·特约综述·

细菌及其代谢物影响乳腺癌发展及治疗的研究进展

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摘　要：乳腺癌是女性最常见的癌症之一，严重威胁女性健康。早期诊断和精准化治疗乳腺癌有助于改善患者预后。本文总结了细菌及其代谢物对乳腺癌发展与治疗的研究现状，详细探讨了细菌及其代谢物在乳腺癌发展及干预中的作用与机制。这些机制包括调控炎症和免疫反应、损伤DNA以及调控细胞生物学特征等。工程菌因其在靶向肿瘤和激活免疫方面的天然优势，近年来已成为乳腺癌治疗领域的热点之一。本文进一步对工程菌在乳腺癌治疗中的研究进展进行了总结，旨在为制定靶向治疗策略及改善患者预后提供重要参考依据。虽然细菌及其代谢物通过多种机制影响乳腺癌的发展与治疗，并能够增强癌症治疗效果，减轻治疗不良反应，但细菌在抗乳腺癌治疗的临床应用中仍面临诸多挑战。细菌组成的高度个体化导致治疗缺乏普适性，而细菌与宿主之间复杂的相互作用进一步增加了研究难度。未来亟需更深入地探索细菌及其代谢物影响乳腺癌发展及治疗的机制，推动细菌在抗乳腺癌治疗中的临床应用。

关键词：乳腺癌；细菌；代谢物；肿瘤；治疗
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Research Progress in Bacteria and Their Metabolites Influence on the Development and Treatment of Breast Cancer

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Abstract: Breast cancer is one of the most common cancers in women, which seriously threatens women's health. Early diagnosis and precise treatment of breast cancer are helpful to improve the prognosis of patients. This article

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summarizes the research status of bacteria and their metabolites in the development and treatment of breast cancer, and discusses in detail the role and mechanism of bacteria and their metabolites in the development and intervention of breast cancer. These mechanisms include regulation of inflammation and immune response, DNA damage, and regulation of cell biological characteristics. Engineering bacteria have become one of the hotspots in the field of breast cancer treatment in recent years due to their natural advantages in targeting tumors and activating immunity. This article further summarizes the research progress of engineered bacteria in the treatment of breast cancer, aiming to provide an important reference for formulating targeted treatment strategies and improving the prognosis of patients. Although bacteria and their metabolites affect the development and treatment of breast cancer through a variety of mechanisms, and can enhance the therapeutic effect of cancer and reduce the adverse effects of treatment, the clinical application of bacteria in anti-breast cancer therapy still faces numerous challenges. The highly individualized composition of bacteria leads to the lack of universality of treatment, and the complex interaction between bacteria and host further increases the difficulty of research. In the future, it is urgent to further explore the mechanism of bacteria and their metabolites affecting the development and treatment of breast cancer, and promote the clinical application of bacteria in anti-breast cancer treatment.

Key words: breast cancer; bacteria; metabolites; tumor; treatment

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作为女性中最常见的癌症类型,乳腺癌严重威胁女性健康。2020年全球因乳腺癌死亡的患者高达68.5万,占女性癌症死亡人数的16%[1-2]。虽然现有研究表明与乳腺癌发展相关的危险因素包括年龄、肥胖、激素水平[3]和乳腺癌家族史等[4],但乳腺癌的发展机制尚未完全阐明。近年来,越来越多的研究揭示了菌群组成的变化与多种癌症的发展及治疗效果存在相关性[5-7]。乳腺在早期被视作无菌组织,但伴随着微生物学检测技术的进步,证明了乳腺组织内存在微生物[8-9],并且乳腺肿瘤组织的微生物构成与健康乳腺组织相比存在明显差异[10]。研究发现,乳腺癌肿瘤组织展现出比胰腺癌、肺癌、骨癌等其他几种肿瘤组织更为丰富、多元的细菌组成[11]。这些发现揭示了乳腺组织中的细菌在乳腺癌发展中可能具有潜在作用。后续相关研究也表明乳腺组织中的细菌可直接或者通过分泌的代谢物影响细胞信号通路、细胞生长及转移等参与乳腺癌的发展[10,12]。此外,乳腺组织外的细菌,如肠道和口腔来源的细菌也能够通过直接或者间接的方式影响乳腺癌的发展及治疗[13-14]。因此,细菌与乳腺癌相互作用的机制以及细菌在乳腺癌治疗中的应用等相关研究,都受到了研究者们的广泛关注[15-16]。本文主要围绕乳腺癌组织、肠道和口腔来源的细菌及其代谢物参与乳腺癌发展与治疗的机制进行综述,旨在为研究细菌与乳腺癌细胞互作影响乳腺癌发展和治疗开辟新的视角,提供新的策略。

