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Hans汉斯

肠道菌群及免疫与胶质瘤关系的研究进展

潘灵峰[1]，茅　敏[1]，宫安静[2*]

[1]青岛大学，山东　青岛
[2]青岛大学附属医院神经外科，山东　青岛
Email: *ajgong@126.com

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摘　要

近年来，肠道菌群与人类疾病的关系研究日益深入，通过不断对肠道菌群的挖掘，发现肠道菌群与人体疾病的发生发展息息相关，并在疾病治疗中起重要作用。肠道菌群对中枢神经系统疾病起重要作用，肠道菌群的失调与阿尔茨海默病、癫痫、脱髓鞘等相关。肠道菌群在机体免疫成熟及调控中起重要作用。肠道菌群在胶质瘤中的研究已有所报道，然而，其与胶质瘤之间的具体关系尚未明确。本文将综述肠道菌群及免疫与胶质瘤之间的关系，为胶质瘤的治疗提供新思路。

关键词

胶质瘤，肠道菌群，肠－脑轴，免疫

Research Progress on the Relationship between Intestinal Flora, Immune System and Glioma

Lingfeng Pan[1], Ming Mao[1], Anjing Gong[2*]

[1]Qingdao University, Qingdao Shandong
[2]Department of Neurosurgery, The Affiliated Hospital of Qingdao University, Qingdao Shandong
Email: *ajgong@126.com

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Abstract

In recent years, the relationship between intestinal flora and human diseases has been further

*通讯作者。

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studied. Through continuous mining of intestinal flora, it has been found that intestinal flora is closely related to the occurrence and development of human diseases, and plays an important role in the treatment of diseases. Intestinal flora plays an important role in disease of central nervous system, and the disorder of intestinal flora is related to Alzheimer's disease, epilepsy, demyelination and so on. Intestinal flora plays an important role in immune maturation and regulation. The intestinal flora has been reported in glioma; however, the specific relationship between intestinal flora and glioma remains unclear. This review will review the relationship between intestinal flora, immune system and glioma, and provide new ideas for the treatment of glioma.

Keywords

Glioma, Intestinal Flora, Gut-Brain Axis, Immune

1. 前言

神经胶质瘤是中枢神经系统常见的原发肿瘤，也是颅内发病率和致死率最高的恶性肿瘤，约占颅内肿瘤的 40% [1]。该病主要特征是肿瘤细胞弥漫性浸润生长，无明确边界，无限增殖，具有高度侵袭性，胶质瘤由于发病位置特殊，目前治疗效果并不理想[2]。其中 IV 级胶质瘤即胶质母细胞瘤恶性程度最高，患者的中位生存期 12~15 个月[3]。目前采用单一手段治疗恶性脑胶质瘤的疗效较差，复发率较高，手术后采用化疗、免疫治疗、化疗联合放疗、化疗联合小分子靶向药物等联合治疗手段可以有效延缓患者复发[4]，但化疗药物更新较慢，目前能够有效抑制恶性脑胶质瘤且耐药性较小的化疗药物较少[5]。由于肿瘤存在免疫耐受，导致免疫治疗难以持续性发挥抑制胶质瘤作用。目前，对胶质瘤的治疗还没有有效的手段能够显著延长生存期及降低复发率。肠道菌群与机体的各种器官存在不同程度、不同方式的联系，且在器官发生发育及疾病的发生发展中起着重要作用。目前已成为多种疾病研究的热点，在其它系统肿瘤病变中研究较为广泛，如胃癌、肝癌、乳腺癌及肺癌中有较多的研究，但在胶质瘤的研究中较为有限。作为远离肠道的高级中枢，肠道菌群及免疫与中枢之间存在复杂的机制。希望进一步阐述胶质瘤与肠道菌群及免疫之间的关系能够为胶质瘤的治疗提供更多新方案。

2. 肠道菌群

肠道菌群被认为是人体的一个隐藏的代谢器官，提供宿主所缺乏的生化途径。平衡饮食和热量限制[6]促进健康微生物群的生长，降低炎症反应促进长寿。人类消化道中大约聚集有 10 万亿余个微生物，约为人体体细胞和生殖细胞总数量的 10 倍[7]。微生物的种类超过 1000 种，编码了 3 百万余个特异基因，达人类基因基因组编码数量的 150 多倍[8] [9]。人体肠道菌群是由益生菌、条件致病菌和病原菌组成的复杂微生态系统，主要为厚壁菌、拟杆菌、放线菌、变形菌等六门组成，其中前两种为主要优势菌群。肠道菌群广泛分布于肠道粘膜，且数量和种类维持着动态平衡，通过保护肠道、营养消化与吸收以及调节机体代谢状态，参与机体稳态调节，从而维护人体健康。

