（MSC-exo）包裹了大量MSC活性分子如微小RNA（micro RNA，miRNA）、mRNA、蛋白质等。MSC-exo能重编程受体细胞，抑制炎症引起的纤维软骨细胞凋亡，促进细胞增殖、

迁移、软骨ECM的合成；磷脂酰肌醇3-激酶（phosphatidylinositol 3-kinase，PI3K）/蛋白激酶B（protein kinase B，AKT）通路是关键机制[46-47]。

2.4　干细胞异常分化

关节盘中存在干细胞。通过纤维粘连蛋白法，可分选恒河猴关节盘前体细胞，这些细胞占关节盘总细胞数量的1%～3%，能在体外扩增超过60次，具有三向分化能力，可分化为与天然关节盘相似的纤维软骨样组织[48]。一项基于单细胞转录组测序的研究发现，小鼠关节盘细胞可以分为成纤维细胞、内皮细胞、巨噬细胞、壁细胞亚群，其中一部分胸腺细胞抗原1（thymus cell antigen-1，THY1）阳性/Notch同源蛋白3（Notch homolog protein 3，Notch3）阳性壁细胞亚群具有干性，另一部分壁细胞趋向分化为功能性盘细胞，表达与纤维软骨有关的基因。然而，关节盘损伤后，$THY1^{+}$/$NOTCH3^{+}$干细胞显著减少，并偏向分化为分泌型卷曲相关蛋白2（secreted frizzled-related protein 2，SFRP2）阳性成纤维型细胞而非Chad阳性类软骨细胞，表明关节盘损伤后修复过程主要表现为干细胞成纤维性而非软骨再生[49]。因此，关节盘破坏中的干细胞分化，尤其是干细胞向成纤维细胞的转化，可能是再生的关键调控靶点。

