三阴性乳腺癌靶向治疗最新进展

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［摘要］ 三阴性乳腺癌(triple-negative breast cancer，TNBC)是一种特殊类型的乳腺癌，占乳腺癌总确诊的15%~20%。其雌激素受体(estrogen receptor，ER)、孕激素受体(progesterone receptor，PR)和人表皮生长因子受体(human epidermal growth factor receptor-2，HER-2)表达均阴性，具有独特的生物学特性和临床病理特征，肿瘤异质性很高，临床上具有复发高、转移早和预后差等特点。目前，临床上缺少有效的治疗手段。该综述介绍了TNBC的临床病理特征、分子亚型、几条重要的通路和靶点，以及目前各靶向药物临床试验研究进度，希望为今后TNBC的治疗提供新的临床思路。

［关键词］ 三阴性乳腺癌；靶点；治疗；

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［**Abstract**］ Triple-negative breast cancer (TNBC) is a special type of breast cancer, accounting for 15%-20% of all diagnosed breast cancer cases. Its estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2) expression is negative, with unique biological characteristics, clinicopathological features and tumor heterogeneity. Its clinical features include high incidence of relapse, early metastasis and poor prognosis. Currently, it lacks effective treatment. This review described the clinicopathological features of TNBC, its molecular subtypes, several important pathways and targets, as well as presented the progress in clinical studies of targeted drugs in the hope of generating new ideas for the treatment of TNBC in the future.

［**Key words**］ Triple-negative breast cancer; Target; Therapy

三阴性乳腺癌(triple-negative breast cancer，TNBC)是一种特殊的类型的乳腺癌，占乳腺癌总确诊的15%~20%。TNBC是指免疫组织化学染色雌激素受体(estrogen receptor，ER)、孕激素受体(progesterone receptor，PR)和人表皮生长因子受体(human epidermal growth factor receptor-2，HER-2)表达均阴性的乳腺癌，具有独特的生物学特性和临床病理特征。其肿瘤异质性很高，临床上具有复发高、转移早和预后差等特点。由于没有相应的激素受体或HER-2表达，因此内分泌治疗、抗HER-2靶向治疗及化疗均不能成为TNBC的有效的治疗方法。虽然TNBC还没有批准的靶向治疗，但是分子谱分析已经发现了几个潜在的分子靶点并开展了相应的临床研究。然而，早期的结果不大令人满意，主要和肿瘤内外的异质性及耐药有关。

1 TNBC临床病理特征

TNBC占所有确诊乳腺癌的15%~20%，年轻女性(小于40岁)多发，黑人多于白人，在非洲或西班牙比较盛行[1-2]。其病理类型以浸润性导管癌常见，肿瘤异质性高，分化低，增殖扩散快，负荷大，临床复发转移早，预后差。TNBC的5年生存率约为70%，远远低于非三阴乳腺癌(non-triple-negative breast cancer，NTNBC)的5年生存率

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(80%)。TNBC较少发生单纯骨转移，NTNBC也容易发生肝、肺转移。

2 TNBC的亚型分类及命名

一项来自21个研究中心的乳腺癌患者基因表达谱分析的数据集显示，TNBC可分为7个亚型(6个可定义亚型和1个不稳定亚型)[3]。具体包括基底细胞样(basal-like，BL)、间充质样(mesenchymal，M)、间充质干细胞样(mesenchymal stem-like，MSL)、腔面雄激素受体表达型(luminal androgen receptor，LAR)、免疫调节型(immunomodulatory，IM)和不稳定型(unstable，UNS)，其中BL又分为BL1和BL2(表1)。

