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· 文献综述 ·

三阴性乳腺癌的生物标记物研究进展

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摘要

三阴性乳腺癌(TNBC)是指雌激素受体(ER)、孕激素受体(PR)和表皮生长因子受体2(HER-2)均为阴性的乳腺癌,以发病年龄轻、易早期发生转移为特点。TNBC对ER、PR为靶点的内分泌治疗和以HER-2为靶点的靶向药物治疗无效,已成为乳腺癌治疗的难点与研究的热点。为改进TNBC的临床诊断与治疗手段,学者们做了大量的研究来寻找更多新的生物标记物。笔者对近年来国内外关于TNBC的生物标记物研究进展进行综述。

关键词

三阴性乳腺癌; 生物标记; 肿瘤; 综述文献
中图分类号: R737.9

Research progress on biomarkers of triple-negative breast cancer

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Abstract

Triple-negative breast cancer (TNBC) is a subtype of breast cancer defined as the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2), and characterized by onset at a younger age and high incidence of early metastasis. TNBC does not respond to endocrine therapy targeting ER or PR and HER-2-targeted agents, and has accordingly become a challenge in clinical treatment and a hotspot in research of breast cancer. A great number of investigations have been done by scholars for finding new biomarkers of TNBC and thereby improving its clinical diagnosis and treatment. Here, the authors present the recent progress on researches concerning the biomarkers of TNBC both at home and abroad.

Key words

Triple Negative Breast Neoplasms; Biomarkers, Tumor; Review
CLC number: R737.9

乳腺癌已经成为女性最常见的恶性肿瘤,其中,三阴性乳腺癌(triple-negative breast cancer, TNBC)约占乳腺癌中的12%~20%。TNBC是以雌

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2(human epidermal growth factor receptor 2,

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HER-2)均缺失为特征的一类乳腺癌亚型,与非TNBC相比,TNBC好发于年轻女性,具有侵袭性强、易转移、预后差的特点^[1-2]。Lehmann等^[3]将TNBC划分为6种分子亚型,分别是基底细胞样1(basal-like 1, BL1)型、基底细胞样2(basal-like 2, BL2)型、间充质细胞样(mesenchymal, ML)型、间充质干细胞样(mesenchymal stem-like, MSL)型、免疫调节(immunomodulatory, IM)型、和腔上皮样雄激素受体(luminal androgen receptor, LAR)型。乳腺癌的治疗方式除了手术、放射治疗和化学治疗外,非TNBC还包括内分泌治疗和靶向药物治疗,但TNBC对ER、PR为靶点的内分泌治疗和以HER-2为靶点的药物无效,使得临床治疗陷入困境。为改善TNBC的临床疗效,探索精准治疗和个体化治疗的方法和药物,学者们在TNBC研究中,除HER-2、ER、PR外,目前已发现的生物标记物有聚二磷酸腺苷核糖聚合酶(poly-ADP-ribose polymerase, PARP)、胰岛素样生长因子结合蛋白(insulin-like growth factor binding protein, IGFBP)、程序性死亡配体1(programmed cell death 1 ligand 1, PD-L1)、白细胞介素8(interleukin-8, IL-8)及糖皮质激素受体(glucocorticoid receptor, GR)等,均有望成为真正意义上的个体化治疗生物标记。

1 PARP

PARP是一类广泛存在于真核细胞中的核苷酸切除修复酶,它能识别并结合断裂的DNA链,然后募集ADP核糖单位、组蛋白以及各种DNA修复相关酶,通过一系列的催化调节反应,修复断裂的单链DNA,从而保持染色体结构完整、参与DNA复制和转录^[4-5]。PARP家族目前已知存在有18种蛋白,其中PARP1对肿瘤的增值、分裂、分化过程起相当重要的作用,它与乳腺癌易感基因(breast cancer susceptibility gene, BRCA)共同作用于DNA单双链的修复。BRCA-1和BRCA-2主要通过同源重组修复(homologous recombination)途径修复损伤的DNA^[6],而在BRCA突变的细胞中,同源重组碱基修复功能不能完成,细胞将更多地依赖PARP来调节DNA修复,但如果PARP同时缺失,就会产生合成致死效应,

导致DNA双链损伤无法进行修复。

一些前期临床试验表明, BRCA1/BRCA2突变的肿瘤细胞株对PARP抑制剂是敏感的,在一项II期临床试验^[7]中, PARP抑制剂olaparib被用于治疗有BRCA1/2突变的进展期乳腺癌患者,其结果显示患者在客观缓解率(objective response rate, ORR)及无进展生存期(progression-free survival, PFS)上有明显获益。然而,在另一项样本数量相当的II期临床实验^[8],而对象为无BRCA突变的TNBC患者时,其结果未示明显获益。O'Shaughnessy等^[9]将吉西他滨联合卡铂添加PARP抑制iniparib作为试验组与吉西他滨联合卡铂添加安慰剂对比用于TNBC患者,试验组客观缓解率显著提高(52% vs. 33%), PFS(5.9个月 vs. 3.6个月)以及总生存期(overall survival, OS)(12.3个月 vs. 7.7个月)延长。但在随后的一项多中心III期临床试验中, iniparib与吉西他滨联合卡铂对比单纯GC方案化疗,两组患者的PFS及OS并无明显统计学差异,与前期实验结果不符^[10]。而更新的一项III期临床试验中,共302例有BRCA突变的TNBC受试者,口服PARP抑制剂olaparib作为试验组,相对接受标准化疗的患者在中位PFS(7.0个月 vs. 4.2个月)和ORR(59.9% vs. 28.8%)上均表现出统计学差异^[11]。这可能说明, PARP抑制剂无论作为单一疗法还是与其他化疗药物联合应用都没有对未经筛选的TNBC患者带来明显获益,但对于有BRCA突变或二线治疗以上的TNBC患者, PARP仍是最有潜力的治疗靶点之一。Domagala等^[12]利用特异性PARP抗体在179例TNBC组织中检测到, PARP1高表达比例达86%。一项Meta分析结果显示,对比非TNBC组, TNBC中PARP1的表达显著升高^[13]。随着研究的继续深入, PARP有望成为一项预测性的生物标记物,帮助筛选获益患者并提供与之相关的靶向治疗选择。