1 细菌-宿主相互作用与乳腺癌发展的关系

细菌与宿主之间存在复杂的相互作用。目前已有研究证明细菌既可以通过调控宿主免疫反应影响肿瘤发展[12],也可以通过与肿瘤细胞直接相互作用来影响肿瘤的进展[17]。乳腺癌肿瘤组织内的细菌可以直接影响乳腺微环境[18],其他部位如口腔[14]、肠道[16]中的细菌可通过血液循环或者其他生理途径迁移至乳腺组织,影响乳腺癌的进展。

1.1 乳腺菌群与乳腺癌发展的关系

人类乳腺组织具有与身体其他部位不同的、独特的细菌组成,Urbaniak等[8]发现乳腺组织中变形菌门相对丰度最高,其次为厚壁菌门。这些细菌可能是从皮肤、口腔经乳腺导管进入乳腺内[19]。并且Urbaniak团队还发现乳腺癌肿瘤组织菌群与正常乳腺组织菌群相比发生了显著的变化[20],肿瘤组织中芽孢杆菌属、葡萄球菌属和肠杆菌科细菌的相对丰度较高[18]。肠杆菌科细菌是促进癌变的有害因素[21],如从癌旁组织分离、培养的大肠埃希菌可在体外诱导HeLa细胞的DNA双链断裂[18],这一现象可能是由于pks^+大肠埃希菌大肠杆菌素(colibactin)的合成[22]或与大肠埃希菌Ⅲ型分泌系统具有将毒素注入细胞内[23]的能力有关。尽管DNA损伤本身不足以直接导致乳腺癌的发生,但DNA损伤会提高女性罹患乳腺癌的风险。乳腺癌

患者癌细胞内检测到的链球菌、乳酸杆菌等细菌可通过调节宿主细胞肌动蛋白网络、改变细胞骨架，提高癌细胞抵抗循环中流体剪切压力的能力，进而起到促进乳腺癌细胞转移的作用[17]。

正常乳腺组织中乳杆菌属、双歧杆菌属等细菌的相对丰度较高[6]。研究发现乳杆菌属相对丰度的升高有利于乳腺癌患者的预后，如使用干酪乳杆菌CRL431发酵的牛奶能够降低乳腺癌小鼠血清中白介素-6（interleukin-6，IL-6）的水平，抑制肿瘤组织中新血管生成，降低趋化因子MCP-1浓度，进一步抑制乳腺癌细胞的生长和转移[24]。但乳杆菌属在乳腺癌肿瘤组织中的相对丰度偏低[6]。此外，Xuan等[25]发现乳腺癌肿瘤组织内鞘氨醇单胞菌的丰度降低，该菌表达的糖鞘脂配体可激活恒定型自然杀伤细胞（invariant natural killer T cells，iNKT），抑制乳腺癌细胞生长[26-27]。由于健康人的血液中只含有极少量的内源性iNKT，因此可根据鞘氨醇单胞菌的特性开发同种异体iNKT应用于肿瘤治疗[28]，但这一设想仍有待更深入的研究。因此，乳腺癌细胞内细菌可通过多种机制促进或抑制乳腺癌的发展。

