·综　述·

乳腺肿瘤微环境靶向治疗的研究进展

杨云松，江一舟，胡　欣，邵志敏

复旦大学附属肿瘤医院乳腺外科，复旦大学上海医学院肿瘤学系，上海 200032

［摘要］ 肿瘤细胞周围的免疫细胞、成纤维细胞、内皮细胞及其驱动分子等组成的肿瘤微环境可以调控肿瘤细胞的生长、侵袭和转移，因此在针对肿瘤细胞进行治疗的同时靶向肿瘤微环境成为乳腺癌综合治疗的新策略。对乳腺肿瘤微环境中的预测标志物，以及如何靶向肿瘤微环境增加抗乳腺肿瘤治疗的疗效进行了综述，为乳腺癌的治疗提供新的思路。

［关键词］ 乳腺癌；肿瘤微环境；免疫治疗

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Research progress of breast tumor microenvironment-targeted therapy YANG Yunsong, JIANG Yizhou, HU Xin, SHAO Zhimin (Department of Breast Surgery, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China)

Correspondence to: SHAO Zhimin E-mail: zhiminqshao@gmail.com

［**Abstract**］ Tumor microenvironment is composed of immune cells, fibroblasts and endothelial cells, and proliferation, invasion and metastasis of tumor cells are regulated by tumor microenvironment. Therefore, targeting both tumor cells and the surrounding microenvironment should be included in the comprehensive treatment of breast cancer. In this review, we summarized the prognostic value of the tumor microenvironment in breast cancer and how to increase the therapeutic effect of anti-cancer therapy through addition of anti-microenvironment therapy.

［**Key words**］ Breast cancer; Tumor microenvironment; Immunotherapy

乳腺癌作为全球女性发病率最高的恶性肿瘤，具有增殖快、易转移和易耐药的特性，其病死率占所有恶性肿瘤的15%，现已成为恶性肿瘤中的第二大杀手[1]。肿瘤微环境是指由肿瘤细胞周围的细胞及非细胞成分所构成的环境，是肿瘤细胞赖以生存的基石。肿瘤微环境作为肿瘤细胞的“土壤”，随着肿瘤细胞的发展与其共同进化，两者相辅相成，共同促进肿瘤的发生、发展。因此，靶向肿瘤细胞及肿瘤微环境近年来成为乳腺癌诊疗的新思路。本文就乳腺癌肿瘤微环境的基础与转化研究进行综述，进一步阐述靶向微环境在肿瘤治疗策略中的重要性，为乳腺癌的治疗提供新的思路。

1　肿瘤微环境细胞对预后及疗效预测的价值

1.1　免疫细胞

肿瘤微环境中的免疫细胞包括肿瘤浸润淋巴细胞（tumor-infiltrating lymphocyte，TIL）、巨噬细胞和中性粒细胞等。TIL在三阴性乳腺癌（triple-negative breast carcinoma，TNBC）中的预后及疗效预测价值已被证实。先后有4项大型临床试验的转化研究提示，TIL对早期TNBC的复发和总生存有预测价值，每增加10%TIL能够降低15%~23%的复发风险[2-4]。不同的是在由美国东部肿瘤协作组（Eastern Cooperative Oncology Group，ECOG）开展的两项临床试验ECOG 2197和ECOG 119的联合分析中，研究者指出间质内肿瘤浸润淋巴细胞（stroma tumor-infiltrating lymphocytes，sTIL）对TNBC的预后更有预测价值，但这可能是由于这两项联合分析仅纳入了481例患者，其中上皮内肿瘤浸润淋巴细胞（intraepithelial tumor-infiltrating lymphocytes，iTIL）的比例仅有15%[2]。除了淋巴细胞，肿

