综　述

三阴性乳腺癌新辅助化疗疗效预测研究进展

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[摘要]　三阴性乳腺癌(TNBC)缺乏有效的靶向治疗方案，化疗是其主要治疗手段，其中新辅助化疗(NAC)为标准治疗策略之一。但TNBC患者对NAC的反应不一，如何在治疗前识别出有效或耐药的个体是目前临床亟待解决的问题。对于TNBC NAC反应的预测包括影像组学、肿瘤免疫学和基因组学等方面，联合不同方面的因素建立预测模型能够提高预测效能。随着基因检测技术的发展，单细胞测序技术可排除肿瘤微环境中非肿瘤细胞的影响，精准地确定肿瘤亚型，揭示耐药机制，未来可应用于NAC，以提高预测精确度。本文就TNBC NAC疗效预测的最新研究进展进行综述。

[关键词]　三阴性乳腺癌；新辅助化疗；疗效预测；单细胞测序

Research progress in efficacy prediction of neoadjuvant chemotherapy for triple negative breast cancer

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[**Abstract**]　Chemotherapy is the main treatment for triple-negative breast cancer (TNBC) due to the lack of effective targeted therapy. At present, neoadjuvant chemotherapy (NAC) is one of the standard treatment strategies. However, the response of patients to NAC is different, and how to identify effective or resistant individuals before treatment is an urgent clinical problem to be solved. The research progress on the prediction of NAC response for TNBC has many aspects, including imageomics, tumor immunology and genomics. Combining different factors to build a prediction model can better improve the prediction efficiency. With the development of gene detection technology, single-cell sequencing technology can exclude the influence of non-tumor cells in tumor microenvironment, accurately determine tumor subtypes, reveal drug resistance mechanisms, and may be applied to NAC in the future to improve the accuracy of prediction. This article reviews the latest research progress in predicting the efficacy of TNBC NAC.

[**Key words**]　triple negative breast cancer; neo-adjuvant chemotherapy; curative effect prediction; single cell sequencing

三阴性乳腺癌(triple negative breast cancer，TNBC)由于缺乏激素受体和人表皮生长因子受体-2(human epidermal growth factor receptor 2，HER2)的表达，目前尚无有效的靶向治疗方案，

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不能从内分泌治疗和抗HER2治疗(靶向治疗)中获益，因此，化疗对于TNBC至关重要[1-2]。近年来新辅助化疗(neo-adjuvant chemotherapy，NAC)已成为TNBC的标准治疗方式，能使不可手术的乳腺癌变为可手术，不可保留乳房的手术变为可保留乳房的手术[3]。TNBC患者经NAC后达到完全病理缓解(pathological complete response，pCR)可明显改善生存[4]，但并非所有的TNBC患者都对NAC有良好的反应，部分患者NAC期间甚至出现进展。因此，早期识别出NAC反应至关重要。目前已开展诸多预测TNBC NAC反应的研究，本文就该领域的最新进展进行综述。

1 影像组学和人工智能

近期多项研究提示了影像组学对NAC反应的早期预测作用。一项纳入586例TNBC患者的临床试验利用影像学数据建立预测模型，结果显示，基于多参数的MRI影像组学预测模型的预测效能高于临床模型(AUC：0.86 *vs.* 0.77)，而结合临床病理高危因素再次组成的预测模型的预测效能高于单独的影像组学和临床模型，特别是在TNBC亚组中更具优势[5]。徐晓曦等[6]研究发现，TNBC NAC中磁共振表观弥散系数(apparent diffusion coefficient，ADC)是pCR的预测因素，且超声在该预测中也起到积极作用[7-8]。

人工智能(artificial intelligence，AI)作为信息技术的重大突破，已逐渐应用于医疗的各个领域[9]。影像组学可利用AI技术从医学影像复杂非确定的大量参数中提取数据用于疾病的诊断和预测。目前AI技术结合影像学预测TNBC NAC反应的研究主要集中在MRI新技术领域。Braman等[10]利用动态对比增强磁共振(dynamic contrast-enhanced magnetic resonance imaging，DCE-MRI)对肿瘤进行检测，并从瘤内和瘤周提取纹理特征，用于训练多个预测NAC反应的机器学习分类器，以提高pCR的预测效能，结果发现预测TNBC/HER2$^+$ pCR的朴素贝叶斯分类器AUC可达0.930 ± 0.018。AI技术使影像组学预测NAC反应的效能不断提升，目前该方向的研究正在不断深入，未来将具有广阔的发展空间。

