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·基础研究·

脱落多配体蛋白聚糖-4在大鼠颞下颌关节骨关节炎中的作用

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【摘要】　目的　探究脱落多配体蛋白聚糖-4(sSDC4)在大鼠颞下颌关节骨关节炎(TMJOA)中的作用机制，以期为TMJOA的防治提供实验依据。**方法**　本实验已获得单位实验动物伦理委员会批准。将12只6周龄雌性SD大鼠随机分为2组，分别于双侧颞下颌关节上腔注射50 μL浓度为4 mg/mL碘乙酸钠(MIA)(TMJOA模型组)和50 μL PBS(对照组)。4周后，取颞下颌关节髁突软骨，用苏木精-伊红(HE)染色、番红O-固绿(SO)染色及Ⅱ型胶原(Col-Ⅱ)免疫组化染色观察髁突软骨退变程度；取颞下颌关节滑膜用免疫组化染色检测白细胞介素-6(IL-6)、肿瘤坏死因子-α(TNF-α)表达以评估滑膜炎症程度；并收集颞下颌关节腔滑液通过酶联免疫吸附法(ELISA)测定sSDC4水平。另外将12只6周龄雌性SD大鼠随机分为His-SDC4组和对照组，每3 d分别于双侧颞下颌关节上腔处注射50μL 100 ng/mL His-SDC4蛋白和50 μL PBS，共28 d，同以上实验取材进行HE、SO染色以及免疫组化染色(Col-Ⅱ、IL-6、TNF-α)观察髁突软骨退变以及检测滑膜炎症程度。体外培养SD大鼠滑膜成纤维细胞和髁突软骨细胞，随机分为His-SDC4刺激(10 ng/mL)组和对照组，进行CCK-8细胞毒性检测和光学显微镜下观察细胞形态学特点，采用实时荧光定量聚合酶链式反应(RT-qPCR)检测IL-6、TNF-α的mRNA表达水平变化，ELISA检测细胞培养上清中IL-6、TNF-α的含量变化。**结果**　与对照组相比，TMJOA组髁突软骨厚度、SO阳性面积百分比、Col-Ⅱ阳性面积百分比降低(均$P<0.001$)；滑膜炎评分升高($P<0.001$)，滑膜IL-6、TNF-α阳性细胞率升高(均$P<0.001$)；滑液中sSDC4水平显著升高($P=0.011$)。关节腔注射His-SDC4后，髁突软骨厚度、SO阳性面积百分比和Col-Ⅱ阳性面积百分比降低(均$P<0.001$)；滑膜炎评分升高($P=0.006$)，滑膜IL-6、TNF-α阳性细胞率升高(均$P<0.001$)。体外细胞实验显示，His-SDC4刺激可显著上调滑膜成纤维细胞和髁突软骨细胞中IL-6和TNF-α的表达水平(均$P<0.01$)，同时培养上清中这两种细胞因子的含量也显著增加(均$P<0.01$)。**结论**　TMJOA进程中滑液中的sSDC4水平显著升高，滑液中的sSDC4可以直接刺激滑膜成纤维细胞和髁突软骨细胞分泌更多的促炎因子，形成恶性循环加速TMJOA进程。

【关键词】　颞下颌关节；　骨关节炎；　多配体蛋白聚糖-4；　脱落多配体蛋白聚糖-4；　软骨；　滑膜；　滑膜炎

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The role of shed syndecan-4 in temporomandibular joint osteoarthritis in rats　HE Kangping[1,2], CHEN Xiaohua[2], LI Jinru[3], ZHAN Ying[2], HE Feng[2], JIANG Tianlu[1], LI Feifei[1], YU Shibin[2].　1. State Key Laboratory of Oral & Maxillofacial Reconstruction and Regeneration, National Clinical Research Center for Oral Diseases, Shaanxi Clinical

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【Abstract】 Objective To investigate the mechanism of shed syndecan-4 (sSDC4) in temporomandibular joint osteoarthritis (TMJOA) in rats, aiming to provide experimental evidence for its prevention and treatment. **Methods** This study was approved by the Institutional Animal Ethics Committee. Twelve 6-week-old female Sprague Dawley (SD) rats were randomly divided into two groups. They received a single intra-articular injection into the bilateral superior cavity of temporomandibular joint, which consisted of either 50 μL of 4 mg/mL monosodium iodoacetate (TMJOA model group) or 50 μL of phosphate-buffered saline (PBS, control group). After 4 weeks, the mandibular condylar cartilage was harvested for hematoxylin & eosin (H&E) staining, Safranin O-fast green (SO) staining, and type II collagen (Col-Ⅱ) immunohistochemical staining to assess the degree of cartilage degeneration. The synovium of the temporomandibular joint was collected for immunohistochemical staining to detect the expression levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) to evaluate the degree of synovial inflammation. Synovial fluid from the temporomandibular joint cavity was collected to measure sSDC4 levels by enzyme-linked immunosorbent assay (ELISA). In addition, 12 6-week-old female SD rats were randomly divided into a His-SDC4 group and a control group, receiving injections into the bilateral superior cavity of temporomandibular joint of either 100 ng/mL (50 μL) of His-SDC4 protein or 50 μL of PBS once every 3 days for a total of 28 days. The same experimental procedures were performed for H&E staining, SO staining, and immunohistochemical staining (Col-Ⅱ IL-6, TNF-α) to observe condylar cartilage degeneration and detect synovial inflammation. Rat synovial fibroblasts and condylar chondrocytes were cultured in vitro and randomly divided into a His-SDC4-stimulated (10 ng/mL) group and control group. Perform CCK-8 cytotoxicity assays and observe cellular morphology under optical microscopy, the mRNA expression levels of IL-6 and TNF-α were detected by real-time quantitative polymerase chain reaction (RT-qPCR), and the levels of IL-6 and TNF-α in cell culture supernatants were measured by ELISA. **Results** Compared with the control group, the TMJOA group showed decreased condylar cartilage thickness, percentage of SO-positive area, and percentage of Col-Ⅱ-positive area (all $P<0.001$); an increased synovitis score ($P<0.001$) and increased percentages of IL-6- and TNF-α-positive cells in the synovium (all $P<0.001$); and a significant increase in sSDC4 levels in the synovial fluid ($P = 0.011$). Following intra-articular injection of His-SDC4, condylar cartilage thickness, percentage of SO-positive area, and percentage of Col-Ⅱ-positive area all decreased (all $P<0.001$); the synovitis score increased ($P = 0.006$), and the percentages of IL-6- and TNF-α-positive cells in the synovium increased (all $P<0.001$). In vitro experiments showed that His-SDC4 stimulation significantly upregulated the expression levels of IL-6 and TNF-α in both synovial fibroblasts and condylar chondrocytes (all $P<0.01$), and the levels of these two cytokines in the culture supernatants also significantly increased (all $P<0.01$). **Conclusion** During TMJOA progression, the level of sSDC4 in the synovial fluid is significantly elevated, which can directly stimulate synovial fibroblasts and condylar chondrocytes to secrete more pro-inflammatory cytokines, forming a vicious cycle that accelerates TMJOA progression.

