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·综述·

肠道微生物与骨病的研究进展

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摘要: 人体肠道微生物菌群基因数量超过人体基因数量的100倍,被称为"人体第二基因库",这些基因赋予各种细菌不同的功能,产生极其复杂多样的代谢产物,对于调节人体消化、免疫、内分泌、乃至神经系统等功能具有重要作用。而处于稳态的肠道微生物不但能依附于肠黏膜表面形成保护屏障,阻止致病菌的生长、繁殖和入侵,还能通过黏膜系统促进免疫系统成熟,有助于机体有效抵抗病原微生物的感染。如果肠道菌群平衡被打破,那么宿主患各种疾病的风险就会随之升高。宿主健康与否会导致肠道微生物发生变化,进而通过间接刺激或抑制成骨细胞和激活破骨细胞而打破骨矿化平衡,影响骨健康。除此之外,它们还可以通过维持免疫系统稳态参与调控骨代谢,通过影响生长因子调节、营养物质吸收和宿主代谢通路等参与骨质疏松症、类风湿性关节炎和强直性脊柱炎等相关骨病的发生。目前关于肠道微生物菌群与骨病的研究较少,且多集中于菌群差异性对骨病的影响,而肠道菌群影响骨病的分子机制亟待进一步研究。本文就近年来国内外对肠道微生物与骨病关系的研究进展进行综述。

关键词: 肠道微生物;骨病;骨质疏松症;类风湿性关节炎;强直性脊柱炎

Research progress of intestinal microorganism and bone diseases

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Abstract: The number of genes that encode microbial flora is 100-fold more than the human genome, known as the "human second gene pool". These genes give different functions to various bacteria and produce extremely complex and diverse metabolites, which play an important role in regulating human digestive, immune, endocrine and even neurological system functions. The steady-state intestinal microorganism not only can attach to the mucous membrane surface to form the protective barrier and prevent the growth, multiplication and invasion of pathogenic bacteria, but also can promote the immune system to mature through the mucous membrane system, thus the organism can resist the pathogenic microorganism infection effectively. If the balance of the intestinal flora is broken, the risk of the host suffering from various diseases will increase. Whether the host is healthy or not can cause the intestinal microorganism to change, and it is now known that intestinal microbes can influence bone health by indirectly stimulating or inhibiting osteoblasts and osteoclasts formation to break the balance of bone mineralization. In addition, they not only can use the immune system to participate in the regulation of bone metabolism, but also through influencing growth factor regulation, nutrient uptake and host metabolic pathway participate in the occurrence of osteoporosis, rheumatoid arthritis and ankylosing spondylitis and other related bone disease. At present, the study on intestinal microbial flora and bone disease is limited and concentrates on the effect of bacterial flora difference on bone disease, and the molecular mechanism of how intestinal flora affecting bone disease needs to be further studied. In this paper, the research progress of the relationship between intestinal microorganism and bone disease has been reviewed.

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Key words: Intestinal microorganism; Bone disease; Osteoporosis; Rheumatoid arthritis; Ankylosing spondylitis

1 肠道微生物菌群

在人体内或人体表面存在着与人们共生共栖并在一定条件下导致各种疾病的微生物群体[1]，而存在于肠道内的微生物菌群是这些微生物群体的主力军，它们被称为肠道微生物菌群[2]。人体和动物肠道中的菌群种类繁多，以人体健康肠道为例，细菌、古菌和真核生物是肠道菌群的主要成分[3]，其内微生物数量与体细胞的比例可以达到 10:1，大约存在超过 10 万亿个细菌[4]。另外人类肠道微生物宏基因组分为拟杆菌属、普里沃菌属和瘤胃球菌属 3 个肠型[5]，这些宏基因组是人类基因组基因数量的 100 倍之多，被称为人体的“第二基因库”[4]。

