

放线菌在骨关节炎进展中的作用

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摘要

骨关节炎作为一种慢性运动系统疾病, 对于中老年人(尤其是绝经后的女性)的生活质量产生了不小的影响, 同时也对社会经济产生了负担。放线菌(Actinomyces)作为肠道微生物(GM)的重要组成部分, 其对骨关节炎的影响暂未有报道。在这篇综述中, 我们讨论了放线菌在骨关节炎进展中的作用。首先阐述了消化系统与骨关节炎之间的关系, 着重阐明了肠-骨轴的作用。随后讨论了放线菌如何引起骨关节炎, 尤其关注了这一过程中影响到的信号通路, 哪些炎症因子有所升高, 并强调了破骨细胞在这过程中的作用。同时也记录了一些其他由放线菌引起的运动系统的炎症性疾病。该研究通过阐述放线菌对骨关节炎进展的影响, 希望为治疗骨关节炎提供一个新的思路 and 方向。

关键词

骨关节炎, 肠道微生物, 放线菌, 肠-骨轴

The Role of Actinomycetes in the Progression of Osteoarthritis

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Abstract

Osteoarthritis, as a chronic musculoskeletal disorder, significantly impacts the quality of life for middle-aged and elderly individuals, particularly postmenopausal women, and also imposes a

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burden on the socio-economic system. Actinomyces, an important component of gut microbiota (GM), has not been previously reported for its effects on osteoarthritis. In this review, we discuss the role of Actinomyces in the progression of osteoarthritis. Initially, we elaborate on the relationship between the digestive system and osteoarthritis, with a particular focus on the gut-bone axis. Subsequently, we explore how Actinomyces may contribute to osteoarthritis, paying special attention to the signaling pathways involved in this process, the elevation of certain inflammatory factors. Additionally, we document some other inflammatory diseases of the musculoskeletal system caused by Actinomyces. This study aims to provide new insights and directions for the treatment of osteoarthritis by elucidating the impact of Actinomyces on its progression.

Keywords

Osteoarthritis, Gut Microbiome, Actinomyces, Gut-Bone Axis

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1. 引言

骨关节炎作为一种慢性运动系统疾病，特点是引起疼痛[1][2]、活动障碍[3]，造成行动不便，进而影响人们的生活质量。目前已有确切研究表明，绝经是骨关节炎这一疾病的一项独立高危因素[4]，这意味着老年女性会更容易罹患骨关节炎这一疾病，我国一项统计结果显示，受调查骨关节炎患者中，女性患者比例达到 10.3%，高于男性的 5.7%，其中多数为老年女性[5]。我国作为一个人口大国，该疾病患者的数量也十分庞大，据估计，截至 2017 年我国正有大约 5000 万人遭受到骨关节炎的困扰[6]，这些患者生活质量受到严重影响[7]，同时如此庞大的患病人数，也给我国经济带来了巨大负担[8]。正因如此，国内外学者多年来致力于研究骨关节炎，以找到防治该疾病的方法。

2. 现有对于骨关节炎发生机制的研究

2.1. 骨关节炎中软骨的变化

在 OA 进展过程中，软骨细胞起到了至关重要的角色，随着疾病发展，软骨细胞相关的多种因子发生变化，细胞外基质稳态失衡，最终导致软骨破坏。在软骨中，细胞外基质这一重要成分不可或缺，占到了关节软骨的 95% [9]。细胞外基质受与多种因子相关，COL2A1 及 ACAN 软骨合成的主要蛋白成分 [10]，在骨关节炎的初期阶段可见这两个因子的升高[11]，这与调节软骨表型和活性的一个转录因子——SOX9 的升高有关[12]，也许是因为在骨关节炎早期软骨细胞外基质成分改变，激活 SOX9，促进 COL2A1 及 ACAN 表达的升高，而随着疾病进展到晚期，可见 SOX9 以及 COL2A1 及 ACAN 的缺失[13]。随着骨关节炎的进展，与细胞外基质降解相关的基质金属酶(MMPs)和金属肽酶(ADAMSTs)表达量逐渐升高，前者主要成员包括 MMP3、MMP13，后者起作用的主要为 ADAMST4、ADAMST5 [14]，在正常软骨中，上述几种基质降解酶的启动子多由于 CpG 点位甲基化导致 DNA 无法与转录因子结合，无法正常表达，因而表达量较低，不出现炎症的表现[15]。随着刺激(如炎症、负荷增加等改变)产生，这些转录因子启动子去甲基化，在染色质层面，表达量逐步上升，分解细胞外基质，产生炎症[16]，这一过程受到多种炎症因子及通路调控[17][18]。在骨关节炎进展的终末期，健康软骨表达的蛋白，如印度刺猬蛋白(IHH)、甲状旁腺激素样蛋白(PTHrP)等发生改变，激活活化甲状腺素(T3)、Wnt、Notch 及 TGF- β 等信号，表达