1.2　肠道菌群与乳腺癌发展的关系

肠道是一个复杂且动态的生态环境，肠道菌群共同维持肠道内微生态的平衡。目前已有证据表明肠道菌群相对丰度的改变可能会影响包括多种癌症在内的疾病进展[29-31]。

Nandi等[32]研究表明，正常人肠道中最具代表性的是厚壁菌门、拟杆菌门、变形菌门和放线菌门。Ma等[33]证明这几种菌门在健康者、乳腺良性病变者和乳腺癌患者中均为优势菌，其中拟杆菌门的丰度被证明与乳腺癌密切相关[34]。Parida等[16]发现拟杆菌门中的产肠毒素脆弱拟杆菌会定植到乳腺导管中并诱导乳腺上皮细胞增生。脆弱拟杆菌毒素通过β-catenin细胞信号通路和Notch1通路短暂刺激乳腺癌细胞后，诱导癌细胞中与细胞运动和转移相关的基因上调，促进乳腺癌细胞的迁移和侵袭[16]。脆弱拟杆菌毒素与乳腺癌细胞上的核苷酸结合寡聚化结构域1蛋白（nucleotide-binding oligodomain-like receptor 1，NOD1）结合，通过增强Numb蛋白的溶酶体降解来激活Notch1-Hey1信号通路，促进乳腺癌细胞干性和化疗耐药性的发生[35]。另外，Siddiqui等[36]发现乳腺癌患者的肠道菌群多样性降低，梭菌目相对丰度增加。研究表明，普拉梭菌培养上清可以抑制乳腺癌细胞中促炎细胞因子IL-6的表达和JAK2/STAT3的磷酸化而呈现抑癌作用[15]。该菌培养上清发挥作用的机制可能与其主要代谢物丁酸、乙酸和丙酸等有关[37]，其中丁酸已被证明可抑制乳腺癌的发展[38]。因此，肠道菌群在乳腺癌的发展中扮演着复杂而关键的角色，提示这些肠道菌群可为乳腺癌的防治提供新策略。

1.3　口腔细菌与乳腺癌发展的关系

有研究发现患牙周炎的女性患乳腺癌的风险增高[39]。具核梭杆菌在牙周炎患者口腔中检出率较高[40]，与乳腺癌的发展存在关联[39]。该菌通过表面凝集素Fap2与乳腺癌细胞表面高表达的Gal-GalNAc结合，从而定植到乳腺癌组织中，并抑制抗肿瘤免疫反应[14]。此外，具核梭杆菌引起促炎细胞因子IL-6、IL-8和IL-1β水平的上调[40]。其中，IL-6水平的升高与乳腺癌的不良预后和上皮间质转化（epithelial-to-mesenchymal transition，EMT）有关[41]。因此，口腔细菌可通过与宿主细胞互作或调节细胞因子的方式影响乳腺癌的发展。本文细菌与乳腺癌进展的主要相关机制研究见表1。

2　细菌代谢物在乳腺癌发展中的作用

细菌除了与乳腺癌细胞直接相互作用，还能通过其产生的代谢物影响乳腺癌的发展。使用代谢组学研究方法筛选乳腺癌肿瘤组织与正常乳腺组织中的细菌差异代谢物，可深入探究这些代谢物与乳腺癌发展的内在关联。部分代谢物甚至有望成为诊断和预测复发的生物标志物[42]。

2.1　氧化三甲胺

氧化三甲胺（trimethylamine-N-oxide，TMAO）是人体内肠道菌群的间接代谢物。红肉、鸡蛋等食物中的胆碱、左旋肉碱等成分在肠道菌群的作用下转化为三甲胺（trimethylamine，TMA），TMA在肝脏中被黄素单加氧酶代谢为TMAO[43]。TMAO与癌症、心血管等多种疾病存在相关性[44-45]。在三阴性乳腺癌免疫调节亚型患者的乳腺组织内，梭菌目菌属占比相较其他亚型更高[12]。该菌属的间接代谢物TMAO能够激活内质网激酶，诱导肿瘤细胞发生焦亡，抑制细胞增殖，同时强化$CD8^+$T细胞介导的