人体肠道微生物菌群就像人体又一器官，它们不仅对免疫功能、营养吸收和宿主细胞各种生命活动具有重要影响[6]，还与人体的各种疾病及健康状况密切相关。肠道微生物菌群通过菌群稳态改变及其产生的代谢产物[7]等因素影响机体，导致机体代谢过程发生变化，进而导致各种疾病的发生。如炎症性肠病中的溃疡性结肠炎[8]和克罗恩氏病[9]等疾病可能由于宿主遗传、饮食和环境变化造成肠道微生物构成改变而导致；肠道微生物构成的变化不但能影响能量代谢导致肥胖发生[10]，其本身还可能与机体固有免疫成分共同激活非特异性免疫反应，诱导胰岛素抵抗，参与 II 型糖尿病的发生[11]。肠道菌群还通过影响免疫系统诱发类风湿关节炎[12]和系统性红斑狼疮[12]等疾病的发生。关于癌症方面的研究，肠道微生物菌群的几个副产物——硫化氢和脆弱拟杆菌肠毒素可直接靶向肠上皮细胞并介导肿瘤的发生[13]。此外，当肠道内革兰氏阳性菌和梭菌菌属（*Fusobacterium*）减少，菌群平衡被打破，使得患结直肠癌的风险增加[14]。菌群-肠道-大脑轴与人的情感和行为关系密切，它们通过改变神经递质代谢导致神经系统功能紊乱[15]，引起抑郁、精神衰弱等问题[16-17]。虽然肠道菌群失衡可以引发多种疾病，但是处于稳态下的肠道菌群却可以预防疾病。比如，肠道微生物菌群依附在肠黏膜上，形成一个保护罩，避免外来病原微生物的侵袭[12]。肠道菌群还可以对肠道产生一定的刺激，这种刺激能够诱导机体产生对微生物抗原免疫球蛋白 G（immunoglobulin G，IgG）的免疫应答，刺激机体产生更多的淋巴细胞[18]，随之产生的 IgG 抗体可以识别革兰氏阴性菌、中和毒素和病毒，调理机体清除病原微生物[19]，促进免疫系统成熟，保证宿主避免炎症和感染的发生，起到提高机体免疫力的作用[9, 19]。

2 肠道微生物菌群与骨病

2.1 肠道微生物菌群与骨质疏松症

骨质疏松症（osteoporosis，OP）是一种由于正常骨转换被破坏，导致骨质量和骨密度降低以及骨微结构改变的代谢性骨骼疾病，其主要受遗传和环境两种因素影响[20]。目前已有不少研究证实肠道微生物菌群与骨质疏松症间具有一定关系。喂食含有地衣芽孢杆菌（*Bacillus licheniformis*）的益生菌膳食补充剂的鸡较喂食普通饲料的对照组其胫骨密度显著增加[21]。雌激素缺乏会导致骨损失诱发骨质疏松症，卵巢切除术（ovariectomy，OVX）可以诱导雌性小鼠缺乏雌激素[22]。在 OVX 小鼠饮用水中加入副干酪乳杆菌（*Lactobacillus paracasei*）DSM13434 或者 *L. paracasei* DSM13434、植物乳杆菌（*Lactobacillus plantarum*）DSM 15312 和 DSM 15313 混合物，6 周后可发现其体内肿瘤坏死因子-α（tumor necrosis factor，TNF-α）和白细胞介素 1β（interleukin-1β，IL-1β）两种炎性细胞因子的表达下调，并且小鼠皮质骨中破骨细胞抑制剂骨保护素（osteoprotegerin，OPG）表达上调[22]，因此它们可能在防止卵巢切除诱导的皮质骨损失和骨吸收方面具有一定作用。另外罗伊氏乳杆菌（*Lactobacillus reuteri*）处理的 OVX 小鼠体内破骨细胞骨吸收标志物 5 型酸性磷酸酶抗体（thrombin receptor activator for peptide 5，TRAP5）、激活剂核因子 κB 受体活化因子配体（receptor activator for nuclear factor-κB ligand，RANKL）以及破骨细胞的生成均显著降低，促进破骨细胞生成的骨髓 $CD4^+$T 淋巴细胞也同样减少[23]，说明罗伊氏乳杆菌（*Lactobacillus reuteri*）可能抑制由雌激素缺乏导致的骨量丢失和骨吸收。I 型糖尿病（diabetes mellitus type I，T1D）可诱导骨质疏松症，骨特异性 Wnt10b 转基因小鼠可免受 T1D 诱导的骨量丢失[24]，据报道使用罗伊氏乳杆菌（*Lactobacillus reuteri*）处理 I 型糖尿病模型小鼠可降低肿瘤坏死因子 TNF-α 介导的 Wnt10b 表达抑制作用，上调 Wnt10b 表达，在防止骨量丢失和预防骨质疏松症方面具有一定作用[24]。

胰岛素样生长因子-1（insulin-like growth factors-

1,IGF-1)是一种有效的骨骼调节因子,可以促进成骨细胞分化[25]。最近有研究发现肠道菌群可增加 IGF-1 表达水平,促进骨骼生长和重塑。另外微生物群发酵纤维产生的短链脂肪酸(short-chain fatty acids,SCFAs)也可诱导 IGF-1 生成并参与调控骨代谢平衡[26]。还有研究证实注射特殊乳酸杆菌菌株(*Lactic acid bacteria*)可诱导无菌小鼠体内生成 IGF-1 或类 IGF-1 样因子,进而促进成骨细胞分化,影响骨代谢水平[27]。

