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靶向衰老细胞在骨关节炎治疗中的研究进展

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摘　要

细胞衰老是指一种永久性的细胞周期终止状态，能够影响机体的发育及动态平衡。它和许多与衰老相关的疾病有关，比如骨关节炎。目前关于衰老细胞与骨关节炎之间的研究主要集中在寻找能够清除衰老细胞或选择性阻断衰老相关分泌表型(SASP)以阻止疾病进展的药物疗法。随着对细胞衰老和SASP新机制以及其靶点的探索，潜在的治疗方法将不断增加。本文将探讨细胞衰老的相关机制，并讨论针对每个靶点的治疗方案及其优势。

关键词

骨关节炎，细胞衰老，衰老相关分泌表型，软骨细胞，综述

Research Progress in Targeting Senescent Cells in the Treatment of Osteoarthritis

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Abstract

Cellular senescence is a state of permanent cell cycle termination that can affect the development

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and dynamic homeostasis of the organism. It is associated with many diseases related to aging, such as osteoarthritis. Current research on the link between senescent cells and osteoarthritis is focused on finding drug therapies that can remove senescent cells or selectively block senescence-associated secretory phenotypes (SASPs) to halt disease progression. As new mechanisms of cellular senescence and SASP, as well as their targets, are explored, the potential therapeutic approaches will continue to grow. This article will explore the mechanisms involved in cellular senescence and discuss therapeutic options for each target and their advantages.

Keywords

Osteoarthritis, Cellular Senescence, Senescent Associated Secretory Phenotype, Chondrocyte, Review

1. 引言

骨关节炎(Osteoarthritis, OA)是一种严重影响患者生活质量的慢性退行性疾病，给患者、家庭和社会造成了沉重的负担[1]。目前治疗 OA 的方法主要包括非甾体抗炎药、关节内注射透明质酸、富含血小板的血浆注射，以及其他可获得短期益处的物理疗法[2]。然而，这些措施都无法阻止或逆转 OA 患者的病情进展。近年来，对 OA 发病机制的深入研究，为其治疗策略提供了新的可能性。通过调节分解代谢信号、调节蛋白酶活性、抑制炎症或软骨下骨重塑等手段，治疗目标从缓解症状拓展到了修复疾病的范畴[3] [4] [5] [6] [7]。

衰老细胞数量的增加及其分泌表型与 OA 进展和软骨降解有关[8]，针对衰老细胞及其在关节组织中产生的相关因子的研究引起了人们的极大兴趣。目前的研究主要包括直接清除衰老细胞、抑制衰老相关分泌表型(Senescent Associated Secretory Phenotype, SASP)和恢复干细胞活力等[9] [10] [11]。针对衰老的治疗靶点的开发面临着衰老细胞表型多样性的挑战，因此，仍然需要更多的研究，以此为新的 OA 治疗方式的开发提供进一步支持。本文将就细胞衰老与 OA 的潜在因果关系及靶向衰老细胞治疗 OA 的进展方面进行综述。

2. 细胞衰老与骨关节炎

成年人的软骨内在修复能力有限，损伤之后极易发生 OA 等不可逆病变。尽管软骨细胞在动态平衡期间增殖水平较低，但却依然保持了一定增殖潜力。例如，在承受外界异常刺激后，软骨细胞可以“去分化”，即在应激下可以代偿性增生却不改变细胞种类，这也被认为是在尝试修复损伤[11]。静息(即可逆的细胞周期停滞)和衰老之间的关系是复杂的，有证据表明，对受损的静息细胞进行促分裂刺激，可以在其重新进入细胞周期时被诱导衰老[12]。

像其他器官一样，关节组织也容易随着年龄的增长而衰老和衰退，衰老细胞的数量与年龄密切相关[13] [14] [15]。随着细胞状态的改变，细胞中的代谢模式随之发生重构，这一变化可能会推动 OA 的病理进程。有研究表明，将衰老的成纤维细胞移植到小鼠的膝关节中会导致软骨侵蚀，这表明衰老的细胞改变了关节内的微环境，导致了 OA [15]。