【Key words】 temporomandibular joint; osteoarthritis; syndecan-4; shed syndecan-4; cartilage; synovium; synovitis
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颞下颌关节(temporomandibular joint, TMJ)是人体最复杂的关节之一,主要由颞骨关节窝、关节盘、下颌髁突等构成,是实现咀嚼、吞咽等生理功能的结构基础。颞下颌关节紊乱病(temporoman-

dibular disorders，TMD）是颌面部的常见疾病，主要表现为关节杂音、下颌运动障碍和颌面部疼痛等[1]，影响患者的正常生活[2]，其具体发病机制尚未完全明确。颞下颌关节骨关节炎（temporomandibular joint osteoarthritis，TMJOA）是TMD的重症表现[3]，主要表现为滑膜炎[4]、软骨退变、软骨下骨病变[5]。

多配体蛋白聚糖-4（syndecan-4，SDC4）是硫酸乙酰肝素类跨膜转运蛋白多糖Syndecan家族成员之一，在细胞迁移、血管生成、炎症反应、细胞增殖等方面发挥重要作用[6-7]。Echtermeyer等[8]研究发现SDC4与膝关节骨关节炎（osteoarthritis，OA）严重程度呈正相关，在OA的发生发展中发挥着重要作用。SDC4的一个显著特点是其胞外段可从细胞膜上脱落，脱落多配体蛋白聚糖-4（shed syndecan-4，sSDC4）仍具有结合功能，可以自分泌或旁分泌的形式参与疾病进展[9]。已有研究表明膝关节OA患者滑液中sSDC4水平升高[10]，然而，sSDC4在TMJOA的发生中的作用机制研究目前尚未见报道。本研究拟探究sSDC4在大鼠TMJOA中的作用，以期为TMJOA的防治提供实验依据。

1　材料和方法

1.1　主要试剂与仪器

鼠源单克隆抗体Ⅱ型胶原（collagen type Ⅱ，Col-Ⅱ）一抗（M2139，Santa Cruz公司，美国）；兔源多克隆抗体白细胞介素-6（interleukin-6，IL-6）一抗（21865-1-AP，武汉proteintech公司，中国）；兔源多克隆抗体肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）一抗（17590-1-AP，武汉proteintech公司，中国）；兔源多克隆抗体β-actin一抗（AF7018，Affinity，美国）；通用二步法检测试剂盒（小鼠/兔增强聚合物法检测系统）（PV-9000，中杉金桥，中国）；SDC4检测试剂盒（酶联免疫吸附试验法）（SEB939Ra，武汉云克隆公司，中国）；Rat IL-6 ELISA Kit（E-EL-R0015，Elabscience，中国）；High Sensitivity Rat TNF-α ELISA Kit（E-HSEL-R0001，Elabscience，中国）；Tripure（Roche，美国）；Bioflex六孔板（包被Ⅰ型胶原）；Ⅰ型胶原酶（Gibco，美国）；碘乙酸钠（monosodium iodoacetate，MIA）（Sigma-Aldrich，St.Louis，MO，美国）；His标签蛋白标记的重组大鼠SDC4胞外段蛋白（His-tagged Syndecan-4，His-SDC4）（RPB939Ra01，武汉云克隆公司，中国）；双抗、DMEM高糖培养基（HyClone，美国）；显微镜（DM2500，Leica，德国）；核酸蛋白测定仪和酶标仪（Eppendorf，德国）；实时荧光定量聚合酶链式反应（real-time quantitative polymerase chain reaction，RT-qPCR）仪（Bio-rad，美国）。

1.2　实验动物分组及大鼠TMJOA模型建立

所有动物实验均已获得空军军医大学医学伦理委员会审核和批准（批件号：IRB-REV-2022028）。SD雌性大鼠购买于空军军医大学实验动物中心，饲养于SPF级环境中，所有大鼠均饲养在温度（20~26℃）和相对湿度（40%～70%）的条件下，保持光/暗环境各12 h循环。动物合格证号：SCXK（军）2017-0021。

为探究sSDC4水平与TMJOA严重程度的相关性，12只6周龄雌性SD大鼠随机分为TMJOA模型组和对照组（n=6）。TMJOA模型组的操作：每100 g体质量腹腔内注射0.3 mL的1%戊巴比妥钠深度麻醉大鼠，持胰岛素注射器插入眼耳连线与颧弓下缘交界处，辅助大鼠进行张闭口运动，感受髁突头位置，调整针头方向，使其进入髁突与颞骨关节面间的上腔隙，触及骨壁回退1 mm，回抽无血注射50μL MIA（4 mg/kg，以PBS为溶剂）。对照组以同样方法注射50 μL PBS[11]。

为探究sSDC4对TMJ的具体作用，另外12只6周龄雌性SD大鼠随机分为His-SDC4组和对照组。His-SDC4组的操作：同样的方式于SD大鼠双侧TMJ关节内上腔注射50 μL浓度为100 ng/mL的His-SDC4，每3 d注射1次，注射4周后取材，对照组注射等量的PBS。

1.3　取材及组织块的处理

动物造模4周后，向大鼠腹腔注射过量戊巴比妥钠（150 mg/kg）麻醉，确认无疼痛反射后，采用颈椎脱臼法处死。取大鼠左侧TMJ，4%多聚甲醛中固定24 h，脱钙2个月后常规石蜡包埋切片。剥离大鼠右侧TMJ周围的肌肉组织，充分暴露关节滑膜，穿刺抽取关节滑液，用于ELISA检测。

1.4　苏木精-伊红染色和番红O-固绿染色实验检测滑膜炎症和髁突软骨退变程度指标

大鼠TMJ样品脱钙后，常规石蜡包埋切片，进行苏木精-伊红（hematoxylin-eosin，HE）染色，用光学显微镜采集图像，Photoshop软件测量软骨中带的厚度（软骨表面到骨软骨交界处的距离）[12]，根据滑膜炎评分表[13]，进行滑膜炎评分。

大鼠TMJ样品石蜡包埋切片后，进行番红O-固绿染色（safranin O-fast green，SO）染色。将切片1%固绿染色1 min，1%醋酸酒精分化30s，待切片

干燥后，1%番红O染色5min，95%（v/v）酒精漂洗15 s。采用Leica DM2500显微镜采集图像，每个样本随机选取3个高倍视野（×200）。采用Photoshop软件计算SO阳性面积百分比。

1.5　免疫组化染色检测Col-Ⅱ及IL-6、TNF-α阳性细胞

大鼠TMJ样品石蜡切片常规脱蜡至水，按照免疫组化试剂盒说明书中描述的SABC法进行Col-Ⅱ抗体（1∶50）染色检测软骨组织，IL-6抗体（1∶400）、TNF-α抗体（1∶200）染色检测软骨和滑膜组织。免疫组化染色结果的判读以特异性染色定位和显著高于背景的着色强度为阳性标准。Col-Ⅱ为胞外基质阳性；IL-6和TNF-α为细胞质阳性。无特异性染色或染色强度与背景一致者判为阴性。采集图像后，在滑膜和软骨中随机选取3个高倍视野（×200），计算阳性面积比例或阳性细胞率。

1.6　大鼠原代细胞提取及实验分组、细胞毒性检测和细胞形态学观察

过量戊巴比妥钠处死3周龄雌性SD大鼠，剪碎滑膜组织和髁突软骨，胰蛋白酶消化20 min，I型胶原酶工作液（2 mg/mL）消化滑膜组织、Ⅱ型胶原酶工作液（2 mg/mL）消化髁突软骨4 h后，加入新鲜配置的DMEM（含1%双抗，10%胎牛血清）。待细胞融合度达到80%时传代，将P4代滑膜成纤维细胞、P2代髁突软骨细胞接种96孔板内（5×10^3 cell/mL，n=5），固定培养24 h后，将细胞随机分为对照组和His-SDC4组，分别添加His-SDC4浓度为0 ng/mL（对照组）和10 ng/mL（His-SDC4组）的细胞培养液（含1%双抗，10%胎牛血清的DMEM），继续培养24、48 h后，在培养板中加CCK-8试剂10 μL，继续孵育1 h，用酶标仪检测450 nm处吸光度值，根据吸光度值计算各组细胞活力，并在光学显微镜下观察细胞形态。随后将以上两组P4代滑膜成纤维细胞、P2代髁突软骨细胞按比例为1∶3传至六孔板，细胞数量约10^4 cell/mL，24 h后收集细胞和上清液进行下一步检测。

