微生物群滋养性免疫在结直肠癌发生发展中的作用

王　磊[1],翟嘉威[2],唐　末[1],顾知恩[1],张　彤[1],陈　悦[2],杨宇飞[1]
(1. 中国中医科学院西苑医院,北京 100091; 2. 北京中医药大学,北京 100029)

摘　要:微生物群滋养性免疫通过抑制肠道有害细菌、真菌的定植和异常扩张,在维持人体肠道微生物稳态、正常肠上皮细胞完整性及重塑宿主免疫系统中发挥了极其重要的作用。肠道微生物稳态的破坏及致病微生物的异常扩张所介导的炎症微环境及免疫功能异常已被反复证实与结直肠癌的发生发展具有紧密的联系。全文就微生物群滋养性免疫在抑制结直肠癌发生发展中的作用进行综述,并解释其中关键的作用机制。

关键词:微生物群滋养性免疫;微生物稳态;肠上皮完整;炎症微环境;宿主免疫;结直肠癌
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The Role of Microbiota-nourishing Immunity in the Development of Colorectal Cancer

WANG Lei[1], ZHAI Jia-wei[2], TANG Mo[1], GU Zhi-en[1], ZHANG Tong[1], CHEN Yue[2], YANG Yu-fei[1]
(1. Xiyuan Hospital Affiliated to China Academy of Chinese Medical Sciences, Beijing 100091, China; 2. Beijing University of Chinese Medicine, Beijing 100029, China)

Abstract: By inhibiting the colonization and abnormal expansion of harmful bacteria and fungi in the intestinal tract, microbiota-nourishing immunity plays an important role in maintaining the homeostasis of human intestinal microorganisms, integrity of normal intestinal epithelial cells and remodeling the host immune system. The destruction of intestinal microbial homeostasis and abnormal expansion of pathogenic microorganisms mediated inflammatory microenvironment and immune dysfunction have been repeatedly confirmed to be closely related to the occurrence and development of colorectal cancer. In this paper, the contribution of microbiota-nourishing immunity in inhibiting the occurrence and development of colorectal cancer is reviewed, and the related mechanism is explained.

Key words: microbiota-nourishing immunity; microbial homeostasis; intestinal epithelial integrity; inflammatory microenvironment; host immunity; colorectal cancer

肠道微生物群已经与人类共生了数百万年,大量研究认为肠道微生物群塑造了人体的免疫系统[1-3],并且宿主已经进化出了一种由专性厌氧细菌可发酵纤维保持肠道微生物群落多样性的策略,这被Byndloss等微生物学家定义为微生物群滋养性免疫(microbiota-nourishing immunity,MNI)[4-6]。既往的研究已经证实肠道微生物群落多样性的破坏是结直肠癌发生的早期生物学特征之一[7-8]。伴随着肠道菌群稳态的持续恶化,MNI被极大削弱,各种有害细菌及真菌在肠道内开始大量地定植和扩张,导致肠道炎症的持续进展,肠上皮细胞在持续的炎症微环境中逐渐发生恶性转化,最后不可避免地发展为结直肠癌[9-10]。本文从肠道微生物稳态、肠上皮功能完整、肠道炎症微环境、宿主免疫等方面综述MNI在抑制结直肠癌发生发展中的作用。

1　肠道微生物群稳态及MNI

在健康人类的肠道中定植着多种共生微生物群

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通信作者:杨宇飞,E-mail:yyf93@vip.sina.com

落，主要包括细菌、真菌等，研究表明肠道菌群多样性的稳定是维持机体肠道健康的重要条件[11-13]。人类肠道因其特殊的生理结构及无氧发酵的消化过程，导致肠道菌群主要以专性厌氧微生物为优势菌落，而兼性厌氧微生物及需氧微生物属于劣势菌落，这间接构成了肠道菌群的稳定状态[14-15]。肠道微生物群落多样性促进了人类肠道 MNI 的形成，这也可以被狭义地理解为肠道的非特异性免疫系统[16]。肠道 MNI 的形成可以抑制致病细菌、有害真菌的定植和扩张，这有助于人体肠道微生物的相对稳定[17-18]。肠道 MNI 的削弱在炎症相关性肠病、溃疡性结肠炎、结直肠癌等疾病的发生发展中都具有重要的作用[19-20]。因此，肠道微生物群落的多样性促进了 MNI 的形成并维持其生物学功能的正常，同时正常的肠道 MNI 是重塑肠道菌群的重要调控手段，以上两者共同保持了人体健康的肠道环境(Figure 1)。