目前，肠道菌群已成为疾病研究的焦点，包括癌症、炎症、代谢、心血管、自身免疫、神经和精神成分的疾病[10]。当宿主发生肠道感染、抗生素、生活方式以及饮食变化时，肠道菌群失衡或移位，或将导致肠道炎症、免疫性疾病、系列代谢性疾病，甚至神经性疾病、癌症等疾患。功能失调的肠道菌群的

致病作用远大于遗传缺陷对发病机制的贡献，饮食结构对肠道菌群变化的贡献远高于基因型[11]。肠道菌群对疾病的发生发展起着至关重要作用，深入研究肠道菌群，有利于早预防、早诊断、提高疾病的治疗效果。

3. 肠道菌群与免疫的关系

从质量和细胞数量而言，胃肠道是人体最大的免疫器官；它拥有最高的微生物密度，通过向免疫系统提供全谱抗原[12]，刺激粘膜(派尔集合淋巴结和固有层)中淋巴组织和包括脾脏、胸腺和淋巴结在内的全身淋巴组织的成熟，从而滋养免疫[6]。肠道菌群对免疫细胞具有持续性的作用，淋巴组织中免疫细胞的稳定扩增和维持依赖于肠道微生物[13]。肠道菌群对免疫的作用在无菌条件下的动物的免疫系统不成熟中得到了明确的证明，这些动物既没有发育出佩耶斑块，也没有发育成成熟的功能性浆细胞[14]。

肠道菌群影响人体免疫机制复杂，包含先天性和适应性免疫反应[15]，先天性免疫反应主要是通过影响炎症小体、炎性细胞因子、小胶质细胞、Toll 样受体等导致机体炎症恶化；适应性免疫反应主要是通过影响如 T 细胞、肥大细胞等加重机体的炎症情况[16]。肠道菌群与免疫系统之间的通信可通过同源相互作用以及通过其分泌的代谢组(包括色氨酸代谢产物、多酚代谢产物和短链脂肪酸生产)发生，这些代谢组可调节免疫细胞的反应性[17]。合生元特异性多酚代谢物可能通过涉及色氨酸的代谢产物激活芳香烃受体的机制改变 Th17/Treg 比率[18]，短链脂肪酸影响维生素 D 的吸收，而维生素 D 受体允许肿瘤基质的重新编程[19]，Toll 样受体和基于 NOD 样受体的治疗可促进微生物群激活先天免疫系统从而增强抗癌反应[20] [21]。肠道菌群的状态决定了机体免疫反应、肿瘤微环境的结构和对肿瘤免疫治疗的反应，并且特定的肠道菌群可以增强免疫抗肿瘤治疗方式的效果[22] [23] [24]，应答者的微生物群可诱导 CD4 和 CD8 T 细胞产生干扰素(IFN)-γ 和颗粒酶 B，有助于招募抗肿瘤巨噬细胞。肠道生态失调，细菌生态系统的不平衡导致细菌的过度表达，有利于慢性炎症和免疫抑制的进行性加重[25]。肠道菌群通过调节外周骨髓细胞、T 细胞和肥大细胞来影响大脑性疾病[26]，包括中风、帕金森病、肌萎缩侧索硬化症和多发性硬化症等与脑免疫功能相关的中枢神经系统病变[27]-[32]。肠道菌群对免疫的影响机制目前尚未研究清楚[33]，还需要大量研究来了解肠道微生物组与免疫系统之间的具体调控机制，尤其在癌症的免疫方面，能够为癌症的免疫治疗开辟新的模式。

4. 肠道菌群与中枢神经的关系

肠道菌群的组成和行为一方面受大脑的调控[34]，另一方面肠道菌群借助内分泌系统、免疫系统、神经内分泌及代谢系统在内的多种通路参与对大脑的调节，组成“肠道菌群－胃肠－脑轴”，而肠道菌群可以构成肠神经系统，它既可以不依赖中枢神经系统而独立行使功能，又能够受中枢神经系统的双重调节。肠神经系统被称为“第二大脑”，亦成为“肠脑”[35]，通过迷走神经与大脑组成“肠道菌群－肠神经－迷走神经－脑”信息传递途径，从而行使重要的生理功能[36]。