1.7　逆转录定量聚合酶链式反应检测IL-6、TNF-α的mRNA表达水平

Tripure裂解滑膜成纤维细胞和软骨细胞，收集mRNA，反转录为cDNA。应用20 μL反应体系：SYBR Premix Ex Taq 10 μL，上游引物0.8 μL，下游引物0.8 μL，cDNA 1 μL，DEPC水7.4 μL。引物名称见表1，根据$2^{-\Delta\Delta Ct}$相对定量方法，以GAPDH为内参，计算相应mRNA的表达量。

表1　引物序列

Table 1　Primer sequences

Gene	Forward (F) and reverse (R) primers(5′-3′)
IL-6	F: ACTTCCAGCCAGTTGCCTTCTTG
	R: TGGTCTGTTGTGGGTGGTATCCTC
TNF-α	F: ATGGGCTCCCTCTCATCAGTTCC
	R: CCTCCGCTTGGTGGTTTGCTAC
GAPDH	F: GGCACAGTCAAGGCTGAGAATG
	R: ATGGTGGTGAAGACGCCAGTA

TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

1.8　酶联免疫吸附法检测细胞培养上清液中的sSDC4、IL-6、TNF-α水平

收集方法1.6的两组细胞培养上清液，离心后收集上清液，按照sSDC4、IL-6、TNF-α酶联免疫吸附测定试剂盒说明书，检测细胞培养上清中的sSDC4、IL-6、TNF-α的含量。

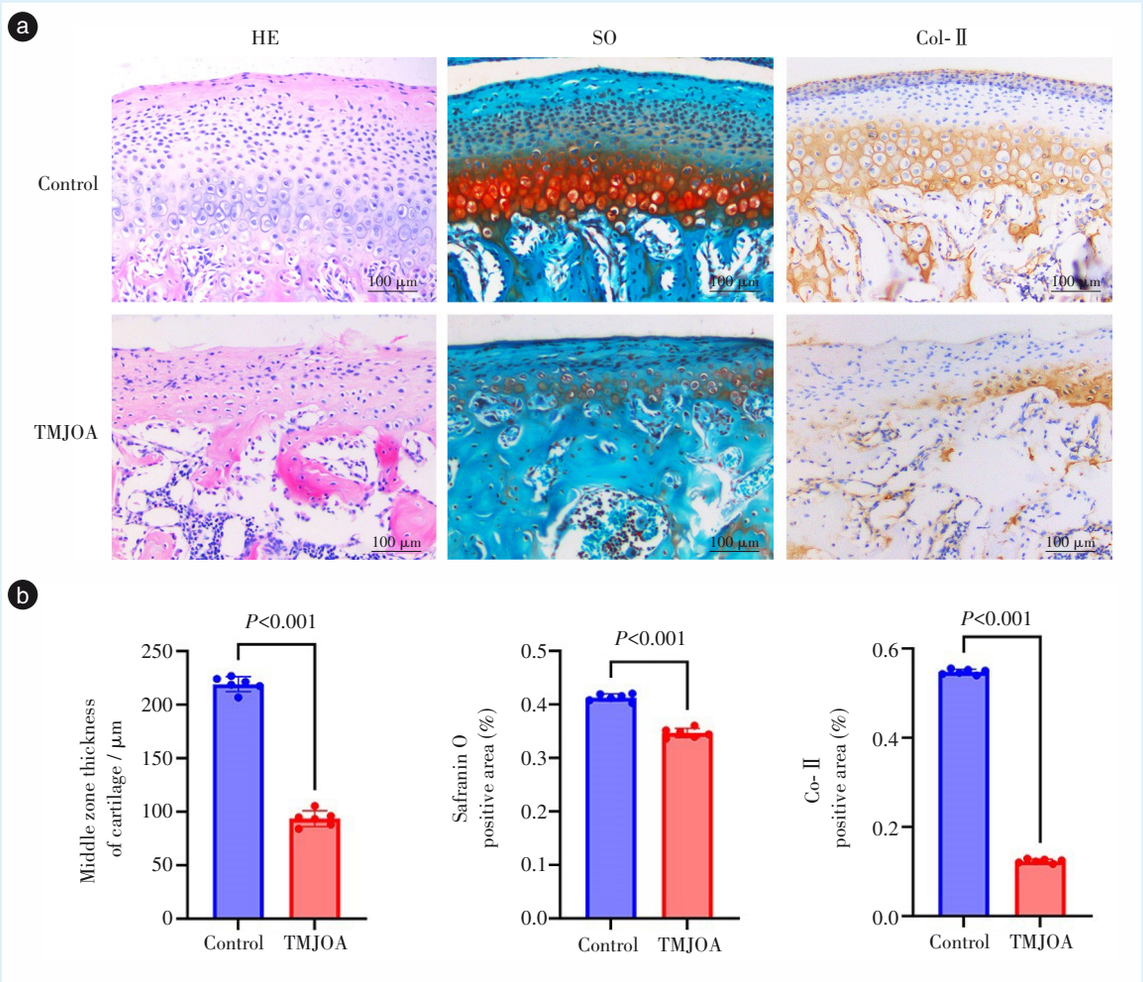
1.9　统计学分析

使用GraphPad Prism 10.0进行统计差异分析，所有数据均从独立样本检测中获得，所有数据在分析前均做方差齐性检验，正态分布的计量资料以均值±标准差表示，组间比较使用非配对t检验，若方差不齐，组间使用校正的t检验，P<0.05被认为差异具有统计学意义。

2　结　果

2.1　MIA诱导的大鼠TMJOA模型中TMJ滑液sSDC4水平升高

TMJ髁突软骨的HE、SO染色及Col-II的免疫组化结果见图1。HE染色结果显示，对照组髁突软骨层次清晰，软骨表面光滑齐整；TMJOA模型组髁突软骨中带厚度变薄（t=15.36，P<0.001），软骨表面粗糙，软骨组织各层细胞稀疏分散排列，分布不均，且软骨下骨骨量显著减少。SO染色结果显示对照组髁突软骨中蛋白聚糖均匀分布于软骨肥大层，且与纤维层及软骨下骨分界明显；而TMJOA模型组蛋白聚糖显著减少，着色分布不均匀，且主要局限于肥大层深部。TMJOA模型组SO染色阳性面积比例低于对照组（t=14.67，P<0.001）。Col-Ⅱ免疫组化染色结果显示：对照组髁突软骨中Col-Ⅱ在肥大层中均匀广泛分布，TMJOA模型组髁突软骨中Col-Ⅱ阳性面积比例低于对照组（t=144.2，P<0.001）。