通信作者：邵志敏　E-mail: zhiminqshao@gmail.com

瘤微环境中的巨噬细胞和中性粒细胞同样也可以作为良好的预后预测指标。有研究发现，高CD4$^+$T细胞、低CD8$^+$T细胞和高CD68$^+$巨噬细胞的患者预后更差，并且其中CD68$^+$巨噬细胞即肿瘤相关巨噬细胞（tumor-associated macrophage，TAM）能够诱导血管新生、介导紫衫类耐药以及诱发CD8$^+$T细胞的失活来抑制肿瘤免疫应答[5]。TAM也存在内部异质性，可以分为能吞噬肿瘤细胞的M1型和促进肿瘤恶性表型的M2型[6]。CD68$^+$CD163$^+$是M2型TAM的特异性表面标志物，有研究表明，乳腺癌间质高表达的CD68和CD163与Luminal A型乳腺癌的不良预后相关[7]。但实际最近的研究发现，不同的TAM亚群行使不同的功能，因此不能简单地用M1和M2型来划分TAM亚群[8]。Azizi等[9]通过单细胞测序技术，在乳腺癌样本中鉴定出了3群TAM，但这3群TAM在表达谱上都与经典的M1和M2型不完全一致，因此对于巨噬细胞M1/M2极化模型提出了质疑。中性粒细胞被证实能够促进肿瘤的转移并介导肿瘤免疫逃逸。多项研究表明，化疗前的高中性粒细胞/淋巴细胞比值（neutrophil lymphocyte ratio，NLR）提示不良预后[10-11]，最近的一项Meta分析纳入了12项研究得到了相似的结论[12]。中性粒细胞能够促进远处转移灶的转移前微环境的形成以利于肿瘤细胞的定植[13]，此外研究者还发现，中性粒细胞祖细胞能够分化为PD-L1阳性的中性粒细胞抑制T细胞的活化[14]。外周血淋巴细胞则与TIL呈正相关，因此低水平的外周血淋巴细胞能够预测抑制性免疫微环境的形成[15]。NLR能够作为简单易行同时具有良好的预测价值的标志物。

乳腺癌肿瘤微环境中的免疫细胞组分是预后及疗效预测指标，但由于免疫细胞的功能与其分布位置及亚群相关，使得不同状态的免疫细胞有着不同的功能及预测价值。在疗效预测方面，现有研究已经证实了高TIL提示TNBC新辅助化疗后的高病理完全缓解（pathological complete response，pCR）率[16-19]，但对于iTIL和sTIL的预测价值观点不一，可能是由于主观判读造成的偏移。有研究提示，iTIL和sTIL均是TNBC新辅助化疗pCR的独立预测因子，PrECOG0105临床试验的后续分析也得到了类似结论[20-21]。此外在Loi等[22]进行的早期TNBC辅助化疗队列研究中已证实高sTIL提示较好的预后，该团队还建立了结合sTIL含量的在线预后评估网站。TIL含量与化疗效果相关可能涉及以下机制：① 化疗可以调节免疫微环境。化疗药物可以杀伤抑制性的免疫细胞如髓系来源的抑制性细胞和调节性T细胞[23-24]。有文献报道，新辅助化疗后的淋巴细胞浸润高于化疗前[25]。② 化疗能够诱导肿瘤细胞释放抗原或诱导肿瘤细胞突变产生新抗原来诱导免疫反应[26]。Li等[27]在HER2阳性乳腺癌队列的血清样本中鉴定出了13个与曲妥珠单抗疗效相关的miRNA，并用其中的4个构建了一个miRNA的模型来预测曲妥珠单抗的疗效，并证实血清中的这些miRNA大部分是来自T细胞、B细胞、NK细胞、单核细胞和粒细胞。

1.2 非免疫细胞

肿瘤微环境中非免疫细胞主要包括肿瘤相关成纤维细胞（cancer-associated fibroblast，CAF）、内皮细胞和间充质细胞等，其中CAF的含量最为丰富，约占80%，并且参与了肿瘤的发生、发展及耐药性的产生[28]。Chang等[29]根据成纤维细胞在体外不同浓度的血清刺激下的表达谱差异，构建了一个基因集用以表征成纤维细胞活化、增殖并分泌胶原修复损伤的状态，该基因集在乳腺癌、肺癌和胃癌等多个癌种中为不良预后的指标，此外这种活跃的修复状态还是Basal亚型乳腺癌的特征。然而，也有研究显示，丰富的间质成分在乳腺癌中提示较好的预后，根据反相蛋白阵列技术（reverse phase protein arrays，RPPA）对乳腺癌进行分型，其中一型为活化型乳腺癌，这是一类富含间质细胞及细胞外基质（extracellular matrix，ECM）但缺乏TIL的乳腺癌，其基于表达谱的内生分型主要是Luminal型乳腺癌，并且预后相对RPPA Luminal、RPPA HER2及RPPA Basal较好[30-31]。此外活化型乳腺癌富含间质成分的同时也缺乏淋巴细胞的浸润，提示丰富的间质成分可能是阻碍免疫细胞浸润的机制之一，而不同研究之间结论的差异提示肿瘤间质同样存在异质性[32-33]。

