肠道共生菌在弓形虫感染过程中的作用研究进展

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摘要 食入弓形虫卵囊和包囊是动物和人类感染弓形虫的主要途径, 弓形虫进入小肠引发Th1细胞免疫反应和肠内稳态失调, 诱导潘氏细胞呈IFN-γ依赖性缺失, 出现共生菌菌群组成改变和细菌易位, 引起肠道急性炎症反应, 加剧弓形虫的感染和入侵。而无菌小鼠感染弓形虫后, 肠道病理损伤轻微, 且小鼠存活时间较长。此外, 部分肠道共生菌在弓形虫感染过程中发挥分子佐剂的作用, 和黏膜免疫共同维持免疫系统平衡防御病原入侵。可见, 在弓形虫感染过程中, 弓形虫感染进程、潘氏细胞缺失程度和肠道共生菌失调三者之间是相互促进的。该文就肠道共生菌与弓形虫感染的相关研究进行综述。

关键词 弓形虫; 肠道共生菌; 潘氏细胞; 黏膜免疫; Th1; 肠内稳态失调

The Research Progress on the Role of Gut Commensal Bacteria Response to *Toxoplasma gondii* Infection

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Abstract Ingestion of *Toxoplasma gondii* oocysts or cysts is the main pathway for infection of *T. gondii* in animals and humans. *T. gondii* enters the small intestine to initiate Th1 cellular immune response and intestinal dysbiosis, and induces Paneth cell loss, the changes of composition of commensal bacteria and translocation causing an acute inflammatory response in the intestine and increasing the infection and invasion of *T. gondii*. However, after germ-free mice infected with *T. gondii*, intestinal pathological damage is milder and the mice maintain a longer survival time. In addition, some gut commensal bacteria play a molecular adjuvant role in the infection of *T. gondii*. The commensal bacteria and mucosal immunity maintain the balance of immune system to defense against pathogen microbiota invasion. During the infection of *T. gondii*, the process of infection, the degree of Paneth cell loss and the process of gut commensal dysbacteria are mutually promoted. This paper reviews the related researchs on intestinal commensal bacteria and infection of *T. gondii*.

Keywords *Toxoplasma gondii*; gut commensal bacteria; Paneth cell; mucosal immunity; Th1; gut commensal dysbacteria

弓形虫(*Toxoplasma gondii*)是细胞内寄生原虫, 有着复杂的生活史和广泛的宿主谱, 可感染人和各种温血动物[1], 引起人畜共患的弓形虫病。食入弓形虫卵囊和包囊是动物和人类感染弓形虫的主要

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途径。经小鼠试验证实, 弓形虫诱导的Th1细胞(T helper cell type 1)免疫反应和肠内稳态失调可加速回肠炎症反应, 引起小鼠死亡[2], 但在弓形虫感染过程中, 肠道共生群促进弓形虫感染的机制尚不清楚。本文对肠道共生菌稳态失调与弓形虫感染的相互作用进行综述, 为从肠道共生菌角度防治弓形虫病提供依据。

1 肠道共生菌特征

肠道共生菌是人体和动物肠道在长期进化过程中形成相互依存、相互制约的共生微生物, 肠道内共生的微生物约有10^{14}个, 30个属, 500种, 主要门类有放线菌门、厚壁菌门、拟杆菌门、变形菌门等[3-5]。这些共生菌能够降解各种植物多糖和其他膳食物质, 提高宿主消化效率并保证微生物的营养供应。刚出生的动物和人体肠道内无菌, 在出生第一年间, 肠道微生物群在多样性和稳定性方面显著增加, 并且在随后的几年中达到成熟个体水平[6-8]。

共生菌群是人和动物免疫系统的重要组成部分, 共生菌的存在有利于宿主免疫系统的正常运行。肠道共生菌可促进肠道相关淋巴组织和外周淋巴器官(派尔氏结和脾脏)细微结构的发育[9], 还可通过多种方式保护宿主免受病原微生物的感染, 包括与病原微生物竞争黏附受体和营养因子、刺激黏膜产生黏液和抗菌物质[10]。此外, 共生菌具有微生物保守的结构特征, 表达的病原相关分子模式(pathogen-associated molecular patterns, PAMPs)抗原可直接刺激天然免疫受体, 激活肠上皮细胞、树突状细胞(dendritic cells, DCs)和巨噬细胞的表面受体, 从而启动髓样分化因子88(myeloid differentiation factor 88, MyD88)依赖和Toll样受体(Toll-like receptor, TLR)依赖的免疫刺激程序, 产生环氧合酶-2(cyclooxygenase-2, COX-2)、角质细胞生长因子1(keratinocyte growth facter-1, KGF-1)、角质细胞生长因子2(keratinocyte growth facter-2, KGF-2)和血管生成素-4等抗菌物质和可调节的转化生长因子β1(transforming growth facter-β1, TGF-β1)[11-12], 维持肠道内稳态。但正常情况下, 肠道对这些共生菌维持免疫耐受, 然而弓形虫经口感染时, 机体丧失对肠道共生菌的免疫耐受能力[13], 从而促进弓形虫的入侵, 但其机制还未阐明。