表1 细菌参与乳腺癌发展的相关机制

Table 1 Mechanisms of bacteria involved in the development of breast cancer

Effect	Bacteria	Action mechanism	References
Promote cancer	*Fusobacterium nucleatum*	Bacterial Fap2 lectin binds to Gal-GalNAc on the cell surface; induce the expression of inflammatory factors	[14]
	Escherichia coli	Causes DNA damage in cells; type Ⅲ secretion system	[18,22-23]
	Enterotoxigenic Bacteroides fragilis	*Bacteroides fragilis* toxin and Notch1, β-catenin cell signaling pathways; NOD1, Numb, Notch1-Hey1 cell signaling pathways	[16,35]
Inhibit cancer	*Faecalibacterium prausnitzii*	Inhibition of IL-6 expression and JAK2/STAT3 signaling pathway	[15]
	Sphingomonas yanoikuyae	Activating iNKT to exert anti-tumor immunity	[25]
	Lactobacillus casei	Reduce the concentration of IL-6 and MCP-1	[24]

NOD1: nucleotide-binding oligodomain-like receptor 1; IL-6: interleukin-6; JAK2: Janus kinase 2; STAT3: signal transducer and activator of transcription 3; iNKT: invariant natural killer T cells; MCP-1: monocyte chemotactic protein-1.

三阴性乳腺癌体内抗肿瘤免疫反应[12]。探索TMAO与乳腺癌免疫治疗的关系有助于抑制乳腺癌的发展。

2.2 短链脂肪酸

短链脂肪酸(short chain fatty acid, SCFA)是长度为1~6个碳的简单脂肪族羧酸[46],由肠道细菌降解膳食纤维所产生[47],是肠腔中最丰富的代谢物之一,可通过调节宿主细胞信号通路抑制乳腺癌的发展,改善乳腺癌的治疗效果。健康人群肠腔中水平最高的SCFAs是乙酸盐、丙酸盐和丁酸盐[46]。研究表明,在乳腺癌患者的肠道内,生成SCFAs的细菌相对丰度降低[48],会导致SCFAs水平下降,乙酸盐、丙酸盐、丁酸盐和异戊酸的水平降低,而异丁酸和戊酸的水平升高[49]。丁酸盐作为一种组蛋白脱乙酰酶(histone deacetylase, HDAC)抑制剂[50],可通过激活半胱氨酸天冬氨酸蛋白水解酶-8(caspase-8)和caspase-3增加乳腺癌细胞内活性氧(reactive oxygen species, ROS)水平、损伤线粒体膜电位而促进乳腺癌细胞的凋亡[50]。丁酸盐通过抑制HDAC活性上调转录调节因子ID2的表达。该因子通过IL-12的信号传导增强体内外细胞毒性$CD8^+$T细胞反应[51]。在临床上,尚未有研究表明丁酸盐可应用于癌症治疗,但在骨关节[52]和肠道疾病的治疗中[53],口服丁酸盐可缓解病人不适症状。

2.3 次级胆汁酸

次级胆汁酸由肠道细菌经初级胆汁酸转化而成。与健康个体相比,乳腺癌患者肠道细菌的多样性减少,血液中次级胆汁酸浓度降低[54]。

石胆酸(lithocholic acid, LCA)在肠道中合成,可经血液转移到乳腺[42]。乳腺癌患者血清LCA水平与Ki67水平呈负相关[55]。LCA接近生理浓度时通过激活跨膜G蛋白偶联胆汁酸受体-5(takeda G-protein-coupled receptor 5, TGR5)限制乳腺癌细胞的增殖。该代谢物还能通过抑制EMT和血管内皮生长因子的表达,抑制乳腺癌细胞转移。早期乳腺癌患者血清中LCA产生减少,提示LCA可能成为乳腺癌早期诊断的潜在标志物[42]。

脱氧胆酸(deoxycholic acid, DCA)通过增加促生存因子FlK-1的表达,降低神经酰胺水平,减少4T1乳腺癌细胞凋亡的发生[56]。

2.4 尿石酸A

尿石酸A(urolithin A)是肠道细菌通过浆果和石榴等水果中的多酚类化合物鞣花酸代谢而产生的。研究发现尿石酸A可以通过阻断自噬关键调节因子EB(transcription factor EB, TFEB)与14-3-3蛋白的结合,促进TFEB核转位,从而促进巨噬细胞通过线粒体自噬-溶酶体途径清除受损线粒体,抑制炎症因子释放[57]。雌激素受体α(estrogen

receptor alpha，Erα）是ER阳性乳腺癌治疗的重要靶点，可抑制雌激素依赖的乳腺癌患者癌细胞的增殖。胆固醇代谢物27-羟基胆固醇（27-hydroxycholesterol，27-HC）是内源性选择性雌激素受体调节剂，可在体内外促进乳腺癌细胞的增殖和转移。该研究表明尿石酸A可与Erα结合，抑制27-HC促进乳腺癌细胞增殖[58]。在临床上，尚未有研究证明尿石酸A可应用于癌症治疗，但口服尿石酸A有助于改善肌肉性能[59]。

