·综 述·

肠道菌群及其代谢产物与心血管疾病关系的研究进展

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[摘 要] 肠道菌群及其代谢产物在心血管疾病(cardiovascular disease,CVD)中具有重要作用。肠道菌群的组成变化及其代谢产物与动脉粥样硬化、心肌梗死、心衰、高血压的发生、发展相关。肠道菌群及其代谢产物对CVD影响的机制已有报道。本文将综述肠道菌群及其代谢产物在动脉粥样硬化、心肌梗死、心衰心功能不全、高血压的发生、发展中的作用和机制,以及在CVD防治方面的潜在价值,为CVD的防治提供新思路。

[关键词] 肠道菌群;代谢产物;心血管疾病

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Progress in the relationship between intestinal floras and their metabolites and cardiovascular diseases

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[**Abstract**] The intestinal floras and their metabolites play an important role in cardiovascular disease(CVD). Changes in the composition of intestinal floras and their metabolites are related to the occurrence and development of atherosclerosis, myocardial infarction, heart failure, and hypertension. The mechanism of the effects of intestinal floras and their metabolites on CVD has been reported. This article will review the role and mechanism of intestinal floras and their metabolites in the development and progression of atherosclerosis, myocardial infarction, heart failure, and hypertension, as well as the potential value in the prevention and treatment of CVD, providing new insights into the prevention and treatment of CVD.

[**Key words**] intestinal floras; metabolites; cardiovascular diseases

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人体肠道中含有大量菌群,这些菌群可以协助机体保持肠黏膜屏障完整,并且能够调节机体免疫功能。肠道菌群代谢产生的活性物质进入体循环后也会影响机体的生理活动。心血管疾病(cardiovascular disease,CVD)是全球高流行率和高死亡率的疾病。越来越多的研究发现肠道菌群及其代谢产物与脉粥样硬化、心肌梗死、心衰、高血压的发生、发展密切相关[1]。然而肠道菌群及其代谢产物对CVD影响的确切机制尚未完全阐明,本文将综述肠道菌群及其代谢产物对动脉粥样硬化、心肌梗死、心衰、高血压的作用及其相关机制,并探讨肠道菌群及其代谢产物在防治CVD方面的潜在价值。

1 肠道菌群及其代谢产物

肠道菌群主要由拟杆菌、厚壁菌、放线菌属、变形杆菌和疣微菌等组成[2]。肠道菌群组成的平衡有助于保护肠黏膜屏障,帮助营养摄取和调节代谢,协助免疫组织成熟,防止病原微生物进入体循环[3]。肠道菌群的改变可能会破坏肠黏膜屏障,引起菌群移位,体循环炎症水平增高,从而影响机体健康。肠道菌群通过食物吸收分解产生大量代谢产物,也与人体健康密切相关。一部分具有生物活性的代谢

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产物可以一种类似人体内分泌器官的方式作用于远处靶器官[4]。如肠道菌群代谢产生的脂多糖和肽聚糖，通过模式识别受体与宿主黏膜表面细胞相互作用，识别病原体相关的分子模式，刺激和指导宿主的免疫应答[5]。

2 肠道菌群及其代谢产物对CVD的影响

越来越多的研究证明肠道菌群及其代谢产物与CVD的发展密切相关。Gan等[6]研究发现给心肌梗死的小鼠喂食鼠李糖乳杆菌GR-1，可以改善小鼠心梗后的左心室功能。肠道菌群通过糖代谢和氨基酸代谢产生大量三甲胺（trimetlylamine，TMA）、短链脂肪酸（short chainfatty acids，SCFAs）、胆碱、胆汁酸、吲哚硫酸盐（indoxyl sulfate，IndS）等物质。三甲胺-氧化物（trimethylamine-N-oxide，TMAO）、胆碱和甜菜碱等与CVD的发生、发展密切相关[7]。此外尿毒症患者中IndS的蓄积具有一定毒性，并且通过氧化应激损坏心脏[8]。以下将分别阐述肠道菌群及其代谢产物对动脉粥样硬化、心肌梗死、心衰、高血压的作用及其相关机制。