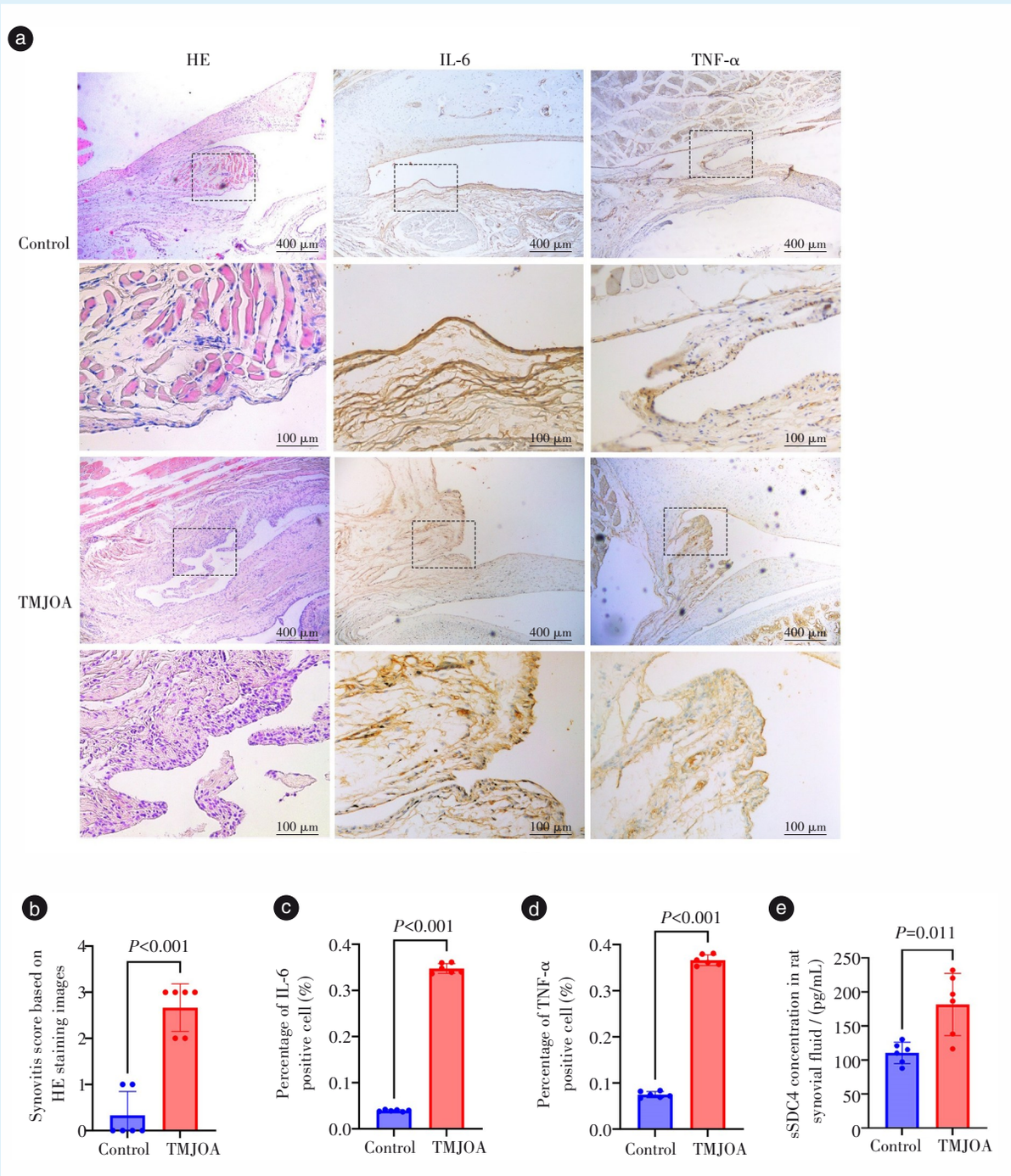
a: HE, SO, and Col-Ⅱ immunohistochemical staining images of the left TMJ cartilage tissues from rats in the control and TMJOA model groups; n = 6, bar = 100 μm. The results of HE staining showed that the condylar cartilage of the control group was clear and the surface of the cartilage was smooth and neat. The condylar cartilage in the TMJOA group was significantly thinner, the surface of the cartilage was rough, the cells in each layer of the cartilage tissue were sparsely dispersed and unevenly distributed, and the amount of subchondral bone was significantly reduced. SO staining results showed that the proteoglycan in the condylar cartilage of the control group was evenly distributed in the hypertrophic layer, and the boundary between the fibrous layer and the subchondral bone was evident. The proteoglycans in the TMJOA group were significantly reduced, the coloring distribution was uneven, and it was primarily limited to the deep portion of the hypertrophic layer. The results of Col-II immunohistochemical staining showed that Col-II in the condylar cartilage of the control group was evenly distributed in the hypertrophic layer, and the positive area of Col-II in the condylar cartilage of the TMJOA group was significantly reduced. b: quantitative analysis results of the middle zone thickness, SO area, and Col-Ⅱ-positive area of the condylar cartilage based on HE-, SO-, and Col-Ⅱ-stained sections. TMJOA group: a single dose of MIA (50 μL, 4 mg/mL) was injected into the bilateral superior joint space in rats; control group: a single dose of PBS (50 μL) was injected into the bilateral superior joint space in rats. HE: hematoxylin-eosin; SO: Safranin O-fast green; Col-Ⅱ: type Ⅱ collagen; TMJ: temporomandibular joint; TMJOA: temporomandibular joint osteoarthritis; MIA: monosodium iodoacetate

Figure 1　Degree of temporomandibular joint condylar cartilage degeneration in an MIA-induced rat TMJOA model

图1　MIA诱导大鼠TMJOA模型的颞下颌关节髁突软骨退变程度观察

TMJ滑膜的HE染色及IL-6、TNF-α的免疫组化结果显示，对照组滑膜结构层次清晰，TMJOA模型组滑膜组织衬里细胞增生，基质细胞排列紊乱、细胞密度增高，可见炎性细胞浸润，滑膜炎评分较高（t=7.826，P<0.001）。TMJOA模型组滑膜组织IL-6、TNF-α阳性细胞百分比高于对照组（IL-6：t=69.08，P<0.001；TNF-α：t=53.36，P<0.001）（图2a-2d）。

对两组TMJ滑液中的sSDC4水平进行ELISA检测，结果显示TMJOA模型组TMJ滑液中的sSDC4水平与对照组相比升高（t=3.627，P=0.011）（图2e）。



a: HE and immunohistochemical staining images (IL-6, TNF-α) from the left TMJ synovium in the control and TMJOA groups; n = 6, bar = 400 μm, 100 μm. The synovial structure of the control group was clear. In the TMJOA group, the synovial tissue lining cells proliferated, the arrangement of stromal cells was disordered, the cell density increased, and inflammatory cell infiltration was observed. The percentage of IL-6 and TNF-α positive cells in the synovial tissue of the TMJOA model group was significantly higher than that of the control group. b: quantitative analysis of the synovitis scores based on HE staining images; c - d: quantitative analysis of the IL-6 and TNF-α positive cell rate, respectively. e: ELISA detection of sSDC4 in rat TMJ synovial fluid, n = 6; TMJOA group: a single dose of MIA (50 μL, 4 mg/mL) was injected into the bilateral superior joint space in rats; control group: a single dose of PBS (50 μL) was injected into the bilateral superior joint space in rats. HE: hematoxylin-eosin; TMJ: temporomandibular joint; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; sSDC4: shed syndecan-4; TMJOA: temporomandibular joint osteoarthritis; MIA: monosodium iodoacetate