肠道微生物还可以通过改变骨免疫状态介导调节骨代谢[28]。无菌小鼠较正常小鼠骨量明显增加,且骨髓产生的 $CD4^+$ T 细胞、破骨细胞与破骨细胞前体细胞数量明显减少,TNF-α 表达下调,但是移植肠道微生物菌群到无菌小鼠体内后这些细胞的数量均恢复正常,且骨小梁和皮层骨质量下降[28]。小鼠肠道内分节丝状菌(*Segmented filamentous bacteria*)可促进辅助性 T 细胞 17(T helper cell 17, Th17)分化引起促炎免疫应答,激活基质细胞上的 RANKL 表达,促进破骨细胞的形成。另外,Th17 细胞还可分泌白细胞介素 17(interleukin-17,IL-17)细胞因子,同样参与调节破骨细胞的分化[29]。

肠道微生物群紊乱可导致炎症性肠病发生[30],炎症性肠病患者则处于骨质疏松和脆性骨折的风险中[31],与炎症性肠病相关的骨质减少主要归因于钙吸收不足,维生素 D 和维生素 K 的循环水平降低[32]等。摄取足量的对宿主健康有益的益生菌或益生元时可增强肠道抗炎特性,如补充益生菌鼠李糖乳杆菌(*Lactobacillus rhamnosus*)剂能够改善肠道通透性,减轻肠道炎症,起到防止骨量丢失的作用[33-34]。利用罗伊氏乳杆菌(*Lactobacillus reuteri*)抗炎、抗 TNF-α 的特性治疗小鼠肠道炎症,发现雄性小鼠骨小梁和椎骨的骨密度和骨量均增加,而雌性小鼠的骨参数却没有影响,其治疗效果存在性别特异[35]。当肠道菌群稳态失衡出现肠炎症时,主要在肠道被吸收的维生素 D 在维持菌群稳态方面具有一定作用,它通过活化调节性 T 细胞(regulatory cell,Treg),避免影响骨健康[36]。维生素 D 对骨骼具有一定的益处[37],在足够的钙供应的情况下,肠道内被吸收的维生素 D 及其代谢物可维持肠道菌群稳态,改善钙平衡并促进骨基质中的矿物沉积,在钙缺乏的情况下,维生素 D 可增强骨吸收,同时抑制骨矿化,从而以降低骨量为代价维持血钙稳态。在小鼠饮食中加入钙之后,其肠道内具有促进骨重建作用的乳酸杆菌(*Lactobacillus*)和双歧杆菌(*Bifidobacterium*)含量均增加[38]。因此补充膳食时加入适量的维生素 D 和钙,对预防骨质疏松的发生具有一定作用。肠道菌群通过发酵未消化的碳水化合物产生 SCFAs 对骨健康也存在一定影响,短链脂肪酸可降低肠道 pH,有利于钙吸收,另外它们还可能通过作为组蛋白脱乙酰酶(histone deacetylase, HDAC)的抑制剂或激活特异性 G 蛋白偶联受体(G protein-coupled receptors,GPCRs)介导抑制破骨细胞的形成[39]。

2.2 肠道微生物菌群与类风湿性关节炎

类风湿性关节炎(rheumatoid arthritis,RA)是一种以关节滑膜慢性炎性病变为主要病理特征的系统性自身免疫性疾病,发病时伴有严重的关节疼痛感[40]。Scher 等[41]通过对类风湿性关节炎患者和健康者粪便中的肠道细菌样品进行 16S 测序发现,类风湿关性节炎初诊患者粪便中的普氏菌(*Prevotella copri*)数量比健康者或慢性已接受治疗的类风湿性关节炎患者更多,普氏菌(*Prevotella copri*)数量过多可能与拟杆菌属(*Bacteroides*)等有益菌减少相关。这是首次证明了肠道普氏菌(*Prevotella copri*)可能在类风湿性关节炎的发病机理中具有潜在的作用。近期 Marietta 等[42]在研究普氏菌属细菌 *Prevotella histicola* 对关节炎易感小鼠的影响时进一步证实了 Scher 等的观点。Marietta 等[42]利用普氏菌属(*Prevotella*)细菌 *Prevotella histicola* 处理一组 II 型胶原诱导的关节炎易感小鼠,同时选取未治疗小鼠作为对照。最终发现 *Prevotella histicola* 可以通过黏膜调节抑制关节炎,使处理的小鼠与对照组相比表现出显着降低的关节炎发生率,而且症状的严重程度也明显降低。

