

肠道菌群影响动脉粥样硬化免疫机制研究进展

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[关键词] 肠道菌群; 炎症反应; 脂代谢; 动脉粥样硬化

[摘要] 动脉粥样硬化(As)与脂质代谢紊乱和炎症密切相关。目前研究发现,肠道菌群也参与As过程,是As独立的危险因素之一。人体肠道是机体最大的消化器官和“最大的免疫器官”。正常的肠道菌群参与胆汁酸代谢,菌群代谢产生的短链脂肪酸抑制炎症,从而抑制As。失衡的菌群通过影响宿主三甲胺代谢途径,扰乱机体胆固醇代谢,引发固有免疫应答和适应性免疫应答,减弱抗炎保护作用,从而促进As。因此,调节失衡的肠道菌群成为治疗As的新靶点。本文将对肠道菌群影响As的免疫机制进行综述。

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Research progress on the influence of intestinal microbial flora on the immune mechanism of atherosclerosis

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[ABSTRACT] Atherosclerosis (As) is closely related to lipid metabolism disorder and inflammation. The current study shows that intestinal microbial flora is also involved in the As process and is one of the independent risk factors of As. The human gut is the largest digestive organ and “the largest immune organ” of the body. Normal intestinal flora participates in bile acid metabolism, and the short-chain fatty acids produced by bacterial metabolism inhibit inflammation, thus suppressing As. Unbalanced intestinal flora affects trimethylamine metabolic pathway of the host, disturbs the metabolism of cholesterol in the body, triggers the innate and adaptive immune responses, and attenuates the protective effect of anti-inflammation, thus promoting As. Therefore, the regulation of unbalanced intestinal flora becomes a new target for the treatment of As. This article will review the immune mechanism of intestinal flora affecting As.

动脉粥样硬化(atherosclerosis, As)是全球的常见病,是冠心病、脑卒中等疾病的主要危险因素,严重危害人类身体健康。高脂血症与As发生关系密切。血中异常升高的低密度脂蛋白被氧化成氧化型低密度脂蛋白,是As发生的先决条件和关键环节,氧化型低密度脂蛋白通过复杂的免疫机制诱导As发生。

人体肠道菌群的组成相对稳定,但具有个体差异性,在不同年龄阶段其组成发生变化,且易受外

界因素影响^[1]。采用16S核糖体RNA测序和宏基因组学分析技术,检测到人体肠道菌群超过1150种共 10^{14} 个细菌^[2-3];已知的52种细菌门类中,有5到7种主要的细菌定植在肠道中,包括厚壁菌门、拟杆菌门、放线菌门、变形杆菌门、疣微菌门等多种细菌。肠道菌群从多方面影响人体^[4-5],包括:(1)参与人体生理过程:如消化营养物质,调节肠道上皮细胞功能,参与机体免疫反应等;(2)参与机体代谢:肠道菌群具备人体不具有的代谢功能,参与并

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影响机体代谢。新近研究发现,肠道菌群失衡,即菌群组分改变和功能失调,能改变脂质代谢和炎症反应,在 As 的发生和发展中起重要作用^[6-7]。临床研究发现;冠心病患者粪便中拟杆菌(*bacteriodes*)减少,乳杆菌目(*lactobacillales*)和梭状芽孢杆菌类 XIVa(*clostridium* subcluster XIVa)增多^[8]。动物实验也证实肠道菌群紊乱可导致 As 模型小鼠斑块数目增多、斑块面积增大^[9-10]。高脂饮食导致 As 模型小鼠肠道菌群失衡,特别是脱硫弧菌属(*desulfovibrio* spp.)细菌增加,损伤肠壁的屏障功能,导致循环中脂多糖(*lipopolysaccharide*, LPS)水平增高^[10]。而给予益生菌乳酸片球菌 R037(*pediococcus acidilactici* R037)^[11],或嗜酸乳杆菌 ATTC 4356(*lactobacillus acidophilus* ATTC 4356)^[12],或药物干预增加益生菌拟杆菌和疣微菌科阿克曼菌(*verrucomicrobiaceae*, *akkermansia*)丰度,则显著减少 As 模型小鼠斑块面积^[10]。

1 肠道菌群的抗 As 作用

1.1 肠道菌群通过参与胆汁酸代谢抑制 As

肠道菌群参与胆汁酸代谢,维持机体肝肠循环,保证脂类的消化及吸收平衡。胆汁酸作为信号分子参与机体脂质代谢、糖代谢及免疫的调控。胆汁酸激活核受体家族成员法尼醇 X 受体(*farnesoid-X receptor*, FXR),减少单核细胞、巨噬细胞、树突状细胞和肝枯否细胞上炎症因子的表达,减轻炎症程度^[9]。肠道菌群分解初级胆汁酸,经 7- α 脱羟后产生的次级胆汁酸,激活核受体(核受体亚家族 1H 组成员 4 和 FXR)和 G 蛋白偶联胆汁酸受体 1(胆汁酸膜受体,其中趋化因子 TGR5 最具代表性),抑制炎症和 As 的发展^[13]。