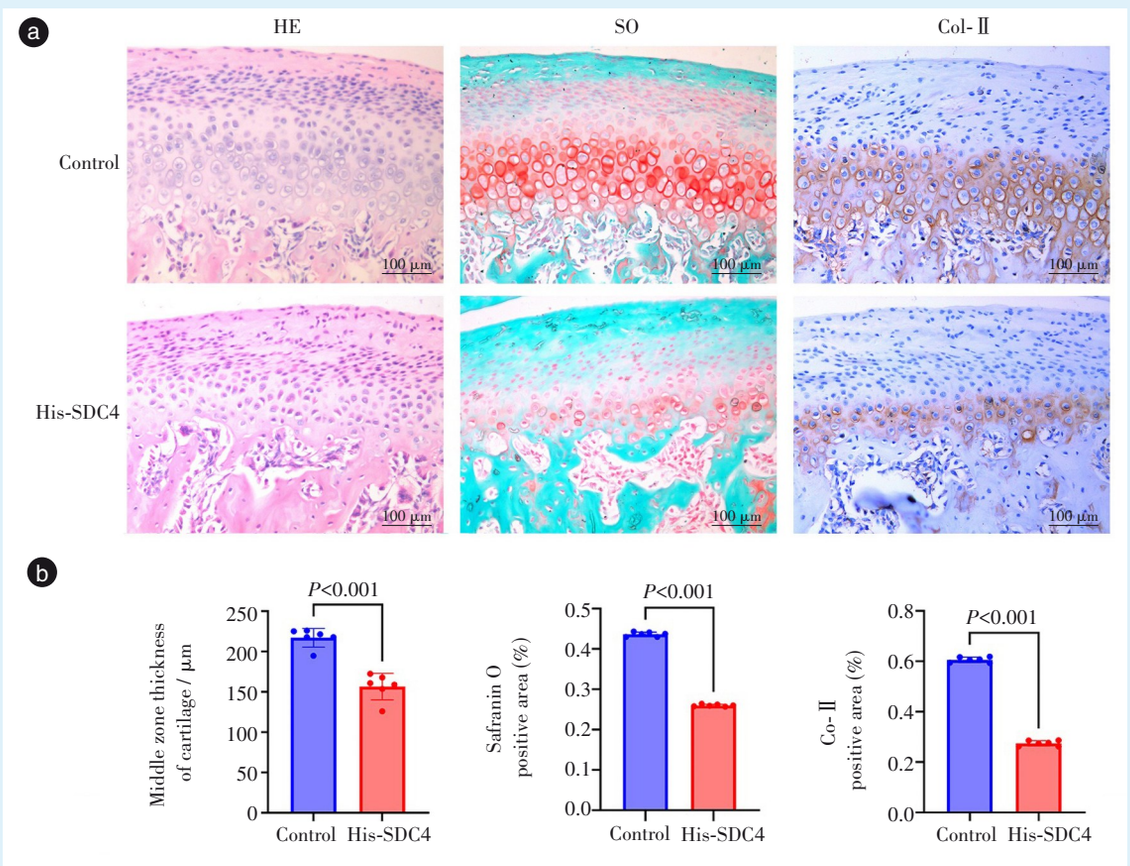
Figure 2　Changes in synovial inflammation and the level of sSDC4 in the synovial fluid of an MIA-induced TMJOA rat model

图2　MIA诱导大鼠TMJOA模型颞下颌关节滑膜炎症程度及滑液中sSDC4水平的改变

2.2　TMJ关节腔注射sSDC4促进髁突软骨退变和滑膜炎

HE染色结果显示，与对照组相比，His-SDC4组髁突软骨细胞数量减少，细胞密度降低，细胞各层次排列紊乱。His-SDC4组的髁突软骨中带厚度较对照组变薄（t=7.385，P<0.001）。SO染色结果显示His-SDC4组髁突软骨中蛋白聚糖呈现不均匀分布特征，SO染色阳性面积比例较对照组降低（t=69.66，P<0.001）。免疫组化染色结果显示His-SDC4组Col-II免疫组化染色阳性面积比例低于对照组（t=53.34，P<0.001）（图3）。

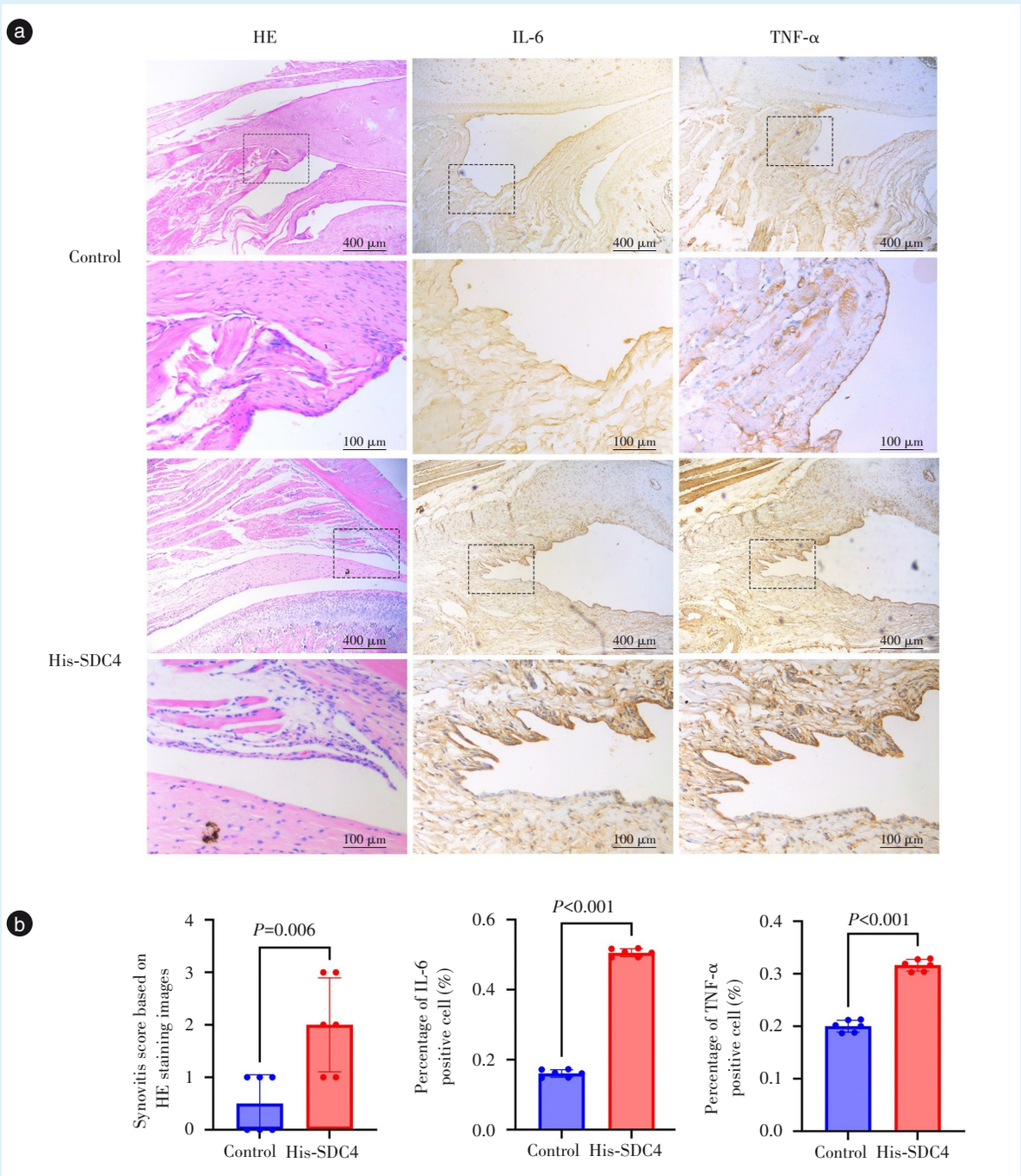
His-SDC4组滑膜组织衬里细胞增生，基质细胞排列紊乱、细胞密度增高，同时可见炎性细胞浸润，滑膜炎评分升高（t=3.503，P=0.006）。His-SDC4组滑膜组织中IL-6、TNF-α阳性细胞百分比均高于对照组（t=53.93，t=17.98，P<0.001）（图4）。