在超过一半的类风湿性关节炎患者中,N-乙酰氨基葡萄糖-6-硫酸酯酶(N-acetylglucosamine-6-sulfatase,GNS)和细丝蛋白 A(filamin A,FLNA)两种蛋白均能够引发 T 细胞与 B 细胞的免疫反应,而健康人体内却没有此类效应[43-44]。因此它们被认为是类风湿性关节炎患者的自身抗原。HLA-DR 提呈的 GNS 蛋白与 *Prevotella* 菌属和 *Parabacteroides* 菌属的硫酸酯酶蛋白的表位具有同源性序列,HLA-DR 提呈的 FLNA 蛋白与 *Prevotella* 和 *Butyricimonas* 菌属蛋白的表位具有同源性。基于这些,肠道微生物分泌的 GNS 和 FLNA 两种蛋白质很可能引发类风湿性关节炎患者体内出现异常免疫反应[43]。

2.3 肠道微生物菌群与强直性脊柱炎

强直性脊柱炎(ankylosing spondylitis,AS)是一

种以脊柱和骶髂关节炎症为主要病理特征的慢性自身免疫系统疾病,与遗传具有一定的相关性[45]。目前已有大量证据表明肠道微生物菌群可能对强直性脊柱炎具有重要作用。较早之前有研究发现肺炎克雷伯杆菌(*Klebsiella pneumoniae*)是强直性脊柱炎发病机制中的触发和促进因素[46]。近年来有报道指出强直性脊柱炎患者体内可能还有其他特定的肠道微生物,采用 16S 核糖体 RNA 基因测序分析技术,通过筛选终末回肠活检中的微生物谱发现强直性脊柱炎患者的肠道微生物构成与健康对照受试者具有显著差异,强直性脊柱炎患者的回肠末端富集了五类细菌,毛螺科菌科(*Lachnospiraceae*)、瘤胃菌科(*Ruminococcaceae*)、紫单胞菌科(*Porphyromonadaceae*)、理研菌科(*Rikenellaceae*)和拟杆菌科(*Bacteroidaceae*),而韦荣球菌科(*Veillonellaceae*)和普雷沃氏菌科(*Prevotellaceae*)却明显减少[47]。除了这些细菌外,还有研究结果显示,人体白细胞抗原 HLA-B27 阳性强直性脊柱炎患者体内耶尔森氏菌(*Yersinia*)、克雷伯氏菌(*Klebsiella*)和沙门氏菌(*Salmonella*)它们的热休克蛋白与健康对照受试者相比具有较高的 IgG 抗体水平[48],说明它们也可能与强直性脊柱炎的发生具有一定关系。最近研究人员们还利用定量宏基因组分析研究了强直性脊柱炎患者与健康人肠道菌群的差异性,发现强直性脊柱炎患者中放线菌属(*Actinomyces*)数量显著升高,它可以调节上皮细胞中介物人核因子 κB 抑制蛋白 α(NF-kappa-B inhibitor alpha,IκB-α)的泛素化,激活 NF-κB 代谢通路,促成炎症反应[49]。而患者体内的拟杆菌属(*Bacteroides*)和肠杆菌属(*Enterobacter*)数量却显著降低,可能造成肠道菌群紊乱,导致强直性脊柱炎病情恶化[49]。

以上关于肠道微生物对骨质疏松症、类风湿性关节炎和强直性脊柱炎影响的主要研究进展可见图 1 肠道微生物与骨病关系。

3 结语

随着肠道微生物研究的不断深入,其在骨病发生过程中的作用逐步得到证实,肠道菌群构成的改变与骨病发生相关联,基于测序技术筛选出的特定肠道菌群可以作为早期诊断和疾病活动监测的新标志物。肠道微生物对骨病的作用主要通过调节宿主免疫系统促进产生生物小分子,进而参与调控骨代谢。此外它们还可通过影响宿主全身代谢,参与骨

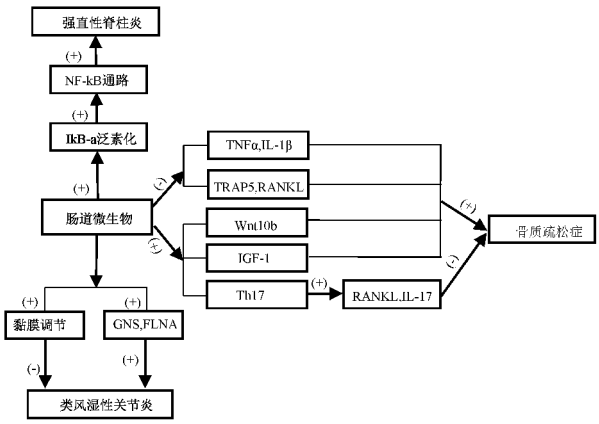

图 1 肠道微生物与骨病关系

Fig.1 The relationship between intestinal microorganism and bone disease

质疏松、类风湿性关节炎和强直性脊柱炎等相关骨病的发生。总之,关于肠道微生物与骨病关系的研究,分别从菌群差异性、功能研究等方面取得的一定进展将为今后深入探讨肠道菌群影响骨病的分子机制提供重要参考。

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