COL10A1、MMP13 等蛋白[19], 上述两种因子都会导致软骨细胞肥大。我国学者发现在 OA 患者膝关节中 Sirt6 表达下降[20], Sirt6 是一种抗衰老蛋白, 这一发现提示着通过该蛋白抑制软骨细胞衰老, 也能有效防治骨关节炎。

2.2. 骨关节炎中破骨细胞的变化

巨噬细胞集落刺激因子(M-CSF)和 NF- κ B 配体的受体激活因子(RANKL), 在破骨细胞分化过程中, 起到了重要作用, 骨保护素(OPG)则起到了相反的作用[21]。在衰老过程中, RANKL/RANK 轴激活, 刺激破骨细胞分化[22], 同时 TLR9 基因表达增加, TLR4 基因表达下降, 增强了破骨细胞对炎症介质和受损相关分子模式(DAMPs)的表达[23], 产生多种炎症因子, 最终造成骨关节炎。

2.3. 骨关节炎中成骨细胞的变化

成骨细胞通过合成矿化的骨基质, 参与骨代谢的调节。而成骨细胞的增值分化和 OPG 的表达, 受到 Wnt/ β -catenin 通路的调控, β -catenin 在成骨细胞胞质中受到激酶刺激后磷酸化产生活性, 并与 APC 共同参与泛素介导的蛋白水解, 最终导致骨关节炎[24][25]。而根据一项日本的研究, 诺氏菌——用于模仿感染放线菌动物状态的一种菌属, 在与小鼠巨噬细胞共同培养时, 可以选择性产生具有 wnt 信号活化作用的环状肽 nocarjamide [26]。除此以外, 骨关节炎中成骨细胞数量的多少, 与前列腺素 E2 和炎症因子表达量高低有着密切关系[27]。一项通过对于 LCN-2 的研究, 学者认为 OA 相关炎症的诱导, 可以降低成骨细胞的存活率, 并增强其释放的 MMP-9 的活性[28], 导致胶原蛋白 1 α 1 (COL1)和骨钙素(OCN)升高, 导致软骨下骨骨硬化, 最终出现骨关节炎[29]。

2.4. 骨关节炎中滑膜的变化

在骨关节炎患者的关节滑膜中, 可见多种细胞, 如滑膜巨噬细胞、滑膜专门间充质细胞、其他如中性粒细胞等。根据现有研究, 我们可以确定在 M-CSF 和 RANKL 同时表达, 或 M-CSF 和表达 RANKL 的骨基质细胞存在的情况下, 滑膜巨[30]噬细胞能够向破骨细胞方向分化[31], 而滑膜巨噬细胞释放的前列腺素和组织蛋白酶, 能够促进破骨细胞对骨质的吸收[32], 也能释放 IL-1 β 、TNF- α 等因子, 这些因子已被证实, 在破骨对骨质吸收过程中起重要作用[33]。间充质细胞可以通过分泌润滑素和透明质酸来润滑软骨, OA 患者润滑素和透明质酸含量都下降, 导致疼痛[34]。OA 患者关节滑液中的细胞代谢产物如 NO [35]、琥珀酸盐[30]常有升高, 导致 IL 水平升高[36], 促进前列腺素的分泌[37], 也能导致 OA 患者的疼痛。

