肠道菌群与肥胖相关骨关节炎关系的研究进展

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摘　要　骨关节炎（osteoarthritis,OA）是常见的骨关节疾病,而肥胖是其重要的诱发因素之一。肠道菌群是一个复杂的生态系统,通过与宿主之间的相互作用影响着宿主的健康状况。多项研究表明,肠道菌群及其代谢产物通过与非特异性免疫系统的相互作用,影响肥胖相关 OA 的发生与发展。本文从肠道菌群失调、肠道菌群代谢产物、非特异性免疫 3 个方面对肠道菌群与肥胖相关 OA 关系的研究进展进行了综述。

关键词　骨关节炎;肠道菌群;免疫,先天;肥胖;综述

骨关节炎（osteoarthritis,OA）是常见的骨关节疾病,是主要的致残性疾病之一,其主要特征为关节软骨乃至整个关节发生病变。OA 的病因尚不明确,肥胖是其重要的诱发因素之一[1]。人体肠道容纳了大量微生物,在遗传和环境因素的共同作用下形成肠道菌群,肠道菌群与宿主之间的相互作用影响着宿主的健康状况[2-3]。肠道菌群在食物和口服药物的消化吸收过程中发挥着“代谢过滤器”的作用,其结构与代谢产物随宿主的年龄、饮食结构和肠道环境变化而动态改变。多项研究表明,肠道菌群与肥胖相关 OA 的发生和发展密切相关,而肠道菌群与非特异性免疫系统之间的相互作用构成了肥胖相关 OA 的生物学基础[4-8]。本文从肠道菌群失调、肠道菌群代谢产物、非特异性免疫 3 个方面对肠道菌群与肥胖相关 OA 关系的研究进展进行了综述。

1　肠道菌群失调

由肠道菌群、肠道菌群代谢产物和肠道黏膜免疫系统形成的稳定环境称为肠道微环境。肠道菌群、肠道微环境以及宿主之间平衡或失衡状态是免疫代谢生理或病理的基本决定因素[9-11]。肥胖相关 OA 与肠道菌群失调之间存在一定的联系[11-13]。Schott 等[14]研究发现,肥胖相关 OA 小鼠肠道内双歧杆菌等益生菌减少,具有促炎作用的菌种增加;通过增加小鼠肠道内双歧杆菌等益生菌,可减少结肠、膝关节等处的炎症反应,抑制 OA 的进一步发展。Horta-Baas 等[15]研究发现类风湿关节炎患者与正常人体的肠道菌群结构存在显著差异,提示肠道菌群失调可能与多种关节炎之间存在联系。

肠道菌群失调能显著提高人体内脂肪的含量,甘油三酯在代谢过程中会释放游离脂肪酸（free fatty acid,FFA）,而过量的 FFA 进入血液能够激活氧化应激和非特异性免疫系统[16-18]。Rodríguez-Carrio 等[19]研究表明,血清 FFA 特征谱的改变与肠道菌群的结构改变有关,其中阿克曼氏菌和乳杆菌菌群不平衡可导致粪便中短链脂肪酸和血清中白细胞介素增加。随着 OA 的恶化,关节滑膜液中 FFA 相关代谢产物也在增加,而一定浓度的油酸能够降低软骨细胞的活性,甚至诱导其凋亡[20-21]。Lippiello 等[22]研究发现,OA 患者的关节软骨组织中有脂肪代谢物沉积,而软骨表面的侵蚀程度与花生四烯酸的含量呈正相关。

2　肠道菌群代谢产物

肠道菌群的多种代谢产物透过肠道壁进入循环系统,进而向全身各个组织传递信号,影响人体的多项生理过程[18,23-24]。肽聚糖（peptidoglycan,PGN）是细菌细胞壁的主要成分,肠道菌群代谢产生的 PGN 可以诱导机体产生炎症反应和免疫应答[25]。Chi 等[24]的研究表明,特定的 PGN 基序能激活脂肪的分解代谢,增强脂肪细胞的细胞毒性,引发高脂血症和全身性炎症。Van Der Heijden 等[26]从 OA 患者关节的滑膜细胞中检测到了 PGN。Kool 等[27]的研究表明,肽聚糖多糖复合物能够诱导关节炎的发生。Schrijver 等[28]进行的体外实验表明,PGN 能够直接刺激滑膜成纤维细胞,诱导基质金属蛋白酶和促炎细胞因子的表达。