2 弓形虫感染对肠道共生菌的影响

2.1 弓形虫感染引起肠道内稳态失调

弓形虫经口感染, 引发的肠道炎症反应与肠道共生菌组成发生变化有关。Me49弓形虫包囊感染第7天, 肠道变形菌门的细菌数量急剧增多, 拟杆菌门细菌减少, 而厚壁菌门的细菌数量基本保持不变。肠道共生菌失调是一过性的, 到弓形虫感染第14天, 肠道共生菌恢复正常[2]。进一步研究发现, 弓形虫感染引起与肠道炎症相关的肠杆菌增多, 特别是大肠杆菌和志贺菌数量增多, 增加Th1细胞因子IFN-γ、IL-12和TNF, 肠道菌群易位到如肠系膜淋巴结、肝脏、肺脏和血液[2,14-15](表1)。

2.2 弓形虫感染诱导潘氏细胞的缺失

潘氏细胞位于肠道隐窝基底部, 是肠道上皮屏障的重要组成部分, 潘氏细胞内的嗜酸性颗粒, 也被称分泌囊泡或致密核心囊泡, 富含α-防御素、溶菌酶、磷脂酶A2、血管生成因子和再生胰岛衍生蛋白3γ(regenerating islet derived protein 3γ, reg3γ), 为小肠干细胞提供小生境以及调控肠道菌群, 保护宿主免受病原入侵[16-19]。潘氏细胞表达较高含量的含有核苷酸结合寡聚化结构域2(nucleotide-binding

表1 Me49株弓形虫包囊灌胃对小鼠肠道共生菌的影响

Table 1 Effect of Me49 *Toxoplasma gondii* cysts on mice gut commensal bacteria by oral

接种剂量 Inoculation dose	小鼠 Mice	增加的细菌 Increased bacteria	减少的细菌 Decreased bacteria	增加的细胞因子 Increased ytokines	细菌易位 Bacteria translocation	参考文献 Reference
50 cysts	Human microbiota associated mice	Aerobic enterobacteria, Enterococci, *Bacteroides/Prevotella* spp., *Clostridium/Eubacterium* spp.	*Lactobacilli* *Bacillus* spp.	IL-12, IFN-γ, NO	Mesenteric lymph nodes, liver, lungs, spleen, blood	[14]
20 cysts	C57BL/6 mice	*Proteus*, *Escherichia coli*, *Shigella*	*Bacteroides*	IFN-γ	Unknown	[2]
1 cyst	Mice harboring a human gut microbiota	Enterobacteria, Enterococci	*Bacteroides*	IFN-γ, TNF	Unknown	[15]

oligomerization domain 2, *NOD2*)、富含亮氨酸重复序列激酶2(leucine-rich repeat kinase 2, LRRK2)、自噬相关基因5(autophagy associated gene 5, *Atg5*)、Atgl6L1等, 可调控潘氏细胞的生理活动。敲除*NOD2*、*Atg5*、受体相互作用蛋白2(receptor-interacting protein 2, *RIP2*)基因, 可减少潘氏细胞自噬, 显著降低小鼠感染弓形虫时的生存率[20-22], 这也证明了潘氏细胞具有直接或间接抗弓形虫作用, 但具体机制尚不清晰。弓形虫感染后, 共生菌和肠道病理学变化的相关研究结果多来自人类和小鼠模型。免疫能力正常的患者食入弓形虫卵囊或包囊, 可引起温和的、可控制的腹泻[23]。强毒力或高剂量弓形虫经口感染健康小鼠, 可启动Th1细胞免疫反应, 引起IFN-γ依赖的免疫反应, 表现为控制或杀灭弓形虫作用, 然而过度激活的Th1反应不利于宿主细胞, 可引起潘氏细胞数量减少[2,24]。弓形虫卵囊或包囊经胃酸及胆汁的作用脱囊, 进入小肠释放子孢子或缓殖子, 攻破肠道上皮屏障进入固有层, 少量肠道共生菌易位进入固有层激活树突状细胞, 同时弓形虫分泌的抑制蛋白激活树突状细胞[25-27], 触发针对共生菌和弓形虫的Th1细胞分化, 引起潘氏细胞数量减少及选择性减少潘氏细胞溶菌酶、防御素[2,24], 而肠道Reg3γ的分泌量并未受到影响。因缺少潘氏细胞及其分泌的抗菌物质, 大肠杆菌数量急剧扩张, 引起肠道菌群易位和内稳态失调, 从而加速了弓形虫病的发展。