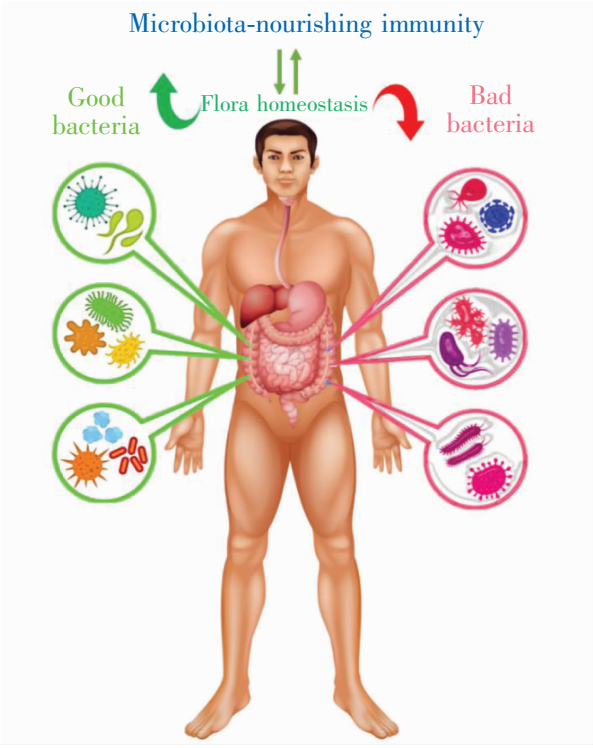

Figure 1　Intestinal flora homeostasis and microbiota-nourishing immunity jointly maintain the health of human intestinal environment

2　MNI 抑制结直肠癌发生发展的机制

2.1　MNI 维持肠上皮完整抑制结直肠癌的发生发展

既往的研究已经证实肠道上皮细胞完整性的破坏是诱发肠道细胞基因突变及恶性转化并最终形成结直肠癌的关键因素之一[21-23]。健康的肠上皮细胞能够通过有益微生物的代谢产物如短链脂肪酸(short chain fatty acids，SCFAs)、纤维素(cellulose，CE)等激活其细胞内的过氧化物酶体增殖物激活受体 γ (peroxisome proliferators-activated receptors-γ，PPAR-γ)通路介导线粒体 β 氧化反应，促进血液来源的氧气在肠上皮细胞内被充分消耗，从而维持了肠道微环境的缺氧状态(Figure 2)，最后保证肠道优势菌(专性厌氧菌)的主导地位，这在维持肠道微生物稳态及维持肠上皮完整抑制结直肠癌的发生发展中发挥了重要作用[24-25]。同时健康的肠上皮细胞通过 PPAR-γ 通路还可以降低肠道微环境中亚硝酸盐、一氧化氮合酶(inducible nitric oxide synthase，i-NOS)等有害物质的含量，并且通过 T-reg 细胞发挥抑制肠道炎症的作用，正如 Byndloss 等在研究中证实下调肠上皮细胞 PPAR-γ 信号通路和减少结肠黏膜中 T-reg 细胞的数量可导致肠道炎症的恶化[26]，这些作用同样在维持肠道微生物稳态及抑制结直肠癌发生发展中具有积极的效应[27]。

许多人类肠道疾病（如炎症性肠病、结直肠癌等)都与肠道 MNI 弱化，导致的肠道微生物群稳态严重破坏有关，其微生物学特征通常是兼性厌氧肠杆菌科扩张及专性厌氧菌减少[28]。事实上在患有严重肠道炎症的患者中(包括炎症性肠病、结直肠癌患者)，均可以观察到肠杆菌科细菌在肠道中的大量扩张[29]。这些定植在人类肠道中的厌氧微生物能够将饮食进入肠道的复杂碳水化合物及粗纤维素等消化为发酵产物，有助于其宿主营养的供给[30]、免疫系统的完整[31]和微生物生态位的保护[32]，用以抵御病原体的入侵和定植[33]。相反兼性厌氧细菌(如上述的肠杆菌科细菌)并不能提供这些有益于宿主的功能，反而通过代谢发酵产物促进肠道炎症的浸润，最终破坏宿主肠上皮细胞的完整性，诱发炎症性肠病和结直肠癌的发生和进展[34-35]。