综上，颞下颌关节盘破坏的分子机制见图1。

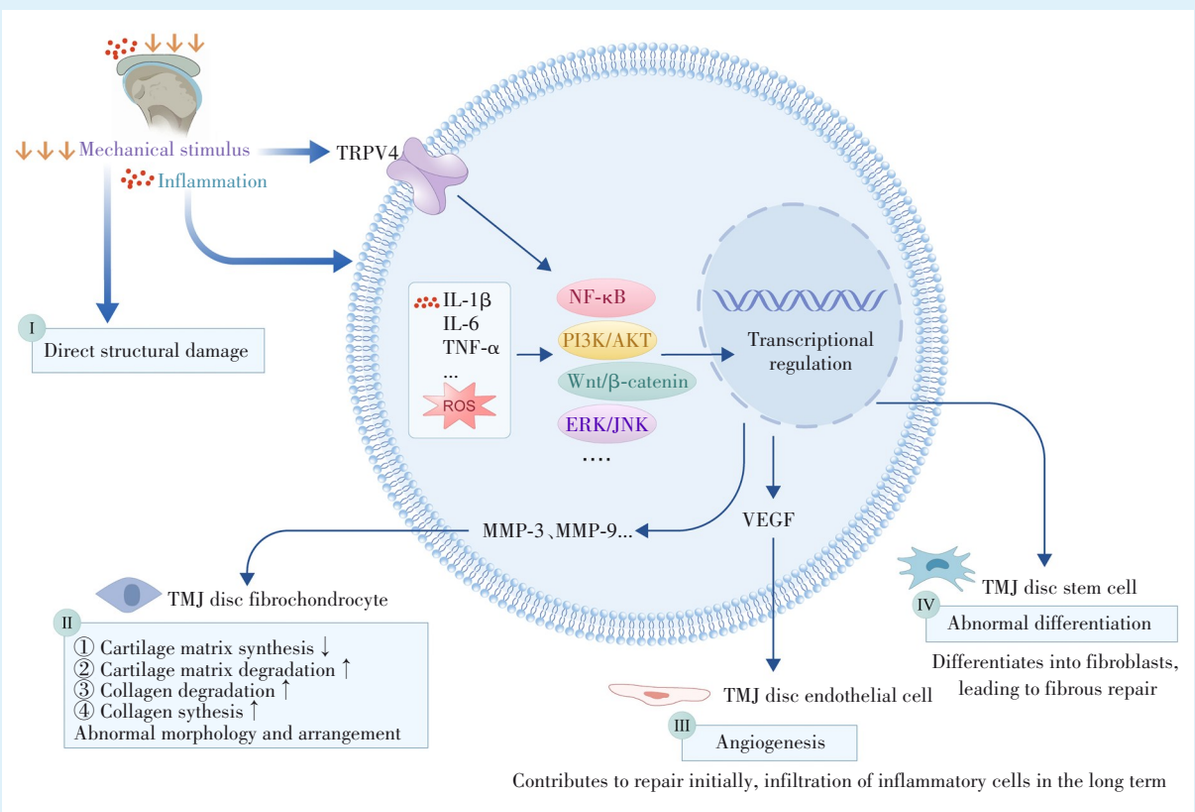

Figure was created with Microsoft Adobe Illustrator 29.5. First, mechanical stimulation directly affects the disc, causing morphological changes and structural damage. Second, mechanical stimuli or inflammatory factors activate multiple signaling pathways, leading to an imbalance in the synthesis and degradation of the ECM in fibrocartilage cells. This alters the composition and structure of the ECM, which makes the TMJ disc more prone to structural damage under stress. Third, angiogenesis is upregulated, leading to inflammatory cell infiltration, which further exacerbates the imbalance in ECM synthesis and degradation. Fourth, stem cells differentiate towards fibroblast-like cells. ECM: extracellular matrix; TRPV4: transient receptor potential vanilloid 4; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; NF-κB: nuclear factor kappa-B; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; ERK: extracellular signal-regulated kinases; JNK: c-Jun N-terminal kinase; MMP-3: matrix metalloproteinase-3; MMP-9: matrix metalloproteinase-9; VEGF: vascular endothelial growth factor; TMJ: temporomandibular joint

Figure 1　Mechanisms of temporomandibular joint disc degeneration

图1　颞下颌关节盘破坏的分子机制

3　组织工程材料修复颞下颌关节盘的实验研究

现有的治疗手段难以完全恢复关节盘形态和功能，其长期疗效存在争议。因此，近年来越来越多研究开始关注组织工程关节盘修复材料，并已取得初步进展。

3.1　细胞来源

MSC易于提取且具有多向分化特性，已成为关节盘组织工程领域最广泛研究的种子细胞[50]。MSC主要包括脂肪间充质干细胞（adipose-derived mesenchymal stem cell，ADSC）、骨髓间充质干细胞（bone marrow stem cell，BMSC）、滑膜间充质干细胞（synovial mesenchymal stem cell，SMSC），这些干细胞不仅具备分化为纤维软骨细胞的潜能，还能通过分泌生长因子、发挥抗氧化等功能，促进关节盘损伤的修复。已有不少实验探索其作为关节盘穿孔修复材料，或用于修复同为纤维软骨的半月板损伤[51-52]。牙髓干细胞（dental pulp stem cell，DPSC）与关节盘有相同的胚胎起源（神经嵴细胞），具有与关节盘细胞相似的基因表达模式。注射DPSC可减轻TMJOA的软骨基质降解[53-54]。此外，位于髁突表面的纤维软骨干细胞（fibrochondral stem cell，FCSC）是关节盘纤维软骨再生的潜在候选细胞。与MSC相比，FCSC具有更强的成软骨潜能[55-56]，且FCSC具有产生血管内皮生长因子的能力[57]，有助于关节盘后带和双板区的修复。一项研究将人诱导多能干细胞（human induced pluripotent stem cells，hiPSC）与关节盘细胞共培养后，hiPSC能够分化为关节盘细胞，hiPSC可作为关节盘再生的潜在组织工程细胞来源[58]。