弓形虫感染过程中, 潘氏细胞缺失是一种可复性病理反应。研究发现, 弓形虫急性感染期(Me49弓形虫虫株, 感染后7天), 小鼠肠道已检测不到潘氏细胞[2]。形态学证据显示, 弓形虫感染后, 潘氏细胞内颗粒的电子密度降低、细胞器变性、细胞膜消失。潘氏细胞数量减少的原因, 不是单纯的坏死或凋亡, 推测为细胞焦亡或线粒体发生损伤[2]。潘氏细胞缺失是可恢复性病理变化, 弓形虫感染进入慢性期, 潘氏细胞恢复至正常的形态和数量[24,28]。

研究发现, 弓形虫感染的TLR11$^{-/-}$或MyD88$^{-/-}$小鼠, 与野生型小鼠比较, 潘氏细胞及其抗菌肽无明显减少, 变形菌和拟杆菌分布数量也无明显变化, 推测TLR11和MyD88调节弓形虫诱导的潘氏细胞数量减少。进一步研究发现, 抑制TLR11和MyD88下游的效应因子IFN-γ的作用, 可完全阻止潘氏细胞数量减少[2]。弓形虫感染IFN-γ$^{-/-}$小鼠, 肠道弓形虫抗原数量增多, 但潘氏细胞是完整的, 这些结果说明, IFN-γ参与调控弓形虫诱导的潘氏细胞数量减少[2]。此外, 抑制CD4$^+$ T细胞或CD8$^+$ T细胞的作用、机体缺乏白细胞介素1受体1(interleukin-1 receptor 1, IL-1R)或抑制IL-1的作用, 均可抑制潘氏细胞数量减少, 减轻肠道损伤, 提高小鼠生存率, 进一步说明IL-1参与潘氏细胞数量减少[2,29]。感染致病性大肠杆菌可引起潘氏细胞数量减少, 而且随着感染天数的增加, 潘氏细胞数逐渐减少[30], 也证明潘氏细胞数量的变化与肠道菌群有关。

2.3 肠道内稳态失调促进白细胞的增生和渗出

因缺少潘氏细胞及其分泌的抗菌物质, 大肠杆菌数量急剧扩张, 肠道内稳态失调, 肠道细菌易位进入固有层和其他器官, 进而引起TLR11介导的严重回肠炎症反应及病理损伤, 嗜中性粒细胞及单核/巨噬细胞携带弓形虫经血道、淋巴道扩散侵染神经、肌肉及其他组织器官[31], 感染小鼠临床表现为死亡率高[32]。人类对弓形虫易感性低于小鼠, 可能与缺少功能性TLR11有关[33]。弓形虫经口感染, 肠道共生菌群易位促进嗜中性粒细胞、巨噬细胞和树突状细胞的增生和浸润, 这些炎性细胞为弓形虫的复制和扩散提供了便利条件[34]。有研究显示, 嗜中性粒细胞和单核细胞在弓形虫感染病灶附近积聚, 吞噬弓形虫或弓形虫入侵这些炎性细胞, 弓形虫进入细胞后, 能够快速形成纳虫泡, 避免溶酶体对其的杀伤, 这些细胞携带弓形虫在肠道中移动, 加速了弓形虫从肠道固有层扩散到肠外组织[35]。细胞感染弓形虫早期, 细胞体积变大, 但未出现凋亡或坏死, 说明在感染早期, 细胞并未识别弓形虫; 感染后期, 弓形虫不断分裂复制, 超过细胞体积的承受容量, 细胞破裂而发生了死亡[1]。弓形虫能够在炎性细胞内寄生, 逃脱细胞的免疫监视, 不被细胞清除, 其中的具体机制仍不太明确。

3 肠道共生菌对小鼠感染弓形虫的影响

近年来, 肠道共生菌对弓形虫感染的影响逐渐引起学者关注。小鼠经口感染弓形虫, 可增加共生菌与肠上皮的黏附[13], 进而共生菌离开肠道移位进入肠系膜淋巴结、肝脏和脾脏。免疫系统是否能区别共生菌和机会性致病菌, 还不清楚。弓形虫感染过程中, 机体免疫系统识别肠道共生菌, 启动针对共生菌的T细胞特异性免疫反应[13]。无菌动物和抗生素处理的小鼠, 可提高小鼠弓形虫感染时的生存率,