表 1 TNBC的亚型分类及命名

Tab. 1 Nomenclature and classification of TNBC

Molecular subclass	Percentage/%	Signaling profiles	Targeted molecular	pCR/%
BL1	21	Proliferation drivers: Cell cycle, cell division, and DNA replication and responses	PARP 1, TTK, PLK1, CHEK1, AURKA/B and RAD51	52
BL2	8	Growth factor and metabolic signaling with myo-epithelial markers	EGFR, MET, EPHA2 and mTOR	0
LAR	1	Hormonal-mediated signaling androgen receptor (AR)	AR, Hsp90, PI3K and FGFR4	10
IM	23	Immune-mediated signaling	JAK1/2, LYN, STATs, IRF1/7/8, BTK and NFKβ	30
M	20	EMT and differentiation	SRC, PI3K, mTOR, IGF1R, PDGFR, and FGFR	31
MSL	10	Modulator of epithelial mesenchymal transition (EMT), differentiation and stemness; Growth factor and angiogenesis mediated signaling (low levels of proliferation drivers)	SRC, PI3K, MEK1/2, mTOR, PDGFR, NFKβ, IGF1R, FGFR and TGFBRⅢ	23
UNS	17	DNA damage responses and cell proliferation	PARP 1, TTK, PLK1, CHEK1, AURKA/B and RAD51	33

3 TNBC相关的信号通路、靶点及抑制剂

3.1 酪氨酸激酶受体(receptor tyrosine kinases，RTKs)信号通路

RTKs是细胞信号传导通路中必不可少的组成部分，在自分泌和旁分泌细胞信号交流中起着至关重要的作用，RTKs参与细胞增殖和分化，调控细胞的生长和代谢，促进细胞的存活和凋亡[4-5]。

3.1.1 表皮生长因子受体(epidermal growth factor receptor，EGFR)及抑制剂

EGFR是一种膜蛋白，它在TNBC中的表达明显高于NTNBC。另外，研究还发现，EGFR和肿瘤的增殖、侵袭和血管形成密切相关，其过度表达在基底样型TNBC中尤为常见，与临床预后成明显负相关[6]。一些针对EGFR的药物已经在临床上应用，包括单克隆抗体(西妥昔单抗和帕尼单抗)和小分子激酶抑制剂(吉非替尼和埃罗替尼)。然而，尽管取得了一些初步成效，这些药物在临床上的应用仍有限。有研究发现西妥昔单抗在治疗TNBC前后肿瘤大小并没有显著变化，进一步研究发现AKT和人表皮生长因子受体3(human epidermal growth factor receptor-3，HER-3)信号通路由于负反馈被激活，因此产生耐药[6-7]。有研究报道，西妥昔单抗联合化疗药物和PARP抑制剂(poly-ADP ribose polymerase inhibitors，PARPi)可以完全根除乳腺癌干细胞，观察200多天没有复发[8]，证明尽管单药耐药，联合治疗仍能获得满意的结果，抗EGFR治疗依然有效。

3.1.2 血管内皮生长因子受体(vascular endothelial growth factor receptor，VEGFR)及抑制剂

VEGF在乳腺癌中的表达明显高于正常的乳腺组织。VEGF的特异性抑制剂贝伐珠单抗以及与血小板衍生生长因子(platelet-derived growth factor，PDGF)的共同抑制剂舒尼替尼均有在TNBC中的相关研究。尤其是舒尼替尼，研究

发现它能够通过VEGF信号通路抑制血管生成，从而减小TNBC异种移植肿瘤体积。贝伐珠单抗是VEGF的特异性抑制剂，Ⅲ期临床试验还研究发现，贝伐珠单抗联合紫杉醇化疗可在很大程度上延长患者的无进展生存期(progression free survival，PFS)(PFS从5.9个月提高到11.8个月)及化疗缓解率，但对总生存率(overall survival，OS)没有影响[9-10]。与此一致的是最近完成的CALGB 40603试验(NCT00861705)，其表明贝伐珠单抗和普通化疗相比能显著增加Ⅱ、Ⅲ期TNBC临床缓解率(59% *vs* 48%)，但还不清楚是否对PFS和OS有影响[11]。

3.2 促分裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)/细胞外信号调节激酶(extracellular signal-regulated kinase，ERK)信号通路