2 靶向肿瘤微环境在肿瘤治疗中的应用

2.1 靶向免疫细胞

免疫细胞是微环境中能直接杀伤肿瘤细胞的细胞成分，但肿瘤细胞可以通过多种机制塑造抑制性的免疫微环境。肿瘤的免疫微环境可以被分为以下3类：① 缺乏淋巴细胞浸润的免疫荒漠型或免疫阻隔型；② 有淋巴细胞浸润但PD-1/PD-L1等免疫检查点通路激活；③ 有活化的淋巴细胞浸润[34-35]。因此需要仔细鉴别每例患者的免疫表型，从而给予不同的免疫治疗方案。例如，针对第1类免疫表型首先需要促进免疫细胞浸润，对于第2类则需要免疫检查点抑制剂来活化免疫细胞。

对于活化免疫细胞的研究，目前的研究重点是解除抑制性因素如PD-1/PD-L1通路、Treg细胞和M2型巨噬细胞等。PD-1/PD-L1通路是目前研究较多的免疫逃逸机制之一，靶向这一通路的免疫检查点抑制剂已经被用于多种癌症的晚期解救治疗[34]。在乳腺癌中，IMpassion130临床试验的中期分析已初步提示白蛋白紫杉醇联合PD-L1抗体一线治疗晚期TNBC能够延长PD-L1阳性患者2年的无进展生存期，这一研究结果提示免疫治疗在TNBC中有着广阔的前景[36]。有研究者设计了一种全新的PD-L1抗体药物偶联物，特异性地靶向糖基化的PD-L1不仅能够竞争性抑制其与PD-1结合，还可以促进抗体和PD-L1的内吞并释放细胞毒性药物，因此可以通过“旁观者效应”杀伤周边PD-L1阴性的乳腺癌细胞[37]。

靶向巨噬细胞也是研究的热点之一，TAM不仅可以促进肿瘤的转移，还参与抑制免疫细胞的浸润和活化[38]。CSF1/CSF1R信号轴对于TAM的招募、活化及存活有着重要的作用，针对这一信号通路的抗体和小分子抑制剂能够抑制乳腺癌、肺癌和宫颈癌等的发生、发展[39-40]。CSF1R的小分子抑制剂BLZ945能够抑制巨噬细胞活化为TAM，同时还增加$CD8^+$T细胞的浸润[41-42]。同时靶向TAM表面的CD40和CSF1R能够促进TAM分化为Ly6C+F4/80intTAM，并分泌TNF-α和IFN-γ活化T细胞[43]。PD-L1的表达水平在微环境细胞中也很高，有研究表明，PD-L1在免疫细胞表面的表达决定了免疫检查点抑制剂的疗效[44-45]。曲妥珠单抗诱发的抗体依赖的细胞吞噬作用能诱导TAM上调PD-L1的表达引起免疫抑制，因此对于HER2阳性的乳腺癌可能需要联用抗HER2靶向治疗和免疫检查点抑制剂来克服免疫抑制性微环境的产生[46]。信号调节蛋白α（signal regulatory protein α，SIRPα）是位于巨噬细胞表面的抑制性免疫受体，其配体是CD47分子，CD47/SIRPα信号轴能够抑制巨噬细胞吞噬$CD47^+$肿瘤细胞，多个CD47及SIRPα抗体正在血液肿瘤及实体肿瘤中进行临床试验[47]。但由于CD47同样在红细胞等正常细胞表面表达，CD47抗体所造成的严重贫血等问题需要注意。最近的研究发现，MHC-Ⅰ/LILRB1信号轴也能够发出类似CD47/SIRPα那样的“Don’t eat me”信号抑制巨噬细胞的吞噬作用，因此同时阻断MHC-I/LILRB1和CD47/SIRPα通路能够最大程度活化巨噬细胞[48]。TAM在肿瘤微环境中有着重要作用，但由于其内部异质性，不同亚群TAM行使不同的功能，因此需要进一步探索特异性的靶点。

2.2 靶向CAF

CAF作为肿瘤微环境中数量最多的细胞在肿瘤的进展过程中有着重要作用，并且由于其基因组相对稳定使其成为良好的靶点[49]。CAF主要通过旁分泌或内分泌的方式分泌各种细胞因子，如转化生长因子-β（transforming growth factor-β，TGF-β）、成纤维细胞生长因子（fibroblast growth factor，FGF）、肝细胞生长因子（hepatocyte growth factor，HGF）、血小板源性生长因子（platelet-derived growth factor，PDGF）、血管内皮生长因子（vascular endothelial growth factor，VEGF）、白细胞介素（interleukin，IL）-6、结缔组织生长因子（connective tissue growth factor，CTGF）、CXC族趋化因子配体12（CXC chemokine ligand 12，CXCL12）等，来促进肿瘤的恶性表型或调控免疫微环境[49]。GPR77被证实是乳腺癌CAF中介导化疗耐药的重要分子，有研究发现，$CD10^+GPR77^+$CAF在新辅助化疗后的样本中富集，