关节组织炎症是 OA 的重要标志[16] [17]，衰老的细胞通过 SASP 参与炎症状态。在 SASP 中具有生

物活性的分子被分泌到周围组织微环境中[18] [19]，导致 OA 患者的关节液中白细胞介素-6 (Interferin-6, IL-6)等细胞因子水平升高[20]，IL-6-STAT3 信号通路又可诱导正常人成纤维细胞提前衰老[21]。另外，细胞因子可以上调基质金属蛋白酶家族(matrix metalloproteinases, MMPs)的表达。MMPs 可以降解软骨中的细胞外基质蛋白。软骨细胞外基质的丢失是 OA 的一个关键早期特征[22]，还有研究表明，衰老细胞可以通过细胞外囊泡或一些细胞因子转移激活衰老途径的 MicroRNA 至周围健康细胞，导致周围细胞进一步衰老和出现 SASP [23] [24]。这进一步表明细胞衰老是 OA 发病的驱动因素。

3. 衰老细胞清除剂

近年的研究表明，清除衰老细胞是治疗年龄相关性疾病的潜在策略。在 OA 相关的研究中，这种疗法改善了骨小梁和皮质骨的微结构[25] [26]。有研究表明，选择性清除小鼠的衰老细胞可以减轻 OA 的严重程度，改善疼痛症状，降低 MMP-13 和其他 SASP 因子的表达，并刺激软骨再生[8]。另外，有研究者发现杀死 OA 浅表区域的软骨细胞对软骨损伤有一定保护作用[27]。他们的研究没有特别针对衰老细胞，这也表明衰老细胞及其相关的 SASP 可能比通过药物去除这些细胞对关节组织破坏性更大。

最先研究清除衰老细胞作用的两个小分子药物是达沙替尼(dasatinib)和槲皮素(quercetin)，在行前交叉韧带离断(Anterior Cruciate Ligament Transection, ACLT)手术的大鼠模型中，这两种药物降低了 SASP 并促进了软骨形成[28]。对颞颌关节的研究提供了进一步的证据，表明达沙替尼和槲皮素可以通过消除衰老细胞来减轻关节退变[29]。除了槲皮素，其他天然的药物还有胡椒碱和非瑟酮，胡椒碱已被证明可以降低血清中 IL-1β、MMP-1 和 MMP-3 的水平，而在通过手术破坏内侧半月板(destabilization of medial meniscus, DMM)稳定而导致骨性关节炎的小鼠中，非瑟酮减轻了软骨损伤并改善了滑膜炎症[30]。UBX0101 是双微体同源基因 2 (mousedouble minute 2, MDM2)和 p53 肿瘤蛋白(tumor protein 53, p53)之间相互作用的抑制剂[8]。对小鼠 ACLT 后关节内注射的研究发现，连续注射 UBX0101 增加了关节内衰老细胞的清除，并降低了幼年动物的 OA 严重程度[31]。BCL (B cell lymphoma)蛋白是另一个潜在的抗衰老药物治疗靶点，相关抑制剂 Navitoclax (ABT-263)已被证明在 DMM 模型中可诱导衰老细胞凋亡和保护关节软骨损伤[32]。

4. SASP 相关分子拮抗剂

SASP 相关分子拮抗剂(Senomorphic)通过靶向 SASP 参与的途径来调节和减少衰老细胞的炎性分泌。SASP 因子包括数百种蛋白质和小分子，包括促炎细胞因子和降解基质的基质金属蛋白酶。虽然 SASP 在组织重塑和修复方面可能是有益的，但它的旁分泌和自分泌效应在骨关节炎的诱导和发展中发挥着重要作用[25] [33] [34] [35]。进一步确定 SASP 的特性及调节它的下游途径是目前开发对抗衰老细胞负面影响的有效方法。

目前正在研究的 SASP 调控途径包括酪氨酸激酶-转录因子(JAK-STAT)、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)，Wnt (Wingless-Type MMTV Integration Site Family)等[36] [37] [38] [39]，抑制或改变这些通路的药物在临床前研究中显示出作为 OA 治疗的潜力。如鲁索利替尼(Ruxolitinib)是一种 JAK1/2 抑制剂，通过下调老年小鼠骨髓基质细胞中 IL-6、肿瘤坏死因子-α (tumor necrosis factor, TNF-α)、MMP-1、MMP-3 和 MMP13 的表达来抑制 SASP 因子[25]。雷帕霉素是 mTOR 复合体(Rapamycin complex 1, mTORC1)的抑制剂，mTORC1 通过差异调节 MAPK 活化蛋白激酶 2 (Mitogen-activated protein kinase-activated protein kinase 2, MAPKAPK2)和 IL-1 的翻译来调节 SASP [36]。二甲双胍是糖尿病患者常用的一种辅助血糖控制的药物，它同时也被认为是一种 Senomorphic 疗法。在小鼠 DMM 模型中，二甲双胍具有软骨保护作用，早期数据表明这一效果是由 AMPK 途径介导的[39]。IL-17 和 Wnt 信号为发展抗骨关节炎药物(Disease-Modifying