2.1 肠道菌群及其代谢产物与动脉粥样硬化、心肌梗死

肠道菌群及其代谢产物与动脉粥样硬化的产生、发展密切相关，此外还会影响动脉硬化斑块的稳定。最近研究发现肠道菌群中接合菌门菌属相对丰度与颈内动脉中膜的厚度负相关，与亚临床动脉粥样硬化的发生相关[9]。肠道菌群通过摄入食物中的胆碱（如胆碱、磷脂酰胆碱和L-肉毒碱等）产生TMA。TMA经过肝肠循环进入肝脏，经过黄素单氧酶氧化形成TMAO，进入体循环[10]。Ma等[11]发现TMAO通过上调血管细胞黏附分子-1的水平，促进单核细胞黏附，并且激活蛋白激酶c（PKC）和核因子κB（NF-κB）通路，使内皮细胞功能紊乱，进而影响早期动脉粥样硬化的病理过程。给拥有正常肠道菌群的小鼠喂食富含胆碱的食物时，循环中TMAO水平升高，引起泡沫细胞聚集，促进动脉粥样斑块形成[12]。Koren等[13]研究发现在动脉斑块中的细菌DNA与肠道菌群相似，这些斑块中的细菌可能与斑块稳定性有关。不稳定的动脉粥样硬化斑块会增加心肌梗死风险。针对肠道菌群及其代谢产物的早期干预，可以帮助我们更好地控制动脉粥样硬化的发生、进展，稳定动脉粥样硬化斑块，进而降低心肌梗死的风险。

肠道菌群及其代谢产物不仅可以通过影响动脉粥样硬化斑块的稳定增加心肌梗死风险，还可通过其他途径影响了心肌梗死的发生、发展。TMAO水平升高可影响心肌细胞线粒体的修复和心肌代谢，使急性心肌梗死的发生风险和严重程度明显增加[14]。TMAO还可通过二磷酸腺苷、凝血酶和胶原等促进胞内释放钙离子，提高血小板的敏感性，进而促进血栓形成，可能直接刺激心肌梗死的发生[15]。在大鼠心肌梗死模型中，使用广谱抗菌药物影响了肠道菌群的构成后，通过影响芳香族氨基酸分解代谢产物和瘦素水平，从而改变了心肌梗死面积[16]。食物中添加植物乳杆菌可显著减少大鼠心肌梗死面积[17]。肠道菌群的组成改变，破坏了肠道黏膜屏障，致使肠道菌群进入体循环，从而增加了心梗后不良心血管事件的发生率。Zhou等[1]研究证实：血液内肠道微生物群（乳杆菌、拟杆菌和链球菌）明显增加的心肌梗死患者，心梗后不良心血管事件发生率明显增加。这个研究还发现使用抗菌药物减轻心梗后小鼠菌群移位，可以减轻其心梗后的全身炎症反应和心肌损伤[18]。肠道菌群及其代谢产物对心肌梗死发生、发展的影响机制极其复杂，需要我们更深入地研究。

总之，肠道菌群组成的改变、肠道菌群的代谢产物都参与了动脉粥样硬化和心肌梗死的发生、发展，评估肠道菌群的组成以及其代谢产物将有助于我们控制动脉粥样硬化和心肌梗死的进展。

2.2 肠道菌群及其代谢产物与心衰

近年来，越来越多的研究证实：肠道菌群与心衰的发生、发展密切相关。有研究发现，肠道血流量较低的心力衰竭患者的免疫球蛋白A-抗脂多糖的血清浓度较高，这与结肠黏膜组织的细菌生长增加相关[19]。Pasini等[20]研究发现慢性心力衰竭患者肠道细菌和真菌数量增加、肠道黏膜屏障破坏，导致其通透性增加。这些研究结果表明，心输出量减少和体循环、肺循环淤血可导致肠道缺血和水肿，肠道黏膜屏障的破坏导致细菌移位和体循环内毒素增加，导致心力衰竭患者发生潜在炎症，进一步加重心衰[21]。此外菌群的失调在也会加重心衰。最近研究发现心衰患者的肠道菌群普氏杆菌减少而活泼瘤胃球菌增加，普氏杆菌的减少可导致机体抗炎作用减弱，其代谢产生的保护性产物丁酸减少也会对心衰有不利影响[22]。未来肠道黏膜屏障功能的评估和肠道菌群种类及数量分析能帮助我们更好的认识心衰的发生及发展。

此外肠道菌群代谢产物与心衰也有着紧密的联系，心衰患者血液中TMAO水平明显高于健康对

照人群,且高TMAO水平的患者预后不良[23]。最近研究表明TMAO直接参与了心衰进展。在动物实验中发现高水平TMAO可促进心衰模型小鼠心肌的重构、纤维化和室腔的扩张,进而加重心衰[24]。此外TMAO直接导致进行性肾小管间质纤维化和功能障碍,可能是心衰进展的潜在机制之一[25]。虽然现在针对代谢产物对心衰影响的机制研究较多,但肠道菌群的构成及代谢产物作用于心衰的具体机制,针对肠道菌群及其代谢产物防治心衰的手段仍有待深入研究。