肠道菌群可影响中枢炎症性疾病。Wekerle 及其同事证明共生肠道菌群控制迁移到中枢神经系统并引起炎症和组织病理学的自动反应性 T 细胞[37]。发现多发性硬化相关的肠道微生物群的改变，确定了参与调节效应细胞和调节性 T 细胞的微生物群的特定成分[38] [39] [40]。由共生菌群控制的抗炎 B 细胞将肠道迁移到中枢神经系统以限制多发性硬化的组织病理学[41]。

肠道菌群可影响血脑屏障结构的完整性。Braniste 及其同事[42]发现，肠道菌群的缺乏与闭合蛋白-5 和咬合蛋白水平的降低以及血脑屏障通透性的增加有关。这种表型从发育到成年持续存在，血脑屏障功能可能依赖于一生中与肠道菌群的持续沟通。同时发现，将无菌小鼠暴露于酪丁酸梭菌(一种产生丁酸盐的细菌菌株)或仅给予丁酸钠可上调 TJ 蛋白表达并恢复血脑屏障紧密性[42]。分离负责肠道菌群调节血脑

屏障完整性的因子可能提供修复疾病中血脑屏障渗漏的新方法。

肠道菌群可以间接影响大脑奖励系统。大脑的奖赏系统是情绪过程中的一个关键回路，在一项小鼠的研究中，奖赏系统减弱了主要免疫部位骨髓的去甲肾上腺素能输入，骨髓源性抑制细胞的免疫抑制作用减弱，从而产生抗肿瘤反应缩小肺肿瘤[43]。

5. 免疫与胶质瘤的关系

大脑受到血脑屏障的保护，血脑屏障由连接紧密的特殊内皮细胞和神经胶质细胞(星形胶质细胞脚板和基底膜的结合)组成[44]。血脑屏障可以维持中枢神经系统的稳态，并限制病原体的侵入。当中枢神经系统处于病理状态下，血脑屏障被破坏，更多血液循环中的免疫细胞可进入中枢神经系统。胶质瘤作为中枢恶性肿瘤，其血脑屏障结构常被破坏，且级别越高，破坏越严重。胶质瘤可产生肿瘤抗原诱导免疫反应，中枢神经系统的适应性免疫反应主要通过免疫细胞触发：抗原呈递细胞、靠近脑膜的树突状细胞、中枢神经系统固有的抗原呈递细胞－小胶质细胞[45]。其中小胶质细胞作为胶质瘤的免疫细胞，在胶质瘤中激活，与血脑屏障分解和炎症有关，可能是血脑屏障功能障碍的原因和后果[46]。血脑屏障的破坏使得脑胶质瘤中可以见到肿瘤浸润的淋巴细胞，并且在胶质母细胞瘤中最为明显。小胶质细胞在经典激活的M1 途径中，主要释放促炎细胞因子，如白细胞介素-1b 和肿瘤坏死因子-a [47]，小胶质细胞分泌的肿瘤坏死因子-a 对抗体的反应导致脑内皮细胞中 MHC I 类的上调，这反过来为 T 细胞迁移到大脑提供了一种机制[48]，小胶质细胞在胶质瘤中破坏血脑屏障同时影响外周 T 细胞的迁移。

胶质瘤免疫治疗局限性的一个关键因素是免疫抑制肿瘤微环境，它抵消了宿主防御活动[49]。胶质瘤导致的机体免疫抑制主要来源于肿瘤细胞对 T 细胞免疫反应的影响，包括具有免疫抑制功能的调节性 T 细胞在内的 T 淋巴细胞亚群在胶质瘤组织及外周血中的异常表达。同时，胶质瘤分泌负责招募天然免疫细胞(如小胶质细胞和单核细胞)的分子，这些细胞约占整个肿瘤的 30%，其存在与患者的生存率呈负相关[50]。浸润性免疫细胞组中自然杀伤细胞对胶质瘤细胞具有直接的细胞毒性活性[51]，它们的缺失阻碍了 IL-15 和环境刺激在胶质瘤中发挥的抗癌作用[52]。