减轻弓形虫引起的肠道病理损伤, 可能与潘氏细胞形态结构完整有关系[2,20]。Burger等[20]进一步研究发现, 肠道共生菌通过诱导IFN-γ触发潘氏细胞中特异性自噬, 缺失自噬蛋白Atg5, 以维持肠内稳态。这些结果表明, 肠道共生菌促进弓形虫感染时肠道炎症的发生, 微生物菌群引发的IFN-γ依赖性潘氏细胞缺失是肠道损伤的基础。虽然这方面的研究多来自小鼠或大鼠的研究结果, 但显示共生菌群可以改变弓形虫感染的进程(表2)。Raetz等[2]分别将大肠杆菌和脆弱拟杆菌移植给无菌小鼠, 然后感染弓形虫, 发现大肠杆菌更易引起肠道病理损伤, 且更易感染弓形虫。Bereswill等[36]研究发现, 非致病大肠杆菌可加重弓形虫感染期间的肠道病理损伤。给小鼠服用动物双歧杆菌后感染弓形虫卵囊发现, 双歧杆菌具有免疫调节功能, 可促进$CD19^+$ B淋巴细胞增殖, 促进小鼠产生较高的抗弓形虫IgG抗体水平, 减轻小肠炎症反应, 减少小鼠大脑弓形虫包囊数量[37]。双歧杆菌和低聚果糖可减少大鼠弓形虫大脑包囊数量, 对抗地塞米松的免疫抑制作用, 延长服用地塞米松的大鼠生存时间[38]。干酪乳酸菌作为弓形虫的疫苗佐剂, 可显著减少弓形虫感染时大脑包囊量, 提高抗弓形虫IgM水平, 对抗弓形虫病[39]。以上研究结果说明, 机会性致病菌有利于弓形虫的复制和入侵, 而乳酸菌不利于弓形虫的感染(表2)。

进一步的研究显示, 无菌的$TLR11^{-/-}$小鼠感染弓形虫, 肠道黏膜不产生白细胞介素12(interleukin-1, IL-12), 但小鼠服用脂多糖后可产生IL-12, 其产量与野生型小鼠无明显差异, 说明脂多糖可与TLR4结合, 激活免疫细胞产生细胞因子, 启动抗弓形虫反应[35]。肠道共生菌可间接刺激机体产生抗寄生虫反应, 激活树突状细胞, 如人类缺少TLR11的功能, 寄生虫不能直接结合TLR11启动炎症反应, 但共生菌可结合树突状细胞的TLR2、TLR4和TLR9激活MyD88途径, 产生IL-12, 从而诱导机体产生抗寄生虫反应[33]。这些研究结果推测, 一部分共生菌在寄生虫感染过程中发挥分子佐剂的作用, 肠道共生菌和黏膜免疫共同维持免疫系统平衡, 病原入侵时, 启动适当的Th1细胞免疫反应, 而不引起明显的肠道病理损伤。

表2 细菌对弓形虫感染进程的影响

Table 2 Effect of bacteria on the process of *Toxoplasma gondii* infection

虫株 Strain	接种数量 Inculation dose	宿主 Host	细菌 Bacteria	细菌含量 Bacterial content	对宿主的影响 Impact on the host	参考文献 Reference
Me49	Oral infection 10^2 oocysts	C57BL/6 mice	*Bifidobacterium animalis*, subsp. *lactis*	1.6×10^7 CFU/day, oral for 15 days	Increased *T. gondii* IgG, increased the number of $CD19^+$ B cells, reduced the amount of brain cysts, alleviated intestinal inflammation	[37]
Me49	Oral infection 10^2 oocysts	C57BL/6j mice	Non-pathogenic *Escherichia coli*	3×10^8~3×10^9 CFU/day, oral for 4 days	Increased the number of T lymphocytes and apoptotic cells, increased ileal inflammatory response, and promoted bacterial translocation to mesenteric lymph nodes, spleen and liver	[36]
BTU 4	Oral infection 10^4 bradyzoites	Wistar rat	*Bifidobacterium animalis*, fructooligosaccharides	2×10^9 CFU/day, oral for 15 days	Reduced the amount of brain cysts	[38]
Me49	Unknown	NIH mice	*Lactobacillus casei*	*T. gondii* antigen adjuvant, intraperitoneal injection	Reduced the amount of brain cysts and increased *T. gondii* IgM	[39]
Me49	Oral infection 20 oocysts	C57BL/6 mice	*Enterobacteriaceae* *Bacteroides fragilis*	Unknown	Severe intestinal inflammation Attenuated intestinal inflammatory response	[2]

4 展望

弓形虫感染后引起肠道内稳态失调, 而发生变化的肠道共生菌也影响弓形虫的复制和入侵。虽然目前有一些关于肠道共生菌与弓形虫感染之间的研究, 但是两者之间的作用机制还不十分清晰。另外, 关于弓形虫感染与病毒、真菌等其他肠道微生物关系的研究还很少, 因此对弓形虫感染后肠道微生物的种类、数量和分布进行研究, 可为从肠道微生物角度研究预防和治疗弓形虫感染提供参考依据。

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