2 免疫学因素

化疗与免疫相互影响，化疗能够通过肿瘤细胞或免疫细胞介导免疫刺激效应，而免疫功能可能影响化疗的疗效[11]。

2.1 血清炎症指标 血清炎症指标包括白细胞、中性粒细胞/淋巴细胞比值(neutrophil/lymphocyte ratio，NLR)、淋巴细胞/单核细胞比值(lymphocyte to monocyte ratio，LMR)及血小板/淋巴细胞比值(platelet-to-lymphocyte ratio，PLR)等。Asano等[12]的研究发现，在乳腺癌患者中，低NLR预示着更高的pCR率(P<0.001)，且低NLR患者多表现为TNBC。Lusho等[13]的研究发现，在TNBC中，低PLR与高pCR率明显相关。潘婉婉等[14]的研究同样证实，低NLR和低PLR均与高pCR率相关。而Corbeau等[15]的研究则显示，NLR或PLR与不同分子分型乳腺癌的NAC反应均无明确关系，但在TNBC中，低白细胞计数(<6.75×10^9/L)是高pCR率的预测因素。一项meta分析结果显示，不论肿瘤的分子分型如何，NLR与pCR均无明显的关系[16]。浙江省肿瘤医院的研究发现，LMR可作为TNBC接受蒽环类序贯紫杉醇类化疗方案pCR的独立预测因素，低LMR的患者更容易获得pCR[17]。因此，血清炎症指标能否作为TNBC NAC疗效的预测因素，目前仍存在争议。

2.2 程序性死亡受体1(programmed death 1，PD-1)及其配体(programmed cell death-ligand 1，PD-L1) PD-1及PD-L1可预测TNBC NAC反应。一项纳入177例患者的临床试验发现，TNBC中PD-1、PD-L1高表达预示着更低的pCR率[18]。而Yam等[19]的研究发现，PD-L1阳性与TNBC的高pCR率相关；徐露等[20]的研究结果则表明，PD-1阳性患者的NAC疗效显著优于阴性患者。

2.3 肿瘤浸润淋巴细胞(tumor-infiltrating lymphocyte，TIL)和肿瘤免疫微环境(tumor immune microenvironment，TME) TME与免疫系统抑制、免疫检测逃避、耐药等相关[21]，可影响乳腺癌化疗的疗效；TIL是TME的重要组成部分，可作为乳腺癌NAC反应的预测因子。一项纳入3771例乳腺癌患者的研究发现，所有分子分型中，高TIL患者的pCR率高于低TIL患者，尤其在TNBC中，高TIL患者的pCR率达到了50%(P<0.001)[22]。另一项临床研究也证实，高TIL与高pCR率明显相关(76.5% *vs.* 21.5%，P=0.001)[23]。FAIRLANE试验中，紫杉醇+安慰剂组pCR患者的TIL水平明显高于非pCR患者[24]。孔天东等[25]的研究提示，CD8$^+$ T淋巴细胞浸润高密度组的pCR率高于低密度组。调节性CD4$^+$ T细胞(regulatory CD4$^+$ T cell，Treg)是TIL中的一种，有研究显示，在TNBC中其含量与NAC后的pCR率呈负相关[26]。胞质细胞周期素E与TIL有协同作用，Karakas等[27]的研究发现，胞质周期素E表达组的pCR率低于不表达组(16.1% *vs.* 38.9%，P<0.0005)。Cerbelli等[23]利用免疫相关生物标志物TILs、PD-L1和CD73建立组织免疫概要(tissue immune profile，TIP)，定义TIP阳性为TILs≥50%、PD-L1≥1%、CD73≤40%，并最终确定TIP阳性是TNBC获得pCR

