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肠道菌群与HER2阳性乳腺癌的相关性研究进展

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摘　要

人表皮生长因子受体2 (HER2)阳性乳腺癌作为侵袭性强、预后较差的乳腺癌亚型，其治疗耐药性与复发转移问题亟待突破。近年来，肠道菌群与肿瘤微环境的交互作用成为研究热点，其通过调控药物代谢、重塑免疫应答及调节炎症微环境等机制，显著影响HER2阳性乳腺癌的发生发展与治疗反应。本文将从肠道菌群与HER2阳性乳腺癌的关系、肠道菌群与HER2阳性乳腺癌的化学治疗、肠道菌群与抗HER2靶向治疗、肠道菌群在HER2阳性乳腺癌中的潜在应用等方面进行文献综述。

关键词

肠道菌群，HER2阳性乳腺癌

Research Advances in the Association between Gut Microbiota and HER2-Positive Breast Cancer

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Abstract

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer, an aggressive subtype

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with poor prognosis, presents a critical challenge due to therapeutic resistance, recurrence, and metastasis. In recent years, the interaction between the gut microbiota and the tumor microenvironment has emerged as a significant area of research. The gut microbiota significantly influences the development, progression, and treatment response of HER2-positive breast cancer through mechanisms such as modulating drug metabolism, reshaping immune responses, and regulating the inflammatory microenvironment. This review aims to provide an overview of the relationship between the gut microbiota and HER2-positive breast cancer, its impact on chemotherapy, its role in anti-HER2 targeted therapy, and the potential applications of gut microbiota in HER2-positive breast cancer.

Keywords

Gut Microbiota, HER2-Positive Breast Cancer

1. 引言

乳腺癌是全球女性中最常见的恶性肿瘤之一，其异质性显著，不同分子亚型的乳腺癌在发病机制、治疗反应及预后方面存在显著差异。其中，人表皮生长因子受体 2 (HER2)阳性乳腺癌约占所有乳腺癌的20%~25%，以其侵袭性强、预后较差而备受关注[1] [2]。随着靶向治疗的普及应用，HER2 阳性乳腺癌患者的生存率得到了显著提升[3]，但仍有部分患者面临耐药性或肿瘤复发转移的问题。因此，探索新的治疗靶点和辅助策略成为当前研究的热点。

同时，肠道菌群作为人体内最复杂的微生态系统之一，已被证实可通过调控药物代谢与吸收、炎症反应以及肿瘤免疫等途径，影响癌症的发生发展与治疗反应[4] [5]。更多的研究表明，肠道菌群的组成和功能变化与乳腺癌的发生、进展及治疗反应有关[6]-[9]。特别是在免疫治疗和化疗领域，肠道菌群的调节作用引起了广泛关注。然而，目前关于肠道菌群与 HER2 阳性乳腺癌之间具体联系及其潜在机制的研究尚处于起步阶段，迫切需要进一步深入探索。

本文旨在综述肠道菌群与 HER2 阳性乳腺癌之间的相互作用及其潜在机制，探讨肠道菌群在 HER2 阳性乳腺癌诊断和治疗中的潜在应用价值，以期为未来研究提供新的思路和方向。

2. 肠道菌群与 HER2 阳性乳腺癌

人类肠道微生物群落构成了一个复杂的生态系统，由数万亿个微生物组成。宿主与这些微生物群落之间建立的共生关系，在维持肠道微生态平衡中扮演着至关重要的角色。一旦这种共生关系遭到干扰，可能会触发宿主的病理生理变化，进而导致多种疾病的发生[10]。既往研究表明，乳腺癌患者与健康对照组相比，其肠道微生物群落在物种组成和功能特征方面呈现显著差异[11]。Wu 等人的研究发现，HER2 阳性乳腺癌患者的粪便样本以较低的 α 多样性以及厚壁菌门中的某些属(如 *Clostridium*，*Blautia*，*Coprococcus*，*Ruminococcus* 等)的水平较低为特征；而与 HER2 阴性患者的粪便样本相比，它们的拟杆菌属(*Bacteroidetes*)更多[12]。Yang 等人的研究发现，在 HER2 阳性乳腺癌患者的肠道中，属于厚壁菌门(如 *Megasphaera*，*Lachnospiraceae*，*Flavonifractor* 和 *Eubacterium*)、拟杆菌门(如 *Barnesiellaceae* 和 *Alloprevotella*)、变形菌门(如 *Moraxellaceae*，*Acinetobacter*，*Pseudomonadales* 和 *Burkholderiaceae*)和放线菌门的(*Enorma*)这些细菌的比例更高[13]。