2.2　MNI 调节肠道炎症微环境抑制结直肠癌的发生发展

炎症微环境是诱发细胞基因突变的关键因素之一[36]，持续的肠道炎症浸润导致肠上皮细胞基因突变的不断积累，最终走向恶性转化的深渊，发展成结

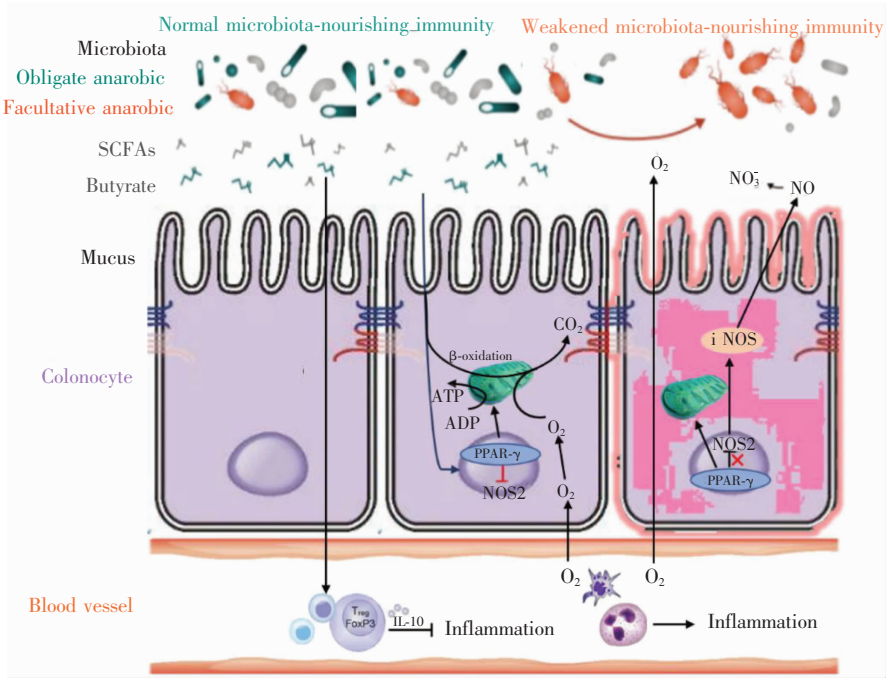

Figure 2　Microbiota-nourishing immunity activates PPAR-γ pathway to maintain intestinal epithelial integrity

直肠癌[37]。肠道炎症微环境的形成往往是因为致病微生物(如致病菌或条件致病菌)激活了肠上皮黏膜的免疫反应，引起免疫细胞募集于病原微生物侵入部位并释放大量的促炎因子，最终形成局部的炎症浸润[38]。肠道微生物群是如此丰富多样，为什么只有部分细菌能够造成肠道炎症微环境呢？解释这个奇怪现象的答案就是肠道 MNI。在人类进化的几百万年期间，人体的免疫系统早已进化出了耐受构成肠道 MNI 的所有共生微生物群落[39]，而对致病微生物则没有这样的作用[40]。因此肠道MNI 的正常在维持肠道健康，抑制肠道发生炎症浸润的过程中发挥了关键作用，同时这也是肠道微生物群重塑人体免疫系统的作用基础[41-42]。

肠道的最基本结构由肠道上皮细胞（由分泌抗微生物多肽 Paneth 细胞和分泌黏液的杯状细胞组成）和上皮内淋巴细胞[分泌免疫球蛋白 A(IgA)阻断细菌黏附上皮细胞，同时能凝集、诱捕和清除细菌，也对细菌的毒力有直接影响]构成[43-44]。正常的肠道微生物群稳态可以维持肠道上皮细胞和上皮内淋巴细胞构成的黏膜层稳定，保证肠道黏膜对病原微生物入侵和感染的抵抗而抑制肠道炎症的发生。既往研究证实肠道微生物群剥离的无菌小鼠具有严重的免疫缺陷，表现为肠道黏液层缺失、Ig A 分泌改变、肠系膜淋巴结形态和功能降低[45-46]。同时共生微生物平衡的破坏可在微生态失调的环境中被观察到，其特征是微生物群多样性和稳定性降低，导致条件致病菌的扩张[47]。微生物稳态受损的地方，局部免疫反应和系统免疫反应破坏黏膜屏障，促使肠道细菌易位和淋巴细胞动员，以改变肠道黏膜内的细胞因子环境和淋巴细胞炎症表型，Th17 细胞和效应 T 细胞活化，导致大量的中性粒细胞募集并浸润(Figure 3)，煽动局部和全身炎症状态[48-49]。总的来说，MNI 维持了肠道菌群稳定，有助于抑制肠道炎症微环境的形成，这在防止结直肠癌的发生发展中具有积极作用[50-51]。