MAPK信号通路调控着肿瘤增殖和生存，有研究发现它在TNBC的发生、发展中被异常激活，该途径的过度激活可能使三阴性乳腺癌细胞获得增殖失控及抗凋亡的能力[12-14]。已有研究证实，丝裂原活化蛋白激酶表达激酶1/2(mitogen-activated protein kinase kinase1/2，MEK1/2)和ERK2是PFS和OS的危险因素[15-16]。MEK1/2抑制剂在实体肿瘤Ⅰ期临床试验中取得的疗效甚微，这是因为MEK1/2抑制剂在灭活MAPK的同时激活了RTKs信号通路。此外，一些TNBC细胞还具有磷脂酰肌醇-3-羟激酶(phosphoinositide 3-kinase，PI3K)和MEK双激活通路，所以必须同时用两个通路的抑制剂才有可能抑制肿瘤细胞。GSK1120212临床试验正在验证MEK联合其他靶点的抑制剂及化疗药物来治疗TNBC。

3.3 磷酸肌醇3-激酶/AKT/哺乳动物靶标雷帕霉素(phosphoinositide 3-kinase/AKT/mammalian target of rapamycin，PI3K/AKT/mTOR)信号通路

PI3K/AKT/mTOR信号通路控制着肿瘤的增殖、代谢、生存和运动，并且和MAPK信号通路有频繁的信号交流[16-17]。AKT在细胞的死亡中起至关重要的作用，然而，mTOR则在转录、蛋白翻译、细胞生存和生长发挥重要的调节作用。约60%的TNBC患者中可以看到PI3K信号通路过度激活。一项刚完成的Ⅰ期临床试验证实，使用PI3K/AKT/mTOR信号通路抑制剂联合化疗可以很大程度上延长转移性TNBC患者的PFS(表2)[18]。PI3K被抑制的TNBC对PARP抑制剂更加敏感，表明可以将PI3K抑制剂和PARP抑制剂联合应用[19]。

3.4 DNA损伤应答机制相关信号通路

针对细胞周期中DNA诱导损伤的研究已成为治疗的一个热点。一些医药公司正在研究检测DNA损伤相关激酶如细胞周期检测点激酶(checkpoint kinase，CHK)的抑制剂，干扰细胞周期引起非正常的细胞周期进展，导致DNA损伤，引起细胞死亡。细胞周期停滞是肿瘤细胞生存的一个重要的机制，其原因是可以给细胞足够的时间让细胞修复损伤的DNA，因此，在细胞自动DNA修复前废除这种自我检测完全可以引起细胞凋亡的级联反应。伴有乳腺癌易感基因*BRCA*基因突变或缺失的肿瘤或细胞株对多聚(ADP-核糖)聚合酶(PARPs)抑制剂比较敏感。其机制主要是“合成致死”效应。所谓“合成致死”效应是指只有当*BRCA*基因和PARP同时受到抑制时，才会引起细胞的死亡，单独缺失其中一个则对细胞的生存无影响。*BRCA*基因突变或缺失的三阴性乳腺癌细胞株通常激素受体(hormone receptor，HR)受损，必须依赖需要PARP1的非同源末端重组或碱基切除通路修复DNA损伤，所以，使用多聚(ADP-核糖)聚合酶(PARPs)抑制剂可以捕获DNA上的PARP1分子[20]，引起复制叉暂停复制，使细胞周期受阻并停留在G_2期。进而阻断癌细胞的这种自我DNA修复功能，引起细胞死亡。关于PARP抑制剂iniparib和(或)联合化疗Ⅰ期临床试验研究表明，和单纯化疗组相比，PARP抑制剂能够明显的提高患者的中位OS(7.7个月*vs* 12.3个月)和无病进展生存(disease free survival，DFS)时间(3.6个月*vs* 5.9个月，表2)。