这些研究提示，特定的肠道菌群特征可能与 HER2 阳性乳腺癌的发生相关。然而，尽管多项研究观察到 HER2 阳性乳腺癌患者的菌群特征变化，但要确立其特异性微生物诊断标志物，仍然任重道远。

3. 肠道菌群与 HER2 阳性乳腺癌的化学治疗

当前 HER2 阳性乳腺癌的临床治疗主要采用多学科综合治疗模式，涵盖手术切除、放疗、化疗及抗 HER2 靶向治疗等方案。值得注意的是，肠道菌群不仅能通过调控化疗药物的生物利用度、毒性和疗效来影响患者预后，其自身在化疗后发生的组成变化同样会对治疗效果产生重要影响。具体而言，蒽环类药物对不动杆菌属具有抑菌作用[14]，而吉西他滨具有杀菌特性[15]。环磷酰胺会损伤肠道黏膜，使其通透性增加，从而使细菌进入血液[16]。甲氨蝶呤会引起与腹泻有关的细菌的多样性和丰度发生变化[17]。在乳腺癌治疗中，使用蒽环类药物、环磷酰胺和紫杉类药物进行新辅助治疗会改变乳腺肿瘤微生物组成，使其 α 多样性降低，同时增加假单胞菌属(*Pseudomonas*)含量，其代谢产物可以增强化疗的疗效[18]。此外，雌激素受体调节剂(如他莫昔芬和雷洛昔芬)联合抗 HER2 药物治疗 HER2 与雌激素受体阳性的乳腺癌患者时，可以改变肠道微生物组的组成[19]-[21]。

肠道菌群在调节化疗毒性方面也起着重要作用。例如，多柔比星诱导的肠道损伤和心脏功能障碍与肠道微生物的失衡有关[22] [23]；而紫杉类药物治疗会减少嗜黏蛋白阿克曼菌(*A. muciniphila*)的丰度，从而破坏肠道屏障完整性，导致神经病变加重[24]。此外，甲氨蝶呤的毒性也受到肠道微生物的调节：肠道微生物可通过 TLR2 信号通路调控多药转运蛋白 ABCB1/MDR1 p-gp 的表达，从而减轻化疗诱导的小肠损伤[25]。因此，一些研究尝试了利用营养干预措施来改善紫杉类及一般化疗药物的不良反应[26] [27]。

除了调节药物代谢和毒性外，肠道微生物还通过直接作用或调节免疫反应来影响药物的疗效。研究表明，阿霉素的抗癌活性可能与肠道特定微生物的缺失相关：在清除菌群的小鼠模型中阿霉素仍保持治疗效力，但经狄氏副拟杆菌(*Parabacteroides distasonis*)定植后，其抗癌效果显著降低[28]；环磷酰胺的抗肿瘤作用是通过革兰氏阳性菌移位至肠道次级淋巴器官所介导的，该过程可激发 Th17 和 Th1 免疫应答[28]。Daillere 等人的研究发现，海氏肠球菌(*Enterococcus hirae*)和人肠道巴恩斯氏菌(*Barnesiella intestini-hominis*)可通过促进肿瘤微环境中细胞毒性免疫细胞的聚集，从而增强环磷酰胺的抗肿瘤疗效[29]。值得注意的是，共生菌特异性记忆 T 细胞与肿瘤相关抗原之间的交叉反应，可能构成了肠道微生物对环磷酰胺疗效影响的基础[30]。