2.5　犬尿氨酸

在人体中，必需氨基酸色氨酸，影响多种病理生理过程，并只通过饮食获得。色氨酸的代谢途径主要有3条，其中约95%的色氨酸经过犬尿氨酸（kynurenine，Kyn）代谢途径被分解[60]。犬尿氨酸代谢途径与包括癌症在内的多种疾病相关，该途径需要色氨酸2，3-双加氧酶（tryptophan 2，3-dioxygenase，TDO）、吲哚胺2，3-双加氧酶1（indoleamine 2，3-dioxygenase 1，IDO1）和吲哚胺2，3-双加氧酶2（indoleamine 2，3-dioxygenase 2，IDO2）的参与[61]，这几种酶有望成为治疗相关疾病的关键靶点。研究发现TDO2或IDO表达上调的癌症患者预后较差。TDO2的表达上调与雌激素受体阴性状态和肿瘤侵袭性相关[61]，而IDO1的表达可以通过非免疫抑制机制促进乳腺癌小鼠肿瘤的生长，以免疫抑制的方式促进小鼠的肺转移[62]。此外，犬尿氨酸可以激活芳香烃受体（aryl hydrocarbon receptor，AhR），该受体的活性与乳腺癌细胞的侵袭和生存相关基因的表达上调有关。然而，若通过外源性配体过度激活AhR，则可能导致乳腺癌细胞侵袭能力降低。此外，活化的AhR可以促进TDO的表达[63]。在临床上，犬尿氨酸通路抑制剂如IDO1抑制剂依帕司他可与免疫检查点抑制剂（immune checkpoint inhibitors，ICIs）联合使用增强抗肿瘤疗效[64]。

代谢物在乳腺癌发展中的影响，提示其在乳腺癌的早期诊断和治疗中具有一定的应用潜力。然而目前相关研究仍存在诸多待深入探索之处，其他可能影响乳腺癌发展的代谢物还需要进行更深入的探究，为乳腺癌的精准诊疗提供更有力的依据和全新的思路。本文细菌代谢物与乳腺癌相关的机制研究见表2。

表2　细菌代谢物参与乳腺癌发展的相关机制

Table 2　Mechanisms of bacterial metabolites involved in the development of breast cancer

Effect	Metabolite	Action mechanism	References
Promote cancer	Trimethylamine N-oxide	Activation of endoplasmic reticulum kinase，$CD8^+$T cell-mediated anti-tumor immunity	[12]
Inhibit cancer	Butyric acid	Increased reactive oxygen species level，consumption of mitochondrial membrane potentia；inhibition of HDAC activity，up-regulate the expression of transcription regulator ID2	[50]
	Lithocholic acid	Activate TGR5；inhibition of EMT	[42]
	Deoxycholic acid	Promote the expression of FIK-1 and reduce ceramide levels	[56]
	Urolithin A	Reduce the secretion of pro-inflammatory factor；binding to Erα inhibits cancer cell proliferation；inhibit the release of inflammatory factors	[57-58]
	kynurenine	TDO，IDO1，IDO2；AhR mediates the degradation of E-cadherin	[61-63]

HDAC：histone deacetylase；TGR5：takeda G-protein-coupled receptor 5；TGR5；EMT：epithelial-to-mesenchymal transition；Erα：estrogen receptor alpha；TDO：tryptophan 2，3-dioxygenase；IDO1：indoleamine 2，3-dioxygenase 1；IDO2：indoleamine 2，3-dioxygenase 2；AhR：aryl hydrocarbon receptor.