3.5 Janus激酶和信号转导与激活转录(janus kinase/signal transducer and activator of transcription，JAK/STAT)信号通路

JAK/STAT通路同样在各种细胞过程中发挥

着关键的监管作用，包括增殖、存活、迁移、分化和细胞凋亡[21]。很多研究发现，JAK/STAT信号通路的下调在TNBC中发挥重要的作用[22-24]。分子形态学研究发现，JAK1和JAK2在TNBC患者中过度表达，和过表达的JAK3一起充当着肿瘤的使动因子使细胞增殖失控，血管形成[24-25]。磷酸化的JAK3在超过50%的乳腺肿瘤中表达，这和乳腺癌的侵袭性和预后差明显相关。临床前研究还发现，仅在小鼠乳腺癌模型中敲除JAK3，就表现明显出肿瘤生长受限和对化疗药物敏感[25]。JAK2抑制剂BSK805能够明显影响肿瘤移植模型肿瘤形成以及消灭干细胞样肿瘤细胞。进一步验证了JAK2/STAT3信号通路是肿瘤形成的使动因素[24]。

表 2 TNBC临床研究中涉及的部分靶点及相应的药物

Tab. 2 Partial therapeutic targets and their agents in clinical research for the treatment of TNBC

Targeted pathway	Targeted molecular	Chemical agent	Combination agents	Phase	Trial reference
RTK	EGFR	Erlotinib	Metforminc	Ⅰ	NCT01650506
			Neoadjuvant chemotherapy	Ⅱ	NCT00491816
			Bendamustine	Ⅰ/Ⅱ	NCT00834678
		Nimotuzumab	Docetaxel Capecitabine	Ⅱ	NCT01939054
		Gefitinib	Nil	Ⅱ	NCT01732276
		Panitumumab	Carboplatin Gemcitabine	Ⅱ	NCT00894504
		Sunitinib	Carboplatin paclitaxel	Ⅰ/Ⅱ	NCT00887575
MAPK/ERK	MEK1/2, ERK2	Trametinib	GSK2141795 (Akt inhibitor)	Ⅱ	NCT01964924
PI3K/AKT/mTOR	mTOR	Everolimus (RAD001)	Gemcitabine cisplatin	Ⅰ/Ⅱ	NCT01939418
			Eribulin mesylate	Ⅰ	NCT02120469
			Cisplatin	Ⅱ	NCT01931163
		Temsirolimus	Neratinib (EGFR and HER-2 inhibitor)	Ⅰ/Ⅱ	NCT01111825
	PI3K and AKT	BKM120	Olaparib	Ⅰ	NCT01623349
			Capecitabine	Ⅱ	NCT02000882
JAK/STAT	JAK1 and JAK2	Ruxolitinib	Nil	Ⅱ	NCT01562873
		Ruxolitinib	Paclitaxel	Ⅰ/Ⅱ	NCT02041429
DNA-damage response (DDR)	Poly (ADP-ribose) polymerases (PARPs)	Veliparib (ABT-888)	Carboplatin paclitaxel doxorubicin cyclophosphamide	Ⅲ	NCT02032277
		Veliparib (ABT-888)	Lapatinib (Tykerb)	Ⅰ	NCT02158507

Details including dosage of the chemical agents under trial, duration of the trial, inclusion and exclusion criteria for recruiting patients, contact and locations where the trial was being conducted, and the current status of the trial could be obtained by searching the 'trial reference' in the US National Institutes of Health Registry (https://clinicaltrials.gov/).

4 结语

TNBC具有较高的肿瘤异质性，分子亚型至少有5~6种，临床上复发转移早、预后差，缺少相应的治疗策略。由于激素受体和*HER*-2基因阴性，常规的内分泌和靶向治疗无从应用，化疗由于耐药性也受到限制，临床上亟需新的治疗方案。从上述分析中可以看出，TNBC靶向药物单一或多个联合或联合化疗等应用，可以获得较满意的临床缓解率，但这些目前仅是临床前研究，到真正应用到肿瘤患者身上还有相当长的时间，未来的趋势可能要对患者进行基因测序分型，具体分型应用具体的药物。

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