的独立预测因子，且TIP的预测准确度较单个生物标志物高。

3 基因组学

基于基因组学的预测因子可分为循环肿瘤DNA(circulating tumor DNA，ctDNA)、单基因标志物、多基因联合模型预测、表观遗传学标志物和单细胞测序5个方面。

3.1 ctDNA ctDNA可在NAC反应的预测中发挥作用。Magbanua等[28]发现，NAC后达到pCR的患者血清中ctDNA均被清除；在紫杉类药物起效后3周，相较于ctDNA清除的患者，ctDNA阳性患者更不易达到pCR(*P*=0.012)。McDonald等[29]的研究也得到了类似的结果，发现NAC后pCR患者的ctDNA浓度明显低于肿瘤残存者。遗憾的是，这两项研究缺少分子分型亚组分析。但Riva等[30]的研究提示，TNBC的pCR率与NAC过程中任何时间点的ctDNA浓度均没有相关性。因此，ctDNA对于特定分子亚型乳腺癌NAC反应是否有预测作用，目前仍未达成共识。

3.2 单基因标志物 目前研究发现，多种基因的表达异常与TNBC NAC反应相关。DNA同源重组修复障碍(homologous recombination deficiency，HRD)是TNBC的重要特征[31]，而引起HRD的基因众多，其中*BRCA*基因突变是引起HRD的重要改变[32]。GeparOcto临床试验入组了914例高危(HER2阳性或三阴型)早期乳腺癌患者，结果显示，BRCA1/2突变患者的治疗反应率高于未突变者[33]。而一项Meta分析结果显示，在传统NAC方案基础上加入卡铂并不能提高*BRCA*突变TNBC的pCR率[34]。*ERCC1*也是引起HRD的重要基因，有临床试验发现，ER阴性患者在以蒽环类为基础的NAC中，低*ERCC1*表达与高pCR率相关；相反，在紫杉类为基础的NAC中，高*ERCC1*表达与高pCR率相关[35]。

Filho等[36]在TNBC标准NAC方案中加入卡铂，利用PAM50分类法对TNBC进行分型，结果显示，基底样型的pCR率高于其他亚型(52.3% *vs.* 35.4%，*P*=0.003)。Gluz等[37]也发现，基底样型的pCR率较其他亚型高。*TOP2A*突变或表达异常可导致乳腺肿瘤对蒽环类药物耐药。有研究显示，TNBC中*TOP2A*扩增型的pCR率较野生型明显减低[38]。我国的一项临床研究提示，TNBC中*TP53*突变型的pCR率较野生型高(43.5% *vs.* 8.0%，*P*=0.002)[39]。另外一项研究探索了lncRNA X染色体失活特异性转录本(X chromosome inactivation specific transcript，XIST)对乳腺癌新辅助治疗敏感性的预测价值，结果表明，TNBC中lncRNA XIST低表达患者更容易获得pCR[40]。

3.3 多基因联合模型 既往有研究发现，多基因联合预测模型在Luminal型乳腺癌中的表现优于TNBC[41]，基于此，有学者不断寻找可用于TNBC的多基因预测模型。我国学者利用基因表达数据库中接受NAC的26例TNBC患者的微阵列数据，构建了由1个lncRNA BPESC1和2个编码基因*WDR72*、*GADD45A*构成的反应评分工具，结果显示，该工具的预测效能较高(AUC=0.931，*P*<0.01)，且高评分患者更易获得pCR[42]。Oshi等[43]构建了三基因(*CDKN2C*、*DEK*、*MCM3*)评分预测模型，其AUC为0.735，并证实该模型不仅是NAC的预测因子，而且是生存的预测因子。

3.4 表观遗传学 DNA甲基化在预测乳腺癌NAC反应中起着重要作用。Pineda等[44]对双基因(*FERD3L*和*TRIP10*)的甲基化程度进行评分，构建了双基因表观遗传学预测模型，并证实该模型能很好地预测TNBC的pCR，预测效能良好，其AUC为0.9056(95%CI 0.805~1.000)。Meyer等[45]也验证了DNA甲基化水平在预测TNBC NAC反应中的作用。