3 细菌及其代谢物影响乳腺癌治疗的研究进展

随着细菌与癌症研究的深入,大量研究表明细菌会通过代谢化疗药物、调节免疫系统等途径影响癌症的治疗效果。因此,将细菌及其代谢物应用到癌症治疗的常规方法中,或者对细菌进行基因工程改造使其有助于抗癌治疗可能会成为有力的癌症辅助治疗手段。

3.1 影响免疫治疗的疗效

目前,细菌在癌症患者的免疫治疗反应性上发挥着重要作用。将对ICIs治疗有效的癌症患者的粪便移植到无菌或者给予抗生素处理的小鼠肠道内,可提高ICIs治疗效果[65]。具核梭杆菌增强抗程序性细胞死亡-配体1(programmed cell death ligand 1, PD-L1)的治疗反应,提高患者的生存率[65]。共生双歧杆菌促进小鼠体内树突状细胞(dendritic cell, DC)活化和$CD8^+$T细胞产生干扰素-γ,提高抗PD-L1药物的疗效[66]。经改造大肠埃希菌与CAR-T细胞合作可以不依赖肿瘤相关抗原靶向肿瘤并抑制肿瘤发展[67]。鞘氨醇单胞菌促进肿瘤细胞分泌趋化因子CCL20,降低$CD8^+$T细胞/调节性T细胞(Treg)的比例,从而降低αPD-1单克隆抗体的治疗效果[68]。因此,细菌可能通过调节宿主免疫系统影响免疫治疗效果。

3.2 影响化疗药物疗效

肠道是化疗药物的重要代谢器官[69],肠道菌群对化疗药物的疗效发挥重要作用。使用抗生素抑制肠道菌群,可增强阿霉素抑制肿瘤细胞增殖、促进肿瘤细胞凋亡和减少肺转移肿瘤数量的疗效,改善三阴性乳腺癌小鼠的预后[70]。同时,使用阿霉素也会改变小鼠肠道菌群组成。伊立替康经肝脏解毒后进入胃肠道,被细菌分泌的β-葡萄糖醛酸酶重新活化,引起严重的腹泻,加重不良反应[69]。合用混合益生菌可减少伊立替康治疗后杯状细胞数量和黏蛋白的分泌,维持肠道内的水和电解质平衡,防止腹泻发生[71]。乳腺癌化疗患者常出现认知障碍这一不良反应[72],肠道菌群变化会增强此作用,降低患者的生活质量[73]。化疗药物引发口腔菌群失调,导致口腔炎症,进一步影响胃肠道,加重如恶心、呕吐等不良反应[74]。另外,化疗药物使用后的肠道菌群紊乱,也可引发肠道炎症[73]。

肠道中菌群组成及相对丰度的改变对化疗效果的影响与细菌代谢物密切相关。Li等[75]表明丁酸盐通过增强依托泊苷诱导乳腺癌细胞DNA双链断裂的能力,阻碍细胞DNA双链断裂修复,增强对乳腺癌细胞的杀伤力。这些研究结果均有力地证实了细菌及其代谢物在化疗过程中所发挥的重要作用。

3.3 影响放射治疗效果

与手术治疗相比,放疗具有非侵入性和潜在器官保护的优点,但是放疗抵抗和辐射的不良反应限制了放疗在乳腺癌中的应用[76]。已有研究发现肠道菌群对于辐射损伤具有一定的影响,如粪菌移植可通过增厚黏液层、增加杯状细胞的数量以及降低肠道通透性的方式缓解辐射所致的肠道损伤,提升受照射动物的存活率[76]。小鼠昼夜节律异常会改变肠道菌群组成从而降低放射治疗的敏感性[77]。使用万古霉素可增强乳腺癌放疗诱导的抗肿瘤免疫反应[78],抑制肿瘤的生长。因此,肠道菌群在减轻放疗不良反应、增强放疗疗效方面发挥重要作用。

3.4 工程菌与乳腺癌治疗

癌症的工程菌治疗策略是将细菌与药物、纳米颗粒等物质结合或通过生物学合成方法对细菌进行改造,使其毒性减弱或消失,增强治疗效果。采用细菌作为载体具有肿瘤靶向性和免疫激活的天然优势,近年来已成为领域研究热点[79]。