a: HE, SO, and Col-Ⅱ immunohistochemical staining images of cartilage tissue from the left TMJ in rats in the control and His-SDC4 groups (n = 6). b: quantitative analysis results of the middle zone thickness, SO area, and Col-Ⅱ-positive area of the condylar cartilage based on HE, SO, and Col-Ⅱ stained sections. The results of HE staining showed that, compared with the control group, the number of condylar chondrocytes in the His-SDC4 group decreased, the cell density decreased, and the arrangement of cells at all levels was disordered. The condylar cartilage in the His-SDC4 group was significantly thinner than that in the control group. The results of SO staining showed that the proteoglycans in the condylar cartilage of the His-SDC4 group were unevenly distributed, and the positive area of SO staining was significantly smaller than that of the control group. The results of immunohistochemical staining showed that the proportion of the positive area of Col-II immunohistochemical staining in the His-SDC4 group was significantly smaller than that in control group. Rats in the His-SDC4 group received bilateral intra-articular injections of His-SDC4 protein (50 μL, 100 ng/mL) into the superior joint space once every 3 days for 28 days; the control group received an equivalent volume of PBS on the same schedule. The rats in the His-SDC4 group exhibited a marked thinning of the cartilage middle zone, along with a decrease in the SO and Col-Ⅱ-positive area ratios. HE: hematoxylin-eosin; SO: Safranin O-fast green; Col-Ⅱ: type Ⅱ collagen; TMJ: temporomandibular joint; His-SDC4: His-tagged syndecan-4

Figure 3　Degree of degeneration in the condylar cartilage of temporomandibular joints in rats after His-SDC4 intervention

图3　His-SDC4干预后大鼠颞下颌关节髁突软骨退变程度观察



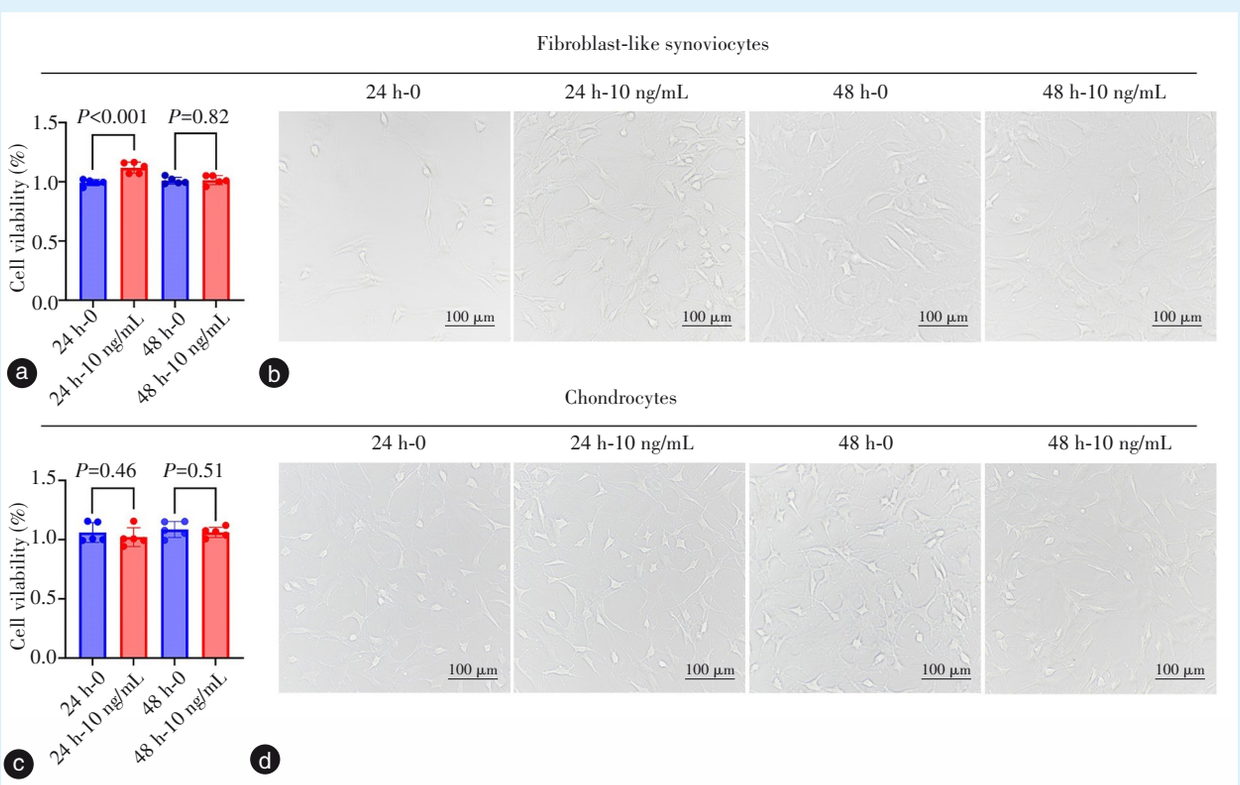
a: HE and immunohistochemical staining images (IL-6, TNF-α) of the left TMJ synovium from the control and His-SDC4 groups (n = 6); bar = 400 μm, 100 μm; b: quantitative analysis of the synovitis scores, IL-6 positive cell rate, and TNF-α positive cell rate. In the His-SDC4 group, synovial tissue lining cells proliferated, stromal cells were disordered, cell density increased, inflammatory cell infiltration was observed, and the synovitis score increased. The percentage of IL-6 and TNF-α positive cells in the synovial tissue of His-SDC4 group was significantly higher than that in the control group. Rats in the His-SDC4 group received bilateral intra-articular injections of His-SDC4 protein (50 μL, 100 ng/mL) into the superior joint space once every 3 days for 28 days; the control group received an equivalent volume of PBS on the same schedule. In the His-SDC4 group, hyperplasia was observed in the lining cells of the synovial tissue, along with disordered arrangement and increased density of stromal cells, and partial inflammatory cell infiltration. Correspondingly, the synovitis scores were elevated, and the positive cell rates of IL-6 and TNF-α also increased. HE: hematoxylin-eosin; TMJ: temporomandibular joint; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α. His-SDC4: His-tagged syndecan-4

Figure 4　Degree of synovitis in temporomandibular joints in rats after His-SDC4 intervention