成体细胞也表现出良好的修复能力。原代关节盘无需诱导即可维持纤维软骨表型，但其来源有限且体外扩增能力差，多次传代后易出现表型飘移。此外，有研究采用猪同种异体肋软骨细胞体外培养，通过细胞自组装形成无支架三维结构，并将其植入猪的关节盘穿孔模型，发现其显著改善了穿孔，并减少了关节的退行性变化[59]。

3.2　支架材料

细胞外基质的脱细胞技术是当前关节盘天然支架研究的热点[60-61]。脱细胞支架具有优异的仿生性和零免疫原性，能够随着新组织的产生逐渐降解或被新组织同化。一种猪小肠黏膜下层脱细胞基质支架在关节盘部分切除后的修复中表现出良好的生物相容性[62]。但脱细胞过程往往伴随胶原结构破坏和力学性能下降[63]。为了增强脱细胞基质的力学性能，有研究采用聚己内酯（polycaprolactone，PCL）力学增强的脱细胞基质作为关节盘替代材料，植入山羊体内6个月后，关节盘和髁突的形态仍保持良好[64]。

明胶/透明质酸-硫酸软骨素水凝胶[65]、壳聚糖/海藻酸钠支架等天然高分子支架，可提供细胞黏附位点，促进MSC分化。与天然高分子支架相比，合成支架力学性能可控，可获得极高强度，更能满足关节盘修复的要求。如PCL具有良好的力学性能和适中的降解速率，可以通过3D打印形成关节盘的各向异性结构[66-67]。聚氨酯[68]、聚氨酯-聚乙烯醇[69]也可作为关节盘材料。

由于关节盘的胶原纤维排列存在各向异性，且该排列方式与其力学性能密切相关，因此构建仿生关节盘的纤维结构成为关键。目前主要采用3D打印与静电纺丝两种技术来模拟这一结构。3D打印技术可通过调整参数精确控制孔隙率和排列方向，形成较大孔径，有利于细胞迁移和成血管[67]；相比之下，静电纺丝能够制备纳米级纤维，其直径小、孔径细，更有利于细胞黏附与基质沉积。近期，利用静电纺丝法制备的三维PCL/聚乳酸/碳纳米管圆盘支架在兔关节盘修复实验中取得了良好效果[70]。

3.3　生长因子

关节盘组织工程领域，生长因子的研究尚不足。在其他纤维软骨组织工程相关的研究中，转化生长因子-β（transforming growth factor-β，TGF-β）、胰岛素样生长因子（insulin-like growth factor，IGF）、血小板衍生生长因子（platelet-derived growth factor，PDGF）、碱性成纤维细胞生长因子（basic fibroblast growth factor，bFGF）较为常见。这些生长因子在刺激软骨合成、胶原合成等关节盘基质的形成中发挥了重要作用。

TGF-β信号是软骨功能的重要调节机制，TGF-β信号异常将导致髁突软骨发育异常[71]。大量研究发现，TGF-β3促进纤维软骨的基质合成。将TGF-β3与结缔组织生长因子（connective tissue growth factor，CTGF）递送到3D打印的支架中，与MSC培养后可产生颞下颌关节盘的纤维软骨基质[72]。TGF-β3也可促进半月板损伤的修复[73-74]和促进椎间盘退行性变的修复[75-76]。IGF-1是促进软骨细胞合成蛋白聚糖的主要刺激物，可显著促进半月板和椎间盘糖胺聚糖形成[77-78]。