6. 肠道菌群与胶质瘤的关系

星形胶质细胞是大脑中最丰富的神经胶质细胞，能够通过控制神经递质和离子浓度来维持神经微环境的稳态平衡，通过调节突触传递和调节免疫反应来帮助支持和保护神经元，能够整合相邻胶质细胞、神经元、血管和免疫细胞的信息来调节神经的兴奋性以及突触形成，在脑代谢中发挥了重要的作用[53]。肠道菌群可通过激活星形胶质细胞芳香烃受体(AHR)的微生物代谢来调节星形胶质细胞活性，星形胶质细胞中 AHR 的特异性失活是单核细胞基因表达 NF-kB 转录反应的负调节因子，促进小胶质细胞活化，神经毒性外周单核细胞向中枢神经系统募集和星形胶质细胞固有的神经毒性活性[54]。微生物群扰动研究表明，肠道共生菌群降解色氨酸产生的代谢物到达中枢神经系统，并激活星形胶质细胞中的 AHR 以限制中枢神经系统炎症[54]。小胶质细胞表达 AHR 和条件敲除小鼠显示 AHR 限制了小胶质细胞中 NF-kB 的激活[54]。由于微生物激动剂也能激活小胶质细胞 AHR，肠道菌群通过该机制调节小胶质细胞和星形胶质细胞反应以及这些中枢神经系统驻留细胞之间的相互作用。AHR 信号可调节外周 T 细胞分化[55] [56]。此外，招募到中枢神经系统的外周 T 细胞控制星形胶质细胞和小胶质细胞反应。芳香烃受体(AHR)配体，包括色氨酸代谢物，如犬尿氨酸、靛蓝、没食子酸、前列腺素和二十烷酸等。Opitz 等人报道，胶质母细胞瘤中的色氨酸 2,3-双加氧酶导致犬尿氨酸的产生，犬尿氨酸以自分泌方式发挥作用，增强肿瘤的侵袭性和复制[57] [58]。Gramarzki 等人报道胶质瘤细胞中的 AHR 驱动 TGF-β 的表达，AHR 信号促进胶质瘤中的免疫抑制微环境[59]。在肿瘤相关巨噬细胞(TAM)中检测到 AHR 表达，它们占胶质母细胞瘤浸润细

胞的 30%以上。Takenaka 等人最近表明，AHR 激活在胶质母细胞瘤 TAM 中诱导抗炎表型[60]。此外，AHR 驱动 TAM 中 CD39 的表达，从而促进 CD8 细胞功能障碍[60]。这些发现提示了肠道微生物可通过调节 AHR，从而调节胶质瘤的发生发展，在胶质瘤免疫逃避中发挥了重要作用，具有作为治疗靶点的潜力。

在小鼠实验和胶质瘤患者肠道菌群分析中发现，胶质瘤小鼠和胶质瘤患者中的肠道微生物在 β 多样性、厚壁菌/类杆菌(F/B)比率以及疣状芽胞菌门和阿克曼菌属的增加方面表现出显著差异，并且，在小鼠中，随着胶质瘤的发展，肠道生态出现失调[61]。另外，Giuseppina D'Alessandro 等人报告了用两种抗生素治疗胶质瘤小鼠后肠道菌群的变化及机体免疫变化：家族水平的肠道微生物群种类及数量的减少；减少了细胞毒性 NK 细胞亚群；改变了小胶质细胞中炎症和稳态蛋白的表达。发现两种抗生素治疗小鼠后，小鼠颅内胶质瘤的生长显著增加，与未用抗生素表现出明显差异。这些结果表明，长期服用两种抗生素会改变微生物群的组成，并有助于调节脑免疫状态，从而为胶质瘤的生长铺平道路[62]。用抗生素治疗小鼠胶质瘤后，肿瘤的发生发展说明肠道微生物与胶质瘤存在着紧密联系，在其发生发展中起着重要作用，然而，由于对于肠道菌群的复杂性及胶质瘤的特殊性，肠道菌影响胶质瘤的具体机制目前尚未研究清楚。

7. 展望未来

肠道菌群与中枢神经有密切的关系，并对机体免疫的成熟、分化及反应性有着重要作用。随着近年来对肠道菌群的深入研究，发现与胶质瘤存在着密切联系，这为胶质瘤的治疗提供了一个新思路。然而，肠道菌群具体调节免疫来影响胶质瘤的机制尚未清楚，还需要更多的研究来填补人类肠道微生物群组成部分以及它们如何相互作用对免疫反应及胶质瘤的治疗作用，尤其在肠道代谢产物通过免疫途径影响外周及胶质瘤微环境免疫。同时，肠道菌群的研究能够为胶质瘤免疫治疗提供更多方案，以期通过调节肠道菌群从而治疗胶质瘤。

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