3.5 单细胞测序 单细胞测序技术加深了人们对肿瘤的认识[46]。Minussi等[47]利用单细胞测序技术揭示了TNBC生长过程中染色体持续畸变并维持亚克隆多样性的现象。Wagner等[48]利用单细胞蛋白组学技术揭示了在相同传统分子分型中不同肿瘤个体的内部异质性，提出肿瘤的分型应结合浸润免疫细胞的表型。Kim等[49]利用单细胞测序技术探索了TNBC NAC的耐药机制，并证实经NAC选择的基因型小片段具有治疗前的耐药基因子集，提示在实施NAC前可探索耐药基因克隆，从而更精准地预测TNBC对NAC的反应。而Shaath等[50]利用单细胞技术分析发现，lncRNA MALAT1启动子缺失增强了TNBC对紫杉醇和阿霉素的敏感性，提示MALAT1在获得性耐药中起着重要作用。以上研究结果表明，在传统分子分型的基础上，利用单细胞测序技术可对不同肿瘤个体的内部异质性及不同NAC的可能反应作出预判，从而为NAC的精准决策提供帮助。TNBC NAC反应相关预测标志物总结见表1。

4 总结与展望

随着人工智能和基因检测技术的发展，TNBC NAC反应预测因素研究在与AI影像组学、肿瘤免疫学、基因组学等方面结合后取得了一定进展。单一的预测标志物尚不能满足临床需要，而联合多个不同类型预测因子组成的预测模型具有优越的预测效能。未来可通过单细胞测序技术在治疗前更精准地识别出TNBC的异质性以及耐药的肿瘤细胞，甚至为每例TNBC患者找出精准的靶点，并利用AI技术

表1 TNBC NAC反应相关预测标志物

Tab.1 NAC response related predictive biomarkers in TNBC

预测标志物	与NAC反应的关系
免疫因素	
NLR	与pCR呈负相关[12,14]，或无明确关系[15-16]
PLR	与pCR呈负相关[13-14]，或无明确关系[15]
LMR	与pCR呈负相关[17]
PD-1	与pCR呈负相关[18]，或正相关[20]
PDL-1	与pCR呈负相关[18-19]
TIL	与pCR呈正相关[22,24]
$CD8^+$淋巴细胞浸润	高密度与高pCR相关[25]
Tregs	与pCR呈负相关[26]
TIP	阳性是pCR的独立预测因子[23]
细胞周期素E	其表达与低pCR率相关[27]
基因组学	
ctDNA	血清ctDNA清除易获pCR[28-29]，或无明显相关[30]
BRCA1/2	突变与高pCR率相关[33]，不能预测铂类的获益情况[34]
ERCC1	在以蒽环为基础的NAC中其低表达与高pCR率相关，紫杉类为基础的NAC中则相反[35]
PAM50分组	基底样型有较高的pCR[36-37]
TOP2A	扩增降低pCR率[38]
TP53	突变获得高pCR率[39]
lncRNA XIST	低表达与高pCR率相关[40]
BPESC1、*WDR72*和*GADD45A*评分	高评分与高pCR相关[42]
CDKN2C、*DEK*、*MCM3*基因评分	高评分与高pCR相关[43]
FERD3L、*TRIP10*双基因表观遗传	高甲基化程度与高pCR相关[44]
MALAT1 (lncRNA)	启动子缺失增强了对紫杉醇和阿霉素的敏感性[50]

TNBC. 三阴性乳腺癌；NLR. 中性粒细胞/淋巴细胞比值；PLR. 血小板/淋巴细胞比值；LMR. 淋巴细胞/单核细胞比值；TIL. 肿瘤浸润淋巴细胞；Tregs. 调节性$CD4^+$ T细胞；TIP. 组织免疫概要；BRCA1/2. 乳腺癌易感基因1/2；lncRNA XIST. 长非编码RNA X染色体失活特异性转录本；pCR. 病理完全缓解；FERD3L. Fer3样bHLH转录因子；TRIP10. 甲状腺激素受体相互作用因子10

整合临床、病理、分子生物学等信息，建立更加精准的预测模型。

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