2.5. 骨关节炎中脂肪细胞的变化

骨关节炎进展过程的众多因素中, 肥胖是一个重要危险因素[38], 肥胖可以通过增加关节负荷导致骨关节炎[39], 除此以外, 肥胖病人存在明显的 M2 巨噬细胞向 M1 巨噬细胞表型转变, 这将导致软骨变性, 并降低组织修复和血管生成能力[40]。同时, 脂肪组织还能分泌脂肪因子(主要为瘦素)[41], 有学者认为瘦素可以通过诱导胰岛素样生长因子-1 和 TGF- β 以及 MMP-2、MMP-9 [42]来介导合成代谢过程, 还能刺激滑膜成纤维细胞中炎症因子的表达, 改变软骨下成骨细胞中 TGF- β 、骨钙素和 I 型胶原的分泌[43], 从而产生减少软骨的形成的作用。

3. 多位学者研究了消化道与骨关节炎的关系。

3.1. 肠道菌群改变通过肠 - 骨轴引起骨关节炎

肠道微生物是其中的一个重要因素[44], 近年来, 多位学者致力于研究肠道微生物对于其他多个器官

的作用,成为当下一个热点。总的来说,肠道微生物对骨关节炎的作用是一个复杂的过程,学者们构建通过无菌小鼠的模型,在某些微生物刺激下,无菌小鼠表现出了低骨量,而在其他一些研究中则相反。[45]说明消化道对运动系统的影响可能受到多个因素影响,产生不同效果,甚至有时会出现相反的结果。但根据目前主流研究结果来看,正常状态下的肠道微生物大多可以通过促进营养吸收,如钙离子、维生素 D,从而防治骨关节炎,改善骨骼健康[46]。而在肠道微生物对运动系统产生影响的途径中,多数微生物的作用都离不开一个重要途径:肠-骨轴。Johnson 和 Foster 提出,肠道和大脑之间关系复杂,肠道内改变引起骨骼变化,通常与神经、激素以及免疫改变都有密切的关系[47],这一过程常由细胞代谢物发挥作用[48]。而在诸多信号传递因子中,又以 5-羟色胺(5-HT)效果较为明显[49]。

3.2. 肠道菌群改变通过影响内分泌引起骨关节炎

除此之外,研究表明,肠道微生物菌群能改变宿主激素水平,如甲状旁腺激素[50][51]、雌激素[52]直接影响软骨发育及去分化[53]等,从而影响骨骼健康。与此同时,肠道微生物还能通过免疫系统,对多种细胞因子,如 IL [54]、TNF- α [55]等产生影响,而这些因子在骨关节炎的进展过程中起到了重要作用[56]。因此,已经有学者尝试通过调节肠道微生物群落,来治疗骨关节炎[57]。

3.3. 肠道菌群改变通过免疫系统引起骨关节炎

有一项临床研究表明,肠道免疫系统疾病,如克罗恩病及溃疡性结肠炎,可以引起 TNF- α 的升高,[58]这也可能产生肠道以外的炎症,导致骨关节炎。据日本学者总结,大量克罗恩病患者的肠道中梭状芽孢杆菌目细菌明显减少,这类细菌是主要的丁酸产生菌[59],而丁酸盐能够抑制骨关节炎患者的离体 T 辅助细胞活化[60],通过控制软骨细胞的自噬和炎症细胞死亡来抑制骨关节炎[61],还能消除人软骨细胞中 II 型胶原的降解[62],从而抑制骨关节炎的进展,克罗恩病患者由于丁酸盐减少,故而比常人更可能患骨关节炎。

4. 肠道放线菌在骨关节炎进展过程中起到的作用。

我国一项研究表明,使用当归这一药物,能够有效降低 ACLT 小鼠肠道内放线菌丰度,通过肠-关节轴,起到治疗骨关节炎的目的[63]。因此本文基于前人研究深入探究了该过程发生的机制。

4.1. 肠道放线菌对软骨细胞的影响引起骨关节炎

我国学者的一项研究表明,免疫性肠病的患者,肠道内放线菌丰度更高,多条炎症通路被激活,其中以 TLR2、TLR4 及 NF- κ B 更显著[64],其中,TLR2 作为 NF- κ B 识别受体[65],而 TLR4 激活后,含 TIR 结构域的衔接蛋白(TIRAPs)募集 MyD88,随后与 IL-1 受体相关激酶(IRAKs)相互作用。这些 IRAKs 自身磷酸化并激活 TNF-受体相关因子 6 (TRAF6),其自身泛素化并激活 TGF- β -激活激酶 1 (TAK1),其导致两种转录因子的激活: NF- κ B 和 AP-1 [66]。而 NF- κ B 通路的激活能产生多种炎症因子,如 IL、TNF- α 等,SOX-9 表达降低,Col2A1、ACAN 下降,MMPs 升高,导致软骨细胞损伤,细胞外基质降解,造成骨关节炎[67]。