2.3 肠道菌群及其代谢产物与高血压病

高血压病是冠心病最常见的危险因素。正常比例的肠道菌群对维持机体的健康是必不可少的,肠道菌群的失调与高血压的发生、进展密切相关。研究发现,高血压大鼠模型的肠道菌群中,厚壁菌与拟杆菌比例显著升高[26]。高血压前期和原发性高血压患者与健康对照组相比,肠道菌群的种类、相对丰度都有显著差别[27]。在治疗难治性高血压时通过联用抗菌药物抑制一部分肠道菌群的生长可以起到降压作用[28]。在高血压患者肠道菌群中,引起血浆中肠道脂肪酸结合蛋白和脂多糖显著增多及肠道黏膜屏障功能破坏的革兰氏阴性杆菌增多,而抑制脂多糖和保护肠黏膜的双歧杆菌却在减少,这都加重了高血压患者的慢性炎症反应[29]。这种肠道菌群失调引起的慢性炎症反应,是肠道菌群影响血压调控的一种途径。Wilck等[30]发现高盐饮食的小鼠肠道内乳酸杆菌减少,导致辅助性T细胞17(T helper 17 cell,Th17)升高,并通过驱动自身免疫引起盐敏感性高血压恶化。此外还有研究发现饮食干预可以通过改变肠道微生物群的组成来预防高血压小鼠高血压的进展[30]。菌群比例的失调、肠道黏膜屏障的破坏以及慢性炎症等在血压调控中都起着重要作用,通过调节肠道菌群控制高血压进展为我们提供了控制血压的新途径。

肠道菌群代谢产物对机体血压的调控有着复杂的影响。短链脂肪酸(short chainfatty acids,SCFAs)是微生物在肠道中厌氧发酵的主要产物,主要包括乙酸、丙酸、丁酸等。SCFAs可以通过G-蛋白偶联受体通路激活嗅觉受体78(Olfr78)、G蛋白偶联受体41(G-protein-coupled receptors 41,GPR41)等影响肾素分泌,从而改变机体的血压水平[31]。在人体中发现产生丁酸丰度较高的*Odoribacter*菌属有利于超重和肥胖孕妇血压的调节[32]。此外肠道菌群产生的胆汁酸可以通过增加假性醛固酮水平引起血压升高。将来更精确的代谢产物分析,将帮助我们从众多的道菌群代谢产物中找到关键分子。这些关键的代谢小分子为临床中调控血压提供精确的指导。

3 肠道菌群及其代谢产物的在防治CVD中的潜在价值

肠道菌群及其代谢产物与CVD的发生、发展密切相关。因此,肠道菌群及其代谢产物可能成为治疗和预防CVD的新靶点。目前防治途径主要包括:①饮食干预是降低CVD的有效方法,有研究报道高纤维饮食有助于益生菌的产生,并有助于控制心肌肥大和纤维化[33];②益生菌的添加可以改变肠道菌群的组成和代谢,进而对心血管产生积极影响;③肠道菌群移植是近年来的一个热门技术,有研究证实通过肠道菌群移植可以改善胰岛素抵抗并减轻肥胖患者体重[34]。菌群移植在CVD中的运用将从其治疗糖尿病、高血脂、肥胖等代谢性疾病中汲取更多经验;④在小分子代谢产物方面,使用胆碱类似物1,3-二甲基丁醇,降低TMA和TMAO水平,进而抑制两者升高引起的动脉硬化,也是预防和控制CVD的重要措施[35]。发现菌群代谢产生的关键性小分子将帮助找到精确分子治疗途径。虽然目前研究仍不足以证明肠道菌群直接参与动脉粥样硬化,但这些研究都为我们提供了新的方向和靶点,为防治冠心病提供了新思路。

4 总结与展望

肠道菌群及其代谢产物与CVD的发生发展密切相关。菌群失调、肠道屏障的破坏、肠道菌群移位相关的慢性炎症、TMAO、胆汁酸、SCFAs、IndS等对CVD的影响均被证实,但作用机制仍有待深入研究。此外,如何排除个体肠道菌群的差异、年龄、环境、饮食等影响因素也是研究的难点。随着技术的发展和研究的深入,使我们更加全面而精确地认识肠道菌群及其代谢产物,从而揭示肠道菌群及其代谢产物对CVD的影响机制,最终为CVD的防治找到新途径。

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