图4　His-SDC4干预后大鼠颞下颌关节滑膜炎症程度观察

2.3　sSDC4对滑膜成纤维细胞和软骨细胞的细胞毒性检测和细胞形态学改变

CCK-8实验结果显示，10 ng/mL His-SDC4处理滑膜成纤维细胞后，24 h细胞增殖加强（t=5.186，P<0.001），48 h细胞活力与对照组相比差异无统计学意义（t=0.240，P=0.82）（图5a）。光学显微镜下观察可见空白对照组的滑膜成纤维细胞呈典型的长梭形，His-SDC4处理24 h后细胞密度增加，48 h后与对照组密度基本一致（图5b）。而同等浓度His-SDC4处理软骨细胞后，24、48 h细胞活力与对照组相比差异均无统计学意义（24 h：t=0.768，P=0.46；48 h：t=0.687，P=0.51）（图5c）。光学显微镜下观察可见空白对照组的软骨细胞生长状态良好，His-SDC4处理24 h和48 h后与对照组密度基本一致（图5d）。为保证后续实验设计的时间一致性，本研究将His-SDC4的药物刺激时间设置为24 h。



a: viability of fibroblast-like synoviocytes treated with His-SDC4 at various time points (24, 48 h), n = 5; b: morphology of fibroblast-like synoviocytes treated with His-SDC4 at different time points (24, 48 h); c: viability of chondrocytes treated with His-SDC4 at various time points (24, 48 h), n = 5. d: morphology of chondrocytes treated with His-SDC4 at different time points (24, 48 h). The 24 h, 10 ng/mL and 48 h, 10 ng/mL groups were cultured in a medium containing 10 ng/mL of His-SDC4 for 24 and 48 h, respectively; the 24 h, 0 ng/mL and 48h, 0 ng/mL control groups were maintained in a His-SDC4-free medium for the corresponding durations. Treatment with His-SDC4 for 24 h induced a transient increase in the density of synovial fibroblasts, which returned to control levels by 48 h. In contrast, chondrocyte density remained stable at both time points, showing no significant difference compared to the control group. His-SDC4: His-tagged syndecan-4

Figure 5　Cytotoxicity assessment of His-SDC4 and morphological analysis by light microscopy

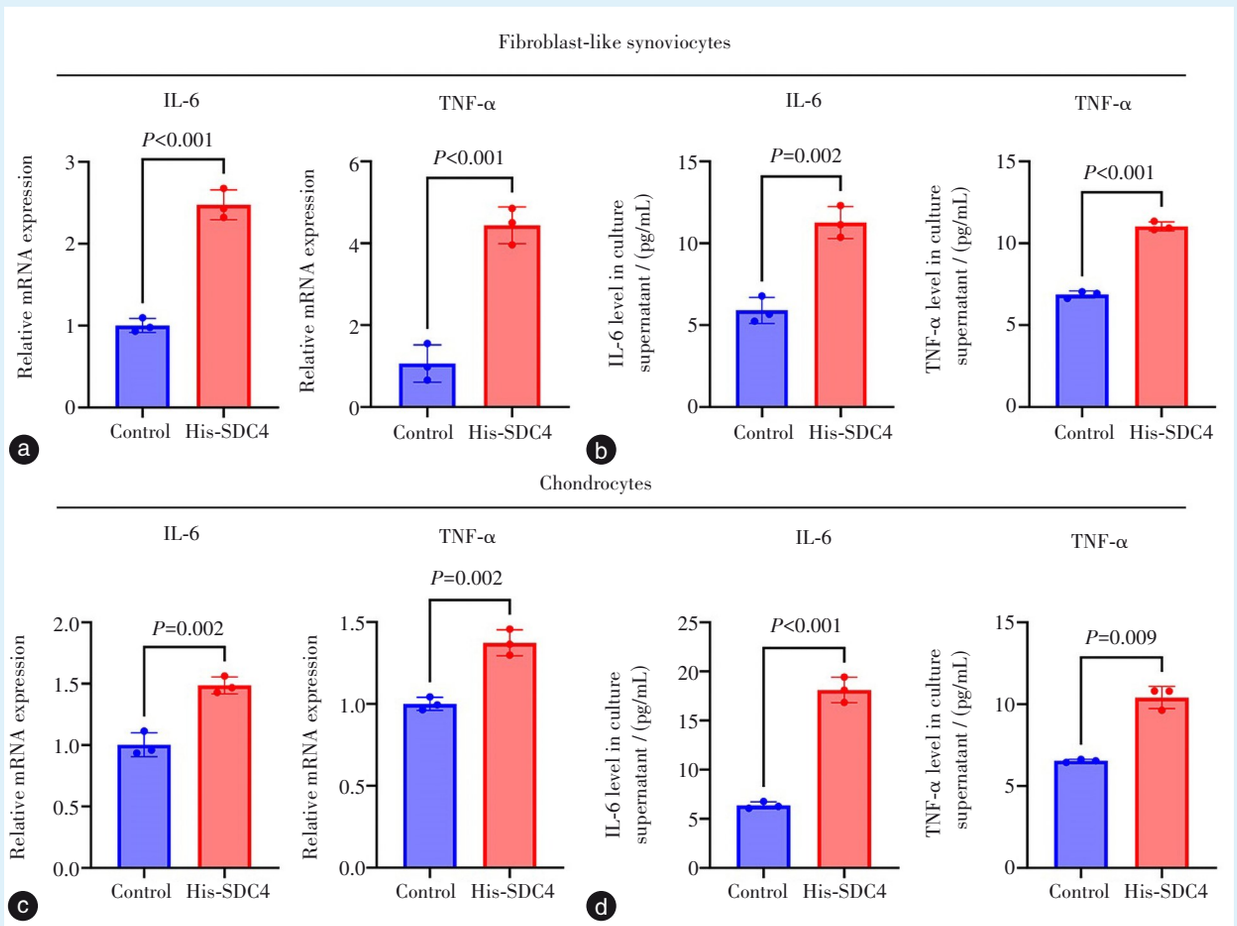
图5　His-SDC4细胞毒性检测和光学显微镜下观察细胞形态学特点结果

2.4　sSDC4刺激会促进滑膜成纤维细胞和髁突软骨细胞的炎性因子分泌

RT-qPCR结果显示：His-SDC4处理24 h后，与对照组相比，His-SDC4组滑膜成纤维细胞和软骨细胞的IL-6、TNF-α的mRNA表达水平升高（均P<0.05，图6a&6b）。ELISA结果显示：His-SDC4刺激滑膜成纤维细胞和髁突软骨细胞24 h后培养上清中IL-6、TNF-α水平均高于对照组（均P<0.05，图6c&6d）。

3　讨　论

TMD是口颌系统的第四大高发疾病，女性相



a: relative mRNA expression levels of IL-6 and TNF-α in rat fibroblast-like synoviocytes after stimulation with His-SDC4. b: relative mRNA expression levels of TNF-α and IL-6 in rat condylar chondrocytes after stimulation with His-SDC4. Gene expression was quantified by qPCR and normalized to GAPDH. n = 3. c: levels of IL-6 and TNF-α (pg/mL) in the culture supernatant of rat fibroblast-like synoviocytes after stimulation with His-SDC4. d: levels of IL-6 and TNF-α (pg/mL) in the culture supernatant of rat condylar chondrocytes after stimulation with His-SDC4. n = 3. Cells in the His-SDC4 group were treated with a medium containing 10 ng/mL of His-SDC4 for 24 h, while the control group was cultured in a regular medium for the same duration. Stimulation with His-SDC4 resulted in significantly increased mRNA levels of IL-6 and TNF-α in both fibroblast-like synoviocytes and condylar chondrocytes, as well as enhanced secretion of these cytokines into the culture supernatant. IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; His-SDC4: His-tagged syndecan-4; qPCR: quantitative polymerase chain reaction

Figure 6　Changes in IL-6 and TNF-α expression in fibroblast-like synoviocytes and chondrocytes after His-SDC4 intervention