4.2. 肠道放线菌对破骨细胞的影响引起骨关节炎

佐藤武德等人发现放线菌的肽聚糖,作用于小鼠骨髓细胞,其 PGN 能通过诱导破骨细胞形成,进而刺激多种炎症因子升高[68],同时还能激活肠道内的 Th17,随后迁移到骨基质内,通过诱导产生 IL-17,加强局部炎症,使得 TNF- α 及 IL-1 表达量上升[69],这一变化也能提高 RANKL 的表达,并激活破骨前体细胞[70][71],最终导致骨关节炎。

4.3. 肠道放线菌通过对成骨细胞的影响引起骨关节炎

Takashi 等人的研究表明,短链脂肪酸乙酸盐和丙酸盐可以直接上调成骨细胞分化[72]。根据我国一项研究,肠道放线菌与乙酸盐、丙酸盐的吸收有关[73]。因此,肠道放线菌数量的增多,会影响乙酸盐、丙酸盐的吸收,进而对成骨细胞分化产生影响,造成骨关节炎。

4.4. 肠道放线菌通过对滑膜巨噬细胞的影响产生骨关节炎

研究表明,活化的滑膜巨噬细胞会促进软骨分泌大量的 MMP-1, MMP-3, MMP-9, MMP-13 [74] [75],造成软骨细胞外基质的破坏,进而引起骨关节炎。据报道,结肠癌患者肠道内放线菌增多时,TLR-2、TLR-4 和 NF- κ B 表达水平明显上升[64],这些因子能有效刺激关节滑膜中的 M2 巨噬细胞向 M1 巨噬细胞表型转变(尤其是 TLR-4),产生大量炎症因子,如 IL-6、IL-1 β 及 TNF- α 等[76],导致软骨细胞炎症,细胞外基质降解,产生骨关节炎。研究表明,放线菌细胞壁中的肽聚糖(PGN)和脂磷壁酸(LTA),也能够激活巨噬细胞的 TLR2 受体使其能够被识别,PAMPs 能够激活 B 细胞上的 NF- κ B 受体,从而促成巨噬细胞炎症反应,导致多种炎症因子如 IL-6、CD80 等的升高[65],从而导致骨关节炎。因此抑制肠道放线菌,可以有效防止巨噬细胞活化,减轻软骨炎症,达到防治骨关节炎的目的。

4.5. 肠道放线菌通过对脂肪细胞的影响产生骨关节炎

肠道内放线菌与脂肪吸收和收集有关,研究表明放线菌数量与 E-DII 等级相关[77],此外,肠道内的放线菌还能产生短链脂肪酸[78],这将导致宿主脂肪组织增加,由脂肪细胞分泌的脂肪因子、炎症因子,如前列腺素 E2、IL-1 β 、瘦素等表达量可能上升。此外,由此途径造成的肥胖还可能导致 LPS 浓度升高,造成 TLR4 和 MMP13 表达量上升,最终导致软骨炎症,产生骨关节炎。然而有意思的是,根据我国一项研究,与超重患者相比,对照组患者肠道内放线菌丰度明显更低[79],说明放线菌可能在人体营养摄入过程中对脂肪吸收起到重要作用,同时产生短链脂肪酸,而肥胖病人的放线菌对骨关节炎的影响还有待进一步探索。

综上,放线菌作为一种常见的肠道菌群,能够通过肠-骨轴,对不同的细胞产生影响,引起关节软骨炎症反应,最终导致骨关节炎。这一发现意味着对于骨关节炎的治疗可以不仅仅停留在止痛抗炎层面,在预防阶段即可通过人工干预胃肠道微生物的方式,延缓骨关节炎进程,乃至达到治疗骨关节炎的效果,这为后续该疾病的治疗,提供了一个全新的思路 and 方向。

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