OA Drugs, DMOADs)提供了进一步的靶点，因为它们可以促进 MMP-13 以及其他 OA 介质的产生，从而促进 OA 的进展[40] [41]。进一步的实验发现，在小鼠 ACLT 后给予 IL-17 中和抗体可降低 MMP-13 和 p21，这种治疗方式保护了组织结构并改善了关节的功能[31]。

5. 细胞因子抑制剂

炎症细胞因子，特别是 IL-1α/β、IL-6、IL-8 和 TNF-α 等，伴随 SASP 的增加而增加，并与 OA 的发生机制有关[42]。虽然在小鼠体内进行的 IL-1 阻断和 IL-1 敲除实验未能证明其可以在胶原酶诱导的 OA 中减轻软骨破坏或滑膜炎症[43]。但这些药物仍然是值得研究的 OA 治疗候选药物，因为它们在治疗几种遗传性自体炎症(斯蒂尔病和白塞病)的过程中，证明了它们的安全性和有效性[44]。目前 FDA 批准的许多用于治疗类风湿性关节炎(Rheumatoid arthritis, RA)等炎症性疾病的细胞因子抑制剂，对 OA 的治疗效果也已进入临床试验[45]。拖珠单抗(Tocilizumab, TCZ)是一种 IL-6 抑制剂，目前被批准用于治疗 RA。在一项有关手部 OA 的 3 期临床试验中，相较于安慰剂，TCZ 在缓解手部 OA 患者的疼痛方面并未展示出更好的治疗效果，不良事件发生率反而有所上升[46]。

6. 基因疗法

治疗 OA 的另一种策略是直接针对衰老及耗竭的干细胞。最近的研究已经确定了一些影响干细胞寿命的因素。DiGeorge 关键区(DiGeorge critical region, DGCR) 8、Yes 相关蛋白(yes-associated protein, YAP)和色盒(Chromobox, CBX) 4 是维持干细胞核仁止血的三个关键因子。缺乏这些因子的间充质干细胞(Mesenchymal Stem Cells, MSCs)会出现过早衰老，通过关节内腺相关病毒(Adeno-associated virus, AAV)基因治疗方法增强这些基因的表达时，研究者观察到小鼠 OA 的发生与发展的推迟[47] [48] [49]。另外，有研究者使用相同的基因治疗方法探索了转化生长因子 βR2 (soluble form of mouse transforming growth factor-β receptor 2, sTGFβR2)和 αKlotho 在 OA 中的协同效应。在 OA 大鼠模型中，研究者观察到软骨细胞特异性标志物和细胞增殖能力的增加[50]。这些结果表明，通过基因治疗使干细胞恢复活力是治疗 OA 的一种可行且有前景的治疗策略。

7. 总结与展望

OA 是一种具有重大全球影响的衰老疾病。细胞衰老和伴随的 SASP 已经成为影响 OA 进展的潜在关键因素[51]。体内和体外研究已经阐明了一系列分子靶点对消除衰老细胞或减少 SASP 的影响。这些靶点已经产生了许多正在进行临床试验的疗法。未来 DMOADs 有可能以衰老细胞或衰老细胞的产物为目标。为了阐明这些干预措施的长期效果，还有大量针对易患人群的研究要做。同时，还需要考虑杀死或改变器官中衰老细胞的负面影响。近期研究表明，衰老细胞可以通过招募巨噬细胞促进早期伤口愈合和组织再生。因此，清除衰老细胞及其相关产物的研究必须考虑到不同的治疗时间对疾病结果的影响，从而开辟出一条通过靶向衰老细胞来治疗 OA 的研究路线。

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