并证实该亚群通过GPR77-NF-κB轴促进CAF分泌IL-6和IL-8（CXCL8）维持肿瘤细胞干性从而介导化疗耐药，靶向GPR77的单克隆抗体能够在小鼠体内逆转乳腺肿瘤细胞对多西他赛的耐药[50]。TNBC细胞可以分泌Hh配体作用于临近的CAF激活SMO促进FGF5的分泌，而间质来源的FGF5又可以维持肿瘤细胞的干性。研究者同时开展了Ⅰ期临床试验，对12例晚期TNBC患者给予SMO抑制剂联合多西他赛治疗，1例患者达到完全缓解、2例患者疾病稳定[51]。Roswall等[52]发现，Basal亚型乳腺癌细胞能够分泌PDGF-CC作用于CAF，诱导其分泌HGF、IGFBP3和STC1来维持雌激素受体（estrogen receptor，ER）的低表达，PDGF-CC单抗则能上调ER的表达诱导Basal亚型乳腺癌对他莫昔芬敏感。

CAF也是微环境中参与抑制免疫细胞的重要成分，因此靶向CAF细胞来消除微环境中的免疫抑制因素是近期的研究热点之一。成纤维细胞激活蛋白（fibroblast activation protein，FAP）阳性CAF被报道与免疫抑制微环境密切相关，研究者鉴定出了一群在TNBC中特异性表达的CAF-S1，其特征是FAP阳性[32]。CAF-S1可以分泌CXCL12并表达OX40L、PDL2和B7H3等，趋化$CD4^+$T细胞并诱导它们成为$FOXP3^+$Treg细胞。在胰腺癌和肝癌中CXCL12受体CXCR4的拮抗剂AMD3100能够在小鼠体内促进T细胞的浸润并能与PD-L1抗体协同发挥作用[53-54]。也有文章报道，FAP+CAF通过FAP-STAT3-CCL2轴来趋化MDSC抑制免疫应答[55]。若能靶向FAP^+CAF、其分泌的效应因子及受体如CXCL12/CXCR4则可以纠正抑制性的免疫微环境。然而在一项转移性肠癌的Ⅱ期临床试验中发现，FAP单克隆抗体西罗珠单抗应答率较低，未能进一步开展Ⅲ期临床试验[56]。随着嵌合抗原受体T细胞（chimeric antigen receptor T cell，CAR T cell）免疫疗法的发明，研究人员设计了靶向FAP的CAR T细胞，在小鼠模型中证实靶向FAP^+CAF能够抑制肿瘤的增殖[57-58]。TGF-β是成纤维细胞活化为CAF并维持相应功能的重要信号分子。FAP^+PDPN^+CAF能够响应TGF-β刺激，分泌胶原蛋白产生致密的ECM来阻止T细胞的浸润，同时还分泌一氧化氮来抑制T细胞的增殖[59]。有研究发现，CAF中TGF-β信号通路的激活与阻隔T细胞的浸润相关，阻断这一通路能在小鼠乳腺癌、黑色素瘤模型及结肠癌的类器官模型中促进免疫细胞的浸润，能够促进PD-L1抗体的效应[60-61]。并且有临床试验初步表明，TGF-β抗体能够增加外周血中单核细胞及$CD8^+$T细胞的数量[62]。因此有研究者设计了抗TGF-β/PD-L1的双特异性抗体（M7824）并在Ⅰ期临床研究中证实其安全性，相关的Ⅱ期临床试验正在进行中（NCT03620201）[63-64]。CAF中的TGF-β信号通路在促进免疫逃逸中有着重要作用，因此靶向TGF-β信号通路和抗PD-L1的联合治疗方案能够将“冷肿瘤”转变为“热肿瘤”增加免疫治疗的效果。