图6　His-SDC4刺激后滑膜成纤维细胞和髁突软骨细胞IL-6、TNF-α表达变化

对更易罹患[14]，TMJOA是TMD的重症形式，其具体发病机制尚未阐明[15]。当前临床对OA的干预策略一般局限于早期的对症治疗和晚期的关节置换手术，因此，探索对OA进行有效的早期阻断治疗方案，一直是相关生物医学领域的研究热点[16]。

SDC4是一种跨膜蛋白，由N-末端胞外区、跨膜区和胞内区组成，在多种细胞中表达，在调控细胞外基质和细胞稳态中发挥着重要作用[17-23]。De Rossi等[24]发现在视网膜病变和肿瘤发育模型小鼠中，SDC4在病理性血管生成过程中表达上调，SDC4基因敲除后，血管内皮细胞钙粘连蛋白（vascular endothelial cadherin，VE-Cadherin）内吞减少从而降低血管通透性和病变处血管新生能力。Li等[25]检测到牙周炎大鼠的牙周组织中SDC4表达升高，会通过激活自噬促进破骨细胞分化。Brooks等[26]发现在受损的皮肤中，SDC4通过蛋白激酶C α型（protein kinase C α，PKCα）的激活调控Ephrin A型受体2（ephrin type-A receptor 2，EphA2），该过程直接影响成纤维细胞接触时的相互作用，调节成纤维细胞的聚集和运动接触抑制状态的切换。Sao等[27-28]研究发现SDC4基因敲除可诱导小鼠发生早发性椎体骨量减少，SDC4可精细调控腰椎骨

细胞外基质的稳态平衡与椎间盘基质的维持功能。发表于Nature Medicine的研究[8]发现，在膝关节OA患者、OA动物模型中，软骨中上调的SDC4通过激活细胞外信号调节激酶1/2（extracellular signal-regulated kinase 1/2，ERK1/2），促进含凝血酶敏感蛋白基序的解整合素金属蛋白酶5（a disintegrin and metalloproteinase with thrombospondin motifs 5，ADAMTS-5）靶向软骨细胞表面从而促进OA进展。Cao等[29]研究发现胆固醇代谢相关基因低密度脂蛋白受体相关蛋白3（LDL receptor related protein 3，LRP3）在OA软骨中表达下调，激活Ras/Raf/MEK/ERK信号通路从而上调SDC4的表达，过表达的SDC4通过结合和激活ADAMTS-5从而诱导软骨外基质退化。Zhou等[30]研究发现抑制SDC4可通过诱导miR-96-5p表达，靶向软骨细胞的低氧诱导因子-2α（hypoxia-inducible factor-2α，HIF-2α）的3′-UTR序列并抑制HIF-2α表达，改善软骨退变。本课题组前期研究已证实，在体内髁突软骨退变及体外髁突软骨细胞程序性坏死发生时，髁突软骨及培养上清中的SDC4显著增多；在基因水平或蛋白水平阻断SDC4的效应可以显著逆转髁突软骨退变[31-33]，即SDC4在OA软骨退变中发挥着重要作用。

SDC4的一个显著特点是其胞外段可以酶切脱落，脱落后的SDC4可以进入软骨细胞外基质、滑液、血液等继续通过自分泌或旁分泌的形式发挥功能[34-35]。在正常生理状态下，细胞膜蛋白SDC4的表达与酶促脱落处于动态稳态；当受到外界异常刺激时，基质金属蛋白酶、纤溶酶及凝血酶等蛋白酶活性骤增，加速SDC4胞外段剪切，生成过量的sSDC4[36-38]。2021年Bollmann等[10]观察到膝关节骨关节炎患者sSDC4滑膜水平随着骨关节炎严重程度显著增加，提出sSDC4可能是OA软骨严重程度的重要指标。在膝关节OA的动物模型中，滑液中sSDC4水平也显著升高[39]。本研究结果显示在MIA诱导的大鼠TMJOA模型中，TMJ滑液内的sSDC4水平出现明显上调，与既往相关研究的变化趋势基本一致。

sSDC4保留了原有的结合特性，可以通过旁分泌或自分泌的方式继续发挥生物功能[40]。在胰岛素作用下，sSDC4从脂肪细胞上脱落，通过其结构中的HS链与活性二聚体脂蛋白脂肪酶（lipoprotein lipase，LPL）结合，在脂肪细胞LPL向内皮的转运过程中发挥稳定LPL活性的作用[41]。Zong等[42]研究发现来源于脂肪细胞的sSDC4会浓缩并将成纤维细胞生长因子2（fibroblast growth factor 2，FGF2）输送到脂肪细胞上的成纤维细胞生长因子1受体（fibroblast growth factor receptor 1，FGFR1），进而通过降低激素敏感脂肪酶（hormone-sensitive triglyceride lipase，HSL）活性来抑制脂解，从而加剧肥胖。另一方面，sSDC4是体内先天免疫系统的效应分子，可以作为损伤相关分子模式（damage-associated molecular patterns，DAMPs），参与先天性免疫调节，可以趋化免疫细胞[43]。Kunnathattil等[44]通过在小鼠腹腔注射脂多糖（lipopolysaccharide，LPS）诱导心肌中的SDC4表达和sSDC4脱落，发现SDC4基因敲除小鼠的sSDC4脱落受阻，免疫细胞募集受损，心功能障碍加重。可见，sSDC4在多种疾病的进展中发挥着重要作用。在OA中，sSDC4也可能通过浓缩炎性因子，例如IL-6、TNF-α，将其富集到软骨细胞和滑膜细胞相关受体，持续激活NF-κB、MAPK、ERK等通路，进一步促进炎性因子的分泌。已有研究发现在小鼠膝关节腔中注射SDC4抗体会上调软骨细胞中的miR-96-5p，从而靶向HIF-2α 3′-UTR序列，抑制小鼠软骨组织和软骨细胞中的HIF-2α信号传导[30]。因此，sSDC4可能通过促进HIF-2α表达，促进炎性因子分泌，破坏软骨稳态。

本研究结果发现，在SD大鼠关节腔注射外源性sSDC4蛋白可以直接诱发髁突软骨退变和滑膜炎症；进一步的体外实验也证实sSDC4刺激会促进滑膜成纤维细胞和软骨细胞中IL-6、TNF-α等炎性因子的分泌，产生促炎作用。本研究结果首次揭示了TMJ滑液中过量的sSDC4通过直接刺激滑膜细胞、软骨细胞分泌促炎因子加速TMJOA进程的作用机制。

综上所述，在TMJOA的进程中，sSDC4脱落加速、关节滑液中的sSDC4显著升高会直接刺激滑膜成纤维细胞、髁突软骨细胞分泌更多的促炎因子。促炎因子的异常升高又会进一步加重关节滑膜的炎症浸润与软骨基质的降解损伤，持续的组织损伤会反过来诱导关节组织中SDC4的进一步脱落、滑液sSDC4水平的持续上升，从而形成恶性循环从而加速TMJOA的进程。因此，sSDC4有可能成为对TMJOA进行早期治疗干预的新分子靶点。然而，本研究尚未深入研究sSDC4在OA中促进炎性因子分泌的具体信号通路。鉴于大鼠TMJOA模型与临床TMJOA患者之间存在显著差异，且本研究样本量有限，仅检测了部分关键促炎因子，未能系

统研究sSDC4调控炎症微环境的分子网络。后续研究将结合临床样本，扩大样本量，进一步阐明sSDC4在TMJOA中的具体作用机制。

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