脂多糖（lipopolysaccharide,LPS）是革兰氏阴性菌

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外膜的主要成分,可引起宿主全身性炎症反应[29]。高脂饮食和肠道菌群失调可损害肠上皮屏障,导致血浆 LPS 浓度增加,引起代谢性内毒素血症[23]。Metcalfe 等[30]认为,代谢性内毒素血症在肠道菌群失调、全身炎症与肥胖相关 OA 之间起着关键作用。Collins 等[31]在肥胖相关 OA 小鼠的血清中检测到 LPS 浓度升高。Huang 等[32]的研究表明,滑膜液中 LPS 浓度与活化的巨噬细胞数量、骨赘严重程度、膝关节间隙狭窄程度及西安大略和麦克马斯特大学骨关节炎指数有关。Haglund 等[33]的研究表明,LPS 能诱导体外培养软骨细胞分泌基质金属蛋白酶和非特异性免疫应答相关蛋白,加速软骨细胞外基质降解,最终导致关节软骨进行性破坏。

3　非特异性免疫

非特异性免疫是人体的第一道免疫系统,能够对肠道菌群进行塑造,肠道菌群亦具有免疫激活功能[34-35]。非特异性免疫系统在肠道菌群与肥胖相关 OA 之间发挥中介作用。

Toll 样受体(Toll - like receptor,TLR)是一类非特异性免疫受体,目前发现的人类 TLR 有 10 种(TLR1 至 TLR10)[36]。TLR4 可被 PGN、LPS 等内毒素及 FFA 激活,在肠道菌群失调与代谢性炎症反应之间发挥重要作用[37]。Kim 等[38]的研究表明,OA 患者关节软骨组织中 TLR2 和 TLR4 过量表达;用 PGN 和 LPS 进一步处理 OA 患者关节软骨组织,TLR2 的 mRNA 表达量显著上调;再用 TLR 配体处理,软骨组织中基质金属蛋白酶、一氧化氮和前列腺素的表达量显著增加;表明 TLR2 在介导内毒素的免疫应答以及 OA 的发生过程中也发挥着重要作用。Kyburz 等[39]的研究表明,PGN 部分通过 TLR2 激活滑膜成纤维细胞免疫应答,促使其表达基质金属蛋白酶和促炎细胞因子,导致 OA 的发生。Xu 等[40]研究发现,白藜芦醇能够抑制软骨细胞中 TLR4 介导的炎症信号通路,是治疗肥胖相关 OA 的潜在药物。

炎性小体是炎性反应的重要介质,是含有一种或多种 Nod 样受体的多蛋白复合物[41]。NOD 样受体蛋白(NOD - like receptor protein,NLRP)3 炎性小体在 OA 患者的关节滑膜组织中表达上调,成为诊断和监测 OA 的新型生物标志物[42]。Henao - Mejia 等[43-44]的研究表明,NLRP3 炎性小体可以影响肠道菌群中致病菌的扩散,调节 TLR 激动剂进入门静脉循环,调控代谢综合征。Clavijo - Cornejo 等[45]的研究表明,膝关节 OA 患者滑膜组织中的 NLRP3 炎性小体的表达与氧化酶的表达高度相关,提示氧化反应可激活 NLRP3 炎性小体的表达,促进 OA 的发展。此外,NLRP1 炎性小体在 OA 患者的关节滑膜组织中表达上调[45]。Zhao 等[46]采用 LPS 刺激体外培养的 OA 患者成纤维样滑膜细胞,结果表明 NLRP1 和 NLRP3 炎性小体能够介导成纤维样滑膜细胞的炎症反应与凋亡。Sun 等[47]的研究表明,姜黄素能够抑制炎性小体的释放,发挥改善 OA 的作用。

4　小　结

肥胖被认为是 OA 的关键致病因素,而肠道菌群失调与肥胖之间存在密切的关系。肠道菌群及其代谢产物通过与人体非特异性免疫系统相互作用,影响肥胖相关 OA 的发生与发展,其中 TLR、NLRP3 炎性小体等在分子层面发挥了关键作用。鉴于免疫系统以及 OA 发病机制的复杂性,肠道菌群与非特异性免疫系统、肥胖相关 OA 之间具体的作用机制,尤其是肠道菌群与宿主之间在肠道与关节组织的局部相互作用机制仍需要进一步深入研究。

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