2.3 靶向血管内皮细胞

持续的血管新生是肿瘤的特征之一，而这一过程依赖微环境中的血管内皮细胞的活化与增殖。活化血管内皮细胞的重要因子是VEGF，其与内皮细胞表面的VEGF受体（VEGF receptor，VEGFR）结合激活下游信号促进内皮细胞的增殖及迁移[15]。贝伐单抗是第一个靶向VEGFR的单克隆抗体，但由于其较小的生存获益和心血管方面的不良反应使其被美国食品药品管理局撤销在晚期乳腺癌中的适应证[65]。而近年来多个VEGFR的小分子酪氨酸激酶抑制剂在多项临床试验中取得较好的结果，其中也包括我国自主研发的阿帕替尼，其在晚期TNBC中显示出较好的有效性和安全性[66]。Incio等[67]发现，肥胖患者血清中较高的IL-6和FGF-2介导了贝伐单抗的耐药。Allen等[68]在小鼠模型中发现，抗VEGFR能够诱导PD-L1上调，抗VEGFR/PD-L1的联合治疗能够增加疗效同时诱导高内皮静脉的形成，促进淋巴细胞的浸润。特异性的靶向内皮细胞表面的LIGHT能够重塑淋巴结的结构，同时诱导高内皮静脉的形成并和免疫检查点抑制剂产生协同作用[69]。抗ANGPT2/VEGFA双特异性抗体A2V能促进$CD8^+$T细胞在血管内驻留，但同时促进

其分泌IFN-γ上调肿瘤细胞PD-L1的表达，因此联用抗PD-1抗体能够增加抗血管生成治疗的敏感性而双特异性抗体A2V也能促进淋巴细胞的浸润[70]。靶向血管内皮细胞的目的已从最初阻断肿瘤的营养供给角度转变为使肿瘤血管正常化以利于免疫细胞的浸润，从而能够和免疫治疗产生协同作用。

2.4 靶向ECM

ECM可以作为屏障阻挡免疫细胞及药物，在肿瘤细胞周围给肿瘤细胞提供保护，因此降解或减少ECM的产生也是靶向微环境的策略之一。赖氨酰氧化酶（lysyl oxidase，LOX）被证实能够交联胶原形成致密的间质微环境，并通过不同的机制来促进肿瘤细胞的转移[71-72]。因此靶向LOX如LOX酶活性抑制剂β-aminoproprionitrile及LOXL2抗体能够抑制胶原交联，降低间质的致密性，从而抑制转移微环境的形成[72-74]。在一项Ⅱ期临床试验中，一种铜螯合剂四硫代钼酸铵被证实能够抑制TNBC的LOX活性、胶原沉积和肺转移的发生[75]。肿瘤细胞依赖整联蛋白家族来感受ECM的变化，随着ECM的分泌增加，整联蛋白家族蛋白也随之表达增加，并通过信号转导激活肿瘤细胞的促癌信号通路，这其中研究最多、最重要的是β1整联蛋白及其下游粘着斑激酶（focal adhesion kinase，FAK）[76-77]。近期Shen等[78]发现，ECM中的Tinagl1蛋白能够结合TNBC表面的整联蛋白受体并竞争性抑制纤维蛋白所介导的整联蛋白/FAK信号通路，外源性的给予重组Tinagl1蛋白能够显著抑制小鼠的肺转移及肿瘤的生长。抑制下游FAK的磷酸化同样能够阻止乳腺癌的增殖，在Ⅰ期临床试验中入组91例晚期实体瘤患者均接受FAK的小分子抑制剂PF-00562271治疗，31例患者达到疾病稳定[76, 79]。此外，靶向FAK还能够增敏免疫治疗。有研究发现，胰腺癌中过度的FAK激活阻止$CD8^+$T细胞浸润到癌巢，而FAK抑制剂和PD-1抗体联合治疗能够诱导T细胞的浸润并延缓肿瘤的生长[80]。在乳腺癌中也存在这种免疫阻隔的状态，因此若能够趋化$CD8^+$T细胞的浸润将能提升免疫检查点抑制剂在乳腺癌中的疗效。

3 总结与展望

目前的研究证实，微环境中的淋巴细胞、巨噬细胞及成纤维细胞等均能够预测预后及化疗效果，并且这些细胞还有助于维持肿瘤的恶性表型，尤其在形成抑制性的免疫微环境方面有着重要作用。免疫治疗是近年也是未来的研究重点，对于免疫治疗的研究由过去增强免疫效应转变为消除微环境中的免疫抑制因素，即免疫正常化的策略[34]，因此如何靶向微环境来增敏免疫治疗将成为未来的研究重点。目前肿瘤微环境的研究难点在动物模型建立难度大、费用昂贵，但随着人源异种移植模型和类器官等新模型的建立以及单细胞测序和质谱流式等技术的发展，未来将能借助新的方法来揭示肿瘤微环境中的复杂调控网络，并从中寻找合适的治疗靶点。

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