值得注意的是，椎间盘、半月板与颞下颌关节

盘在结构和功能上十分相似，近期对椎间盘、半月板修复材料的研究可为颞下颌关节盘修复材料的开发提供参考方向[79-80]。半月板材料主要包括细胞因子递送水凝胶、细胞递送水凝胶、机械增强型水凝胶。例如，引入动态硼酯键的水凝胶具有可注射性、自愈合性，便于临床操作；在该动态共价水凝胶中包入负载抗炎、促成软骨药物的聚乳酸-羟基乙酸微球，形成促再生的人工半月板[81]。将抗炎抗氧化的药物大黄素封装到介孔二氧化硅颗粒，表面以促软骨分化的生长分化因子修饰，包入水凝胶中，可促进切除的半月板再生[82]。基于甲基丙烯酸缩水甘油酯修饰的丝素蛋白光固化水凝胶，加入苯基硼酸离子液体和TGF-β1，苯基硼酸离子液体具有湿润粘附性，TGF-β1促进软骨基质合成，经紫外光固化后，水凝胶能迅速凝固，在半月板撕裂处形成坚固结构[83]。半月板的特殊微纳米结构是实现高效能量耗散的基础。半月板-骨界面的多尺度强化机制（如无定型磷酸钙和羟基磷灰石结合）能显著增强拉伸强度和黏附能力，优化软硬界面微观结构，对提高关节盘耐用性提供了参考[84]。就分子机制而言，椎间盘退行性变的主要病理特点是细胞衰老与凋亡，细胞外基质变性、纤维化、钙化[85-87]。半月板损伤后也常出现COL1聚集[88]。纤维化是由慢性炎症引起、肌成纤维细胞参与的组织修复失调，广泛发生在各种器官的病理过程中[89-90]。颞下颌关节盘损伤后的纤维化可能与椎间盘、半月板及其他器官如肺纤维化类似，因此其治疗可能存在共同靶点[91]。

4　展　望

目前TMJOA的基础研究主要聚焦髁突软骨，而关节盘在TMJ力学稳定及TMJOA进展中的关键作用仍未得到充分关注，关节盘破坏的基础研究相对匮乏。此外，组织工程材料的力学匹配性、长期稳定性以及临床转化仍存在一定挑战[64]。未来的研究可以围绕以下几个方面展开。

4.1　深入探索分子机制

①机械生物学是研究机械力如何影响细胞行为、组织结构和疾病进展的交叉学科[92]。运用机械生物学的研究方法，分析ECM的力学环境对关节盘细胞生物学行为的影响，揭示关节盘破坏的潜在调控靶点。②借鉴膝关节骨关节炎研究方法[93-94]，分析经典的细胞死亡模式以及新型的细胞死亡模式在关节盘损伤中的作用。③借鉴其他疾病研究方法[95-96]，探讨氧化应激、代谢重编程在关节盘损伤中的作用。④借鉴膝关节骨关节炎及软骨再生领域的研究方法[97-98]，整合多组学数据，系统分析不同细胞亚群在基因表达、蛋白质表达、代谢物丰度的时空变化及关联，深入揭示关节盘损伤与修复的分子机制。⑤整合多组学数据，构建关节盘胚胎发育时空图谱以指导再生[99-100]。

4.2　优化组织工程材料设计

①关节盘组织工程材料需在长期稳定性、大动物模型、临床转化方面取得突破。②融合多种小分子药物，如各种金属、非金属、核酸纳米颗粒，优化材料设计。③将有限元分析融入材料开发中，重点关注关节盘材料的力学稳定性。④从微纳米结构角度关注关节盘能量耗散机制，为高强度、高韧性的关节盘材料设计提供参考。

4.3　人工智能辅助颞下颌关节盘破坏研究

目前，人工智能在关节盘破坏领域的研究主要集中在辅助诊断与风险预测两个方面。如卷积神经网络（convolutional neural networks，CNN）可高效分析关节盘形态变化，辅助诊断关节盘破坏伴积液[101]。基于锥形束CT的深度学习模型在预测关节盘前移位方面也表现优良[102]。结合CNN与多尺度生物力学模型发现，较小下颌骨和平坦髁突通过改变咬合力比例、降低氧气和葡萄糖供应，进一步加重关节退行性变[103]。因此，未来研究可进一步探索：①通过机器学习优化纳米材料设计；②通过机器学习从多组学中筛选关节盘修复的关键靶点；③基于机器学习和深度学习算法，结合影像数据和临床数据，实现多模态数据融合。

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