2.3　微生物群稳态重塑宿主免疫功能抑制结直肠癌的发生发展

肠道菌群稳态促进了 MNI 的形成，同时 MNI 抑制有害病原微生物的定植和扩张反馈性地维持了肠道微生物群稳态[52-53]。这一系列相互作用在维持肠道上皮细胞完整性和抑制肠道炎症微环境形成过程中做出了重要的贡献[54]。这也是肠道 MNI 在肠道局部层面抑制结直肠癌发生发展的重要机制。同时功能正常的肠道微生物群稳态能够重塑宿主免疫系统，这并不仅体现在加强宿主固有免疫系统，还表现在激活宿主特异性免疫系统，以阻断病原微生物的定植、扩张和易位，这在预防全身炎症风暴，降低基因突变及致癌风险中发挥了重要作用[55]。

大量研究表明，宿主免疫细胞可通过 CLRs - SYK-CADR9 信号抑制肠道有害真菌和细菌的扩张，降低有害致病菌对肠道上皮细胞的损伤从而降低炎症性肠炎及结直肠癌的发生[56]。胱天蛋白酶募集域蛋白(caspase recruitment domain-containing protein

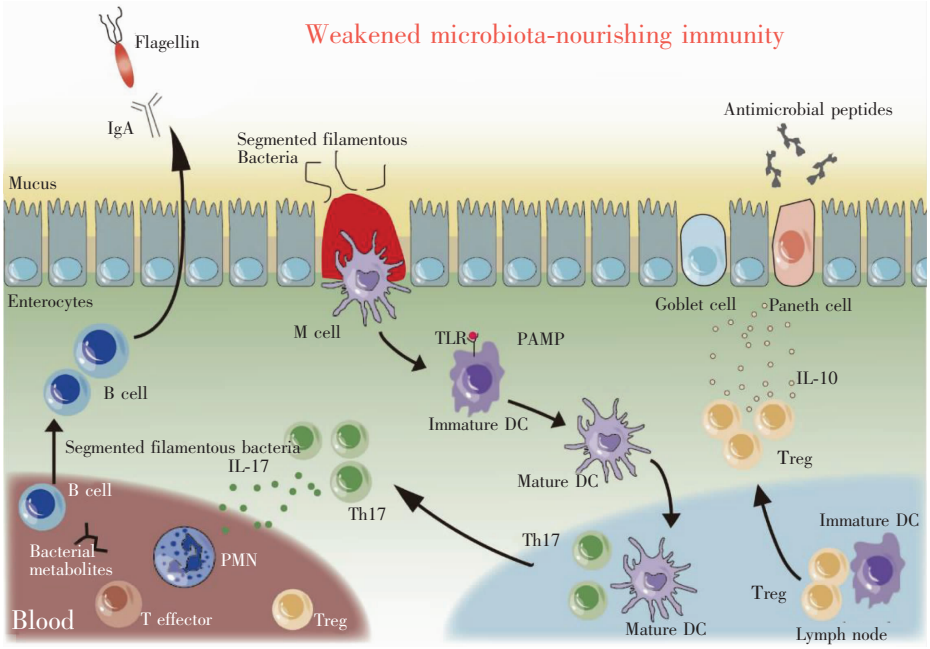

Figure 3　Imbalance of microbial homeostasis promotes the formation of intestinal inflammatory microenvironment