1.2 肠道菌群代谢产物短链脂肪酸等抑制 As

厚壁菌门的梭状芽孢杆菌等分解盲肠和结肠中未消化的膳食纤维和抗性淀粉,产生碳链中碳原子数为 1~6 的短链脂肪酸(*short-chain fatty acid*, SCFA),包括乙酸、丙酸、异丁酸、丁酸、异戊酸、戊酸等,具有抗 As 作用^[2,14],机制:(1) SCFA 促进糖代谢和脂质代谢,如丙酸增强 β 细胞的功能以增加胰岛素的分泌,维持人体血糖的平衡^[15],乙酸降低高胆固醇饮食大鼠血浆总胆固醇和甘油三酯的水平^[16];(2) SCFA 减少免疫细胞的迁移和增殖,减少炎症因子的表达,诱导凋亡,如丁酸降低 As 损伤处单核细胞黏附因子和基质金属蛋白酶 2 的表达,抑

制巨噬细胞的迁移和胶原的沉积^[17],促进 As 斑块稳定;(3) SCFA 与游离脂肪酸受体 2 结合,抑制 LPS 刺激的炎症因子释放,加强中性粒细胞的趋化作用^[18];(4) SCFA 在组蛋白去乙酰化酶介导下,减少结肠固有层巨噬细胞释放炎症因子^[19]。

肠道菌群的其他代谢产物也具有抗 As 作用。结肠菌群分解浆果、水果和绿茶中的花青素产生原儿茶酸,上调巨噬细胞三磷酸腺苷结合盒转运体 A 和三磷酸腺苷结合盒转运体 G 的表达,促进三磷酸腺苷结合转运,减少泡沫细胞的形成^[20]。由肠道共生菌脆弱拟杆菌产生的两性离子多糖 PSA 具有免疫调节作用^[21],诱导 CD4⁺ 的 T 细胞分泌白细胞介素 10(*interleukin-10*, IL-10),促进 CD4⁺ 的 T 细胞分化,抑制炎症^[22]。肠道菌群分解食物中的色氨酸产生吲哚类衍生物,激活芳香烃受体(*aryl hydrocarbon receptor*, AhR)和孕烷 X 受体(*pregnane X receptor*, PXR)。AhR 促使 3 型固有淋巴细胞分泌 IL-22,维持肠壁的完整性^[23]。PXR 增强上皮屏障功能,抑制炎症^[24]。由宿主和细菌分解精氨酸产生的多胺,抑制 LPS 刺激的单核细胞、巨噬细胞炎症细胞因子表达,增加肠黏膜的稳定^[25-26]。

1.3 肠道共生菌的免疫耐受和免疫激活

正常情况下,机体通过以下途径对肠道共生菌产生免疫耐受:(1) 耐受性树突状细胞(*dendritic cell*, DC)识别无害的抗原,并递呈给调节性 T 细胞(*regulatory T cell*, Treg),Treg 分泌抑炎因子,产生免疫耐受^[27];(2) 耐受性 DC 分泌维甲酸,维甲酸与转化生长因子 β 共同作用,促进 Treg 的产生^[28];(3) 耐受性 DC 也识别有害的抗原,递呈给效应性 T 细胞,导致效应性 T 细胞的凋亡和无反应^[29]。

有害抗原激活机体的免疫。炎症性 DC 识别有害抗原,递呈给 Th1 和 Th17 辅助细胞,分别产生干扰素 γ 和 IL-17,同时炎症性 DC 也产生 IL-12,激活免疫反应^[29]。

2 肠道菌群失衡促进 As 发生发展

肠道菌群失衡是 As 独立的危险因素之一^[30]。肠道菌群失衡表现为菌群组分的改变,即菌群数量、丰度、比例、结构发生变化。研究发现,症状明显的 As 患者肠道中柯林斯菌属较正常人群增多^[31];肥胖人群肠道菌群的物种多样性和基因丰富度比正常人偏低^[32];肥胖小鼠的肠道中厚壁菌门/拟杆菌门比例升高^[29,33]。As 患者肠道菌群失衡,菌

群代谢扰乱机体胆固醇代谢;失衡的肠道菌群激活天然免疫应答,促进炎症反应,从而加速高脂血症和血管炎性损伤^[34]。

2.1 肠道菌群失衡与三甲胺代谢

目前,已经明确肠道菌群失衡产生三甲胺(trimethylamine, TMA),影响胆固醇代谢,促进 As。肠道菌群分解过量摄入的肉类,产生 TMA^[35],TMA 被肝脏里的黄素单氧化酶氧化,生成氧化三甲胺(trimethylamine N-oxide, TMAO)^[36]。TMAO 与肥胖^[37]、代谢综合征^[38]、脂肪肝^[39]、哮喘^[40]、肿瘤^[41]和 As^[30]等多种慢性疾病相关。TMAO 在 3 个环节影响 As:(1)上调巨噬细胞清道夫受体 SR-A1、CD36 的表达,促进泡沫细胞的形成^[9];(2)降低胆汁酸合成酶 Cyp7a1、Cyp27a1 水平,减少胆汁酸的分泌^[42];(3)降低胆汁酸转运酶 Oatp1、Oatp4、Mrp2 和 Ntcp 的表达,抑制胆固醇逆转运(reverse cholesterol transport, RCT),促使胆固醇在组织细胞内堆积^[42]。研究发现,抗生素可恢复胆碱、肉碱,抑制小鼠 RCT^[42]。此外,TMAO 还提高细胞内 Ca²⁺ 释放,增加血小板反应性,促进血栓的发生^[43]。