4. 肠道菌群与抗 HER2 靶向治疗

目前，以 HER2 为靶点的治疗策略已经构建起一套完整的药物体系，覆盖了从早期新辅助治疗到晚期姑息治疗的整个疾病管理过程。具体而言，临床可用的 HER2 靶向药物主要包括：(1) 单克隆抗体类药物，如曲妥珠单抗及其衍生物帕妥珠单抗；(2) 小分子酪氨酸激酶抑制剂，包括第一代拉帕替尼和第二代奈拉替尼；(3) 抗体药物偶联物，如恩美曲妥珠单抗和德曲妥珠单抗。这些药物通过不同的作用机制实现对 HER2 信号通路的精准调控，显著提高了治疗效率。

尽管 HER2 阳性乳腺癌患者的临床预后已得到显著改善，但患者对靶向药物的反应仍存在高度异质性。即使在根治性治疗后，患者仍可能面临疾病复发或进展的风险。宿主免疫反应在抗 HER2 单克隆抗体的活性中起着关键作用。特别是曲妥珠单抗通过与 HER2 受体特异性结合，不仅抑制 HER2 受体二聚化及其下游信号通路传导，其 Fc 段还可与自然杀伤细胞(NK 细胞)、巨噬细胞及中性粒细胞等免疫效应细胞表面的 Fc 受体结合，进而激活抗体依赖性细胞毒性或吞噬作用。这一机制显著增强了肿瘤抗原在免疫微环境中的暴露程度，促进抗原呈递细胞对抗原的摄取、加工和呈递过程[31]。

在一项 HER2 阳性乳腺癌的临床前模型研究中，Di Modica 等研究了肠道微生物对曲妥珠单抗的抗肿

瘤疗效的影响。抗生素诱导的肠道菌群失调能够显著增加癌旁组织中炎症细胞浸润，且能够上调炎症因子表达；不同的肠道菌群状态可影响抗 HER2 靶向药物曲妥珠单抗的治疗效果；将患者的粪便微生物群移植到 HER2 阳性乳腺癌小鼠模型中，小鼠重现了患者对曲妥珠单抗的治疗反应[32]。这一发现为后续研究提供了重要方向，提示应深入探讨特定肠道微生物及其代谢产物在调控 HER2 阳性乳腺癌治疗应答中的潜在机制及临床应用价值。

5. 肠道菌群在 HER2 阳性乳腺癌中的潜在应用

肠道菌群在乳腺癌进展和治疗应答中的调控作用已逐渐得到证实，这为开发基于微生物组的干预策略提供了理论依据。通过靶向调控肿瘤相关微生物群的关键组分或调节肠道菌群稳态，有望实现降低抗肿瘤治疗相关毒性、增强治疗敏感性，并最终改善乳腺癌患者的远期预后。目前，微生物组调控主要包含以下几种方法：(1) 粪菌移植，该技术已在肿瘤免疫治疗领域开展临床研究[33]-[35]；(2) 特定功能菌群移植[36] [37]；(3) 基于益生元补充或膳食干预的菌群调节策略[38]；(4) 广谱或选择性抗生素介导的菌群耗竭方案[39]。

尽管针对微生物组与 HER2 阳性乳腺癌关联的研究尚处于初步探索阶段，但现有证据显示，饮食干预作为调节肠道微生物平衡的重要因素，再结合益生菌和益生元的补充，可能为 HER2 阳性乳腺癌风险的调控以及治疗效果的提升提供一条潜在的干预路径。

6. 总结与展望

近年来，关于肠道菌群与 HER2 阳性乳腺癌相互关联的研究取得了显著进展，本综述总结了肠道菌群在 HER2 阳性乳腺癌发生、治疗应答及预后调控中的多维作用。特定菌群特征可能作为 HER2 阳性乳腺癌的潜在生物标志物，而菌群干预策略在增强化疗敏感性、减轻靶向治疗毒性方面展现出独特潜能。尽管研究前景广阔，该领域仍面临以下关键挑战：现有证据多源于临床前模型或小样本研究，缺乏针对 HER2 阳性乳腺癌的大规模多中心队列验证，且个体化差异(如饮食、遗传背景)对菌群干预效果的影响亟待量化。总之，肠道菌群作为可调控的“治疗靶标”，为突破 HER2 阳性乳腺癌耐药瓶颈提供了新思路。通过融合微生物学与肿瘤免疫学等多学科手段，有望实现从机制探索到临床应用的跨越，最终推动个体化抗癌策略的革新。

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