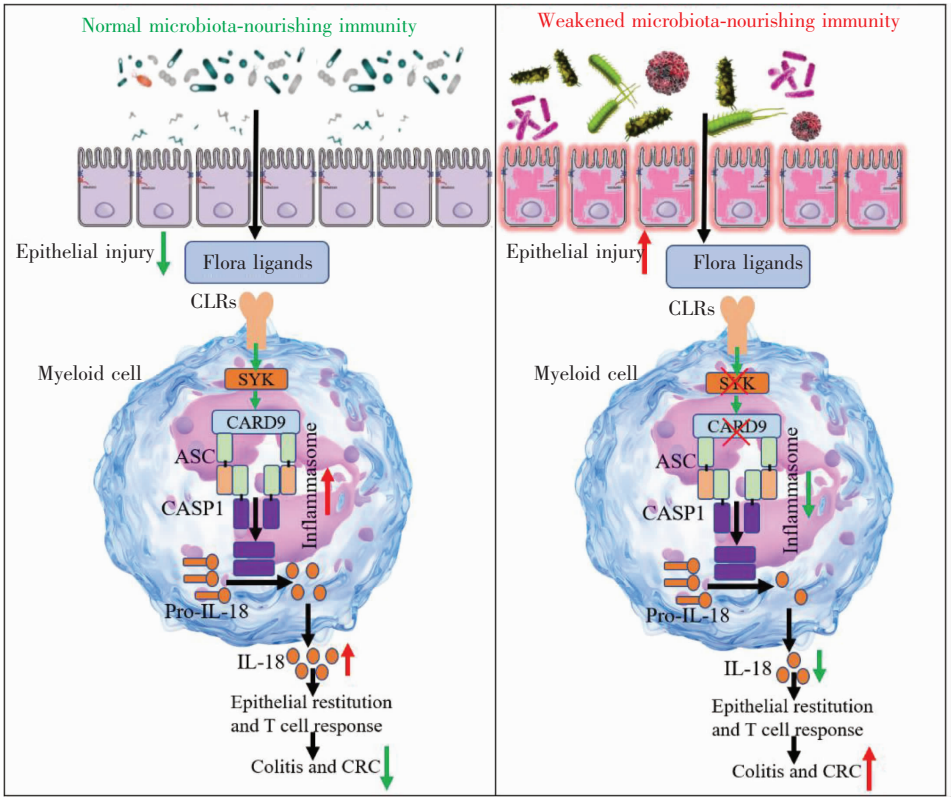

Figure 4　CLRs -SYK-CADR9 pathway inhibits the expansion of harmful intestinal flora and reduces the risk of colorectal cancer

9,CARD9)是一种表达于髓系免疫细胞的关键接头蛋白,是C型凝集素样受体（C-type lectin receptors,CLRs）和脾酪氨酸激酶（spleen tyrosine kinase，SYK）的下游分子[57-58]。当CLRs受体识别细菌、真菌、病毒和内源性危险信号后，刺激SYK磷酸化及CARD9活化，介导炎症小体的形成,促使髓样性免疫细胞释放IL-18，这一系列级联反应最终促进了肠上皮细胞完整性的恢复,并引起效应T细胞的响应,从而降低了炎症性肠病和结直肠癌的发生发展[59]。Wang等[60]在研究中发现CARD9敲除鼠比野生鼠更易患炎症相关性结肠肿瘤，且CARD9敲除鼠肠道中条件致病真菌C. tropicalis的数量显著高于正常鼠。同时CARD9也是NF-κB和MAPK等炎症信号通路的上游分子,在真菌和细菌感染性疾病中发挥了重要的作用[61-62]。而正常的肠道MNI维持了微生物群落的稳态,这是发挥肠道免疫功能,抑制结直肠癌发生发展的前提(Figure 4)。

3　问题与展望

肠道MNI在维持肠道微生物群稳态、保护肠上皮功能完整、抑制肠道

炎症微环境形成、重塑宿主免疫功能等方面均发挥了积极作用，从而抑制炎症性肠病及结直肠癌的发生发展[63-65]。MNI是微生物群与宿主经过数百万年相互作用、相互适应、相互进化而形成的一种特有“免疫模式”，是肠道对致病微生物的重要防御系统，近年来被证实与结直肠癌的发生发展关系密切[66]。本文通过肠道微生物群稳态、肠上皮功能完整、肠道炎症微环境、宿主免疫等角度深入论述了MNI在抑制结直肠癌发生发展中的贡献。我们认为通过评估肠道MNI的强弱，预测结直肠癌的发生及进展风险，针对性地进行调整肠道MNI具有重要的临床价值和意义。

鉴于肠道MNI抑制结直肠癌发生发展是在肠道微生物群稳态、肠上皮功能完整、肠道炎症微环境、宿主免疫等方面发挥作用的，因此，针对结直肠癌高危人群及患者，临床检测有必要动态地评估受检者肠道群分类、肠上皮功能完整度、肠道炎症评分、免疫功能等，用以预测患癌风险及治疗疗效。同时进一步加深对肠道MNI在结直肠癌发生发展中的研究是十分有必要的。

总之，对肠道MNI在结直肠癌中的研究不仅丰富了人们对结直肠癌发生发展的认识，同时为结直肠癌高危人群及患者的预防和治疗提供了新的思路。但是目前对肠道MNI在结直肠癌发生发展中更深层次的研究还尚且不够，无法全面地揭示肠道MNI在结直肠癌发生发展中的深层次科学内涵。并且基于当下的研究进展仍存在一些具有争议性的结论，因此，更为全面深入地研究肠道MNI与结直肠癌发生发展的关系及作用途径和机制，对于结直肠癌高危人群及患者的预防和治疗具有重要意义。其或许能够降低我国结直肠的发病率及死亡率，为减轻国家医疗负担及构建健康中国发挥一定作用。

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