肠道菌群种类影响机体 TMAO 水平。普雷沃菌门菌比拟杆菌门菌产生更多的 TMAO^[44]。与素食主义者相比,杂食主义者粪便中梭菌科和消化链球菌科细菌含量更丰富,毛螺菌属和胞杆菌属细菌含量少,其血浆和尿液中的 TMAO 水平更高^[42]。

2.2 肠道菌群失衡在 As 免疫损伤中的作用

现代医学认为,As 不仅是血管局部炎症病变,而且是多种免疫细胞异常导致的全身免疫紊乱^[45]。失衡的肠道菌群引发机体免疫损伤,损伤机体天然固有免疫和获得性免疫,促进 As。

2.2.1 肠道菌群失衡在固有免疫应答中的作用

固有免疫是机体抵御病原微生物入侵的第一道防线,参与固有免疫的细胞有单核细胞、巨噬细胞、树突状细胞、粒细胞、自然杀伤细胞和自然杀伤 T 细胞。失衡的肠道菌群通过革兰阴性杆菌产生 LPS 和阳性细菌细胞壁的成分肽聚糖(peptidoglycan, PGN),引发机体固有免疫应答。

(1)LPS 作用。肠道共生厚壁菌门和拟杆菌门等细菌释放 LPS。LPS 与巨噬细胞表面的病原体相关分子模式 Toll 样受体 4 结合,上调巨噬细胞表面低密度脂蛋白受体、极低密度脂蛋白受体和脂联素受体 2 的表达,促进脂质摄入;LPS 降低转录因子肝 X 受体的表达,减少胆固醇外流,促进泡沫细胞形成;LPS 还降低胰高血糖素样肽 2 和肠道 L 细胞的

产生,减弱肠壁保护作用,致使肠道细菌外流,引发炎症^[46]。

(2)PGN 作用。PGN 是免疫增强剂,能刺激单核细胞、巨噬细胞和内皮细胞释放炎症因子肿瘤坏死因子 α 、IL-1、IL-6、IL-8、IL-12、干扰素 α 等,促进炎症^[47]。PGN 的降解产物能被固有免疫模式识别受体核苷酸结合寡聚化域受体 NOD1 和 NOD2 识别,在适配蛋白 RIP2 的作用下,激活核因子 κ B 和丝裂素活化蛋白激酶信号通路,产生炎症因子,促进 As^[48]。

2.2.2 肠道菌群在适应性免疫应答中的作用

肠道菌群能够影响肠道内 CD8⁺T 细胞向 CD4⁺方向分化,以及 T 细胞向不同亚型分化^[49-50],效应性 T 细胞和 Treg 分别产生炎症因子和抑炎因子 IL-10、转化生长因子 β 、细胞毒性 T 淋巴细胞抗原 4,影响 As 发展^[51]。肠道菌群能被机体 DC 识别,并根据抗原危害性质分别递呈给不同的 T 细胞(包括调节性 T 细胞、效应性 T 细胞及 Th1 和 Th17 辅助细胞),并促使 T 细胞亚型的分化^[49],产生免疫耐受或免疫激活^[27,29]。

此外,SCFA 也参与适应性免疫应答。丁酸和丙酸不仅抑制 DC 的成熟^[52],在固有免疫和适应性免疫发挥重要作用,还促进叉头/翼状螺旋转录因子 p3 在 Treg 的表达^[53],抑制 As。SCFA 还抑制 B 细胞组蛋白去乙酰化酶调节抗体基因的表达,促进抗体的生产^[54]。

3 调节肠道微生物治疗动脉粥样硬化的展望

综上所述,调节肠道菌群有望改善 As:(1)改善饮食结构,通过饮食调节肠道微生物的组成及代谢,减少摄入含有三甲胺基团的肉类可以抑制 As^[55];(2)增加益生菌,改变肠道微生物的组成,益生元的摄入能够改善肠道微生物的菌群结构和功能,如乳酸杆菌等^[56];(3)药物治疗肠道菌群紊乱,例如应用抗生素和 3,3-二甲基-1-丁醇来减少 TMA 转为 TMAO,从而抑制 As^[57]。

近年来对于肠道微生物与 As 的关系已有大量研究。但是具体怎样对肠道微生物调节,在何种机制上调节,肠道微生物的组成及其菌群之间的关系如何影响 As,还需要进一步研究。随着对肠道菌群研究的不断深入,将为防治 As 提供一个新的思路,带来新的曙光。

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