干酪乳杆菌(*lactobacillus casei*, LC)存在于乳制品、植物以及人类肠道等部位。有证据表明其与肿瘤血管形成、肿瘤的大小、细胞外渗相关[80]。硒纳米颗粒(selenium nanoparticle, SeNPs)与细菌组合用于药物递送、免疫系统调节、抗肿瘤等方面的作用受到学者的关注[81]。有研究发现LC培养上清与SeNPs合成的干酪乳杆菌-硒纳米颗粒(LC-SeNPs)可诱导乳腺癌细胞凋亡,抑制癌细胞的侵袭和迁移[82]。

鼠伤寒沙门氏菌是一种理想的基因治疗递送载体,具有特异性靶向肿瘤、在肿瘤内表达效应基因的优点[83]。鼠伤寒沙门氏菌通过表达金黄色葡萄球菌透明质酸酶的*HysA*基因,可以降解乳腺癌细胞外基质(extracellular matrix, ECM)的主要成分透明质酸从而降低肿瘤微环境中的间质液压力,抑制乳腺癌细胞的增殖,增强化疗药物的治疗效果[84]。

铜绿假单胞菌-甘露糖敏感血凝素菌株通过基因工程改造和热灭活构建的铜绿假单胞菌-甘露糖

敏感血凝素菌株，这株菌表达具有细胞毒性的甘露糖敏感血凝素Ⅰ型菌毛。该菌毛通过激活凋亡途径抑制癌细胞的生长[85]。将该菌与化疗药物卡培他滨联合使用，可降低常见不良反应的发生率[86]；与紫杉醇和卡铂（paclitaxel+carboplatin，PCb）联合使用，可提高Her-2阴性乳腺癌患者的化疗反应率[87]。

目前工程菌在乳腺癌治疗中的研究大多仍处于体外实验阶段，尚未有应用于临床研究的报道。但细菌在其他肿瘤上已有少量的临床应用，为未来乳腺癌的工程菌治疗提供了一定的参考。研究报道改良后的分枝杆菌卡介苗VPM1002BC具有增强免疫的作用[88]，在非肌层浸润性膀胱癌患者的膀胱内的临床试验中显示出较好的安全性[89]。在接受VPM1002BC治疗1年的患者中，有近一半的患者无复发[88]。因此，通过不同的修饰和转化方式，进一步提高工程菌对乳腺癌的靶向性、治疗效果和安全性，使其更好地与化疗、放疗和免疫治疗等方法联合应用，将是未来工程菌应用于乳腺癌的重点研究方向。

4　总结与展望

细菌与癌症发展和治疗的关系引起了学者的广泛关注。与健康乳腺组织相比，乳腺癌肿瘤组织中的细菌组成发生变化，可能影响乳腺癌的发展与治疗。如一些有益细菌及其代谢物被证明能够发挥潜在的抗肿瘤作用[24]。未来需要更深入的研究去探索乳腺组织、肠道和口腔等来源的细菌影响乳腺癌发展及治疗的内在作用机制。此外，现有的细菌对乳腺癌发展及治疗的研究大多集中在基础医学领域，应用于临床的细菌相关疗法较少。因此，需挖掘更多发挥细菌与肿瘤相互作用的靶点和通路，以期发现可用于临床的抗乳腺癌新靶点以及可用于早期诊断的新标志物。另外，细菌具有易于大规模制备和工程改造的优势，因此，对细菌进行工程改造，以发挥细菌抗肿瘤的作用，可为乳腺癌的治疗提供新方法。目前细菌与癌症的研究仍存在一些局限性。首先，动物模型与人类的差异大[29]，可能影响结果准确性。因此，亟需开发更接近人类乳腺癌的动物模型或用类器官模型等体外系统，以精准模拟肿瘤与细菌的相互作用。其次，相关研究中样本量的不足[90]，难以反映真实关系。建议开展多中心、大样本量研究，建立全国性乳腺癌微生物组研究网络，以提高结果的代表性和普适性。

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