2 IGFBP

IGFBP是胰岛素样生长因子(IGF)的配体结合蛋白,是一个包括IGFBP1至IGFBP6的系列家族标记物, IGFBP通过增加游离的IGF数量及延长IGF半衰期来调节肿瘤的发生发展^[14]。IGF又

经与胰岛素样生长因子受体1 (IGF-R1) 结合激活PIK3/AKT通路启动肿瘤增值及抗凋亡效应^[15]。IGFBP2是一种在新生细胞中过表达的生长因子, 尤其是HER-2阴性的乳腺癌细胞中^[16]。迄今为止对于IGFBP2在TNBC中的作用机制探索尚未完全清楚, 作为TNBC的标记物的探讨也有不同的解释, 有学者^[17]认为IGFBP2通过与 α 雌激素受体 (ER- α) 结合使细胞内源性磷酸酶-张力蛋白 (PTEN) 水平上升, 负性调控PI3K通路以促进肿瘤细胞增殖。有研究^[18]指出, 在接受新辅助化疗的TNBC患者中, IGFBP2可作为预测无复发生存期 (recurrence-free survival, RFS) 的一项单独指标。然而, Hernandez等^[19]在2015年的一项调查中否定了这一观点, 调查测试了不同人种中IGF和IGFBP表达情况与生存率的关系, 包括亚洲人、太平洋岛民及高加索人种, 调查结果为IGFBP的表达与乳腺癌患者的生存率呈负相关关系, 且IGFBP2的表达在不同种族人种间有差异性, 同时调查表明, TNBC的发生与IGF1及IGFBP2表达下降相关。但此测试中TNBC高发的非裔美洲人群却未包含在试验对象人群内。因此, IGFBP2有希望在与其它标记物结合分析的情况下成为个别群体预后的生物标记物, 但要使之成为更有力的证据判断需要更大规模的人群测试。

IGFBP3与IGFBP2作用机制类似, 它能绑定IGF-1以及IGF-2延长其半衰期, IGF又同IGF-1R结合导致肿瘤发展。另有研究^[20-21]结果表明, 在TNBC患者中IGFBP3可以经由激活神经鞘氨醇激酶1引起EGFR表达升高, 进而诱发肿瘤细胞增殖、血管生成及转移。血液中高浓度IGFBP-3的患者可能有更高的死亡风险^[19]。

经由对其机制的探讨, IGFBP有可能作为TNBC的一项预后生物标记物^[22], IGFs、IGFBP、IGF-1R以及有相互作用的其他信号系统也都能作为潜在的治疗作用靶点, 对胰岛素样生长因子/胰岛素系统、配体、配体蛋白和受体相关抑制剂虽然还未有相关的正式报道, 但其探索价值值得期待。

3 PD-L1

PD-L1 (B7-H1, CD274) 是被CD274基因编码的一类跨膜蛋白, 也是机体免疫应答的关键调

控位点^[23-24]。PD-L1主要表达于B细胞、NK细胞及血管内皮细胞的细胞膜, 通过与PD-1结合在T细胞的活化增殖过程中发挥负调作用^[25]。PD-L1/PD-1结合能产生抑制白细胞介素2 (IL-2)、T细胞活化及增值的生物学作用, 以此来负性调控机体免疫应答, 导致肿瘤细胞免疫逃避的发生^[23]。TNBC中PD-L1的表达预计高于20%, 这一数值普遍认为高于非TNBC中的表达^[26-27]。PD-L1在TNBC中表达上调的具体机制还有待进一步探索, 目前研究^[27]内容表明PD-L1表达可能与PTEN的缺失相关。另一说法是 γ -干扰素 (interferon- γ , IFN- γ) 可以上调肿瘤细胞表面的PD-L1^[28-29]。

不久前, 一项临床路径^[30]显示, PD-L1阳性的转移性TNBC患者接受高亲和力的PD-L1抗体 pembrolizumab 治疗, 使用单药疗法的患者OS达到18.5%。在另一项I期临床试验中^[31], 应用PD-L1单克隆抗体 atezolizumab 治疗PD-L1阳性TNBC患者, 其客观有效率为33%, 这些实验提示PD-L1可以作为TNBC个体化免疫治疗中的预测性生物标记物。也有研究^[32-33]表明, 组织中高表达PD-L1的TNBC患者往往获得更长的DFS, 虽然这些研究中PD-L1的表达与否还未在OS上表现出差异, PD-L1仍有可能作为预后性的生物标记物应用于TNBC的临床工作。

4 IL-8

IL-8或称CXCL8是由IL-8基因在染色体4q13-q21上编码的一类趋化因子。Bendrik等^[34]发现IL-8在ER阴性的乳腺癌细胞株中呈过度表达, 而在ER阳性的乳腺癌细胞株中则表达较低。另外, Choi等^[35]报道IL-8在TNBC细胞中有更高分泌量, 而于此对应的患者预后相对较差。IL-8是TNBC细胞在缺氧条件下产生的物质, 它可以向肿瘤区域补充间充质干细胞 (mesenchymal stem cells, MSC)^[36]。MSC通常在骨髓和脂肪组织中, 但当它被TNBC诱导时, 它会定位于乳腺肿瘤并在周围形成一个仿肿瘤干细胞特性的微环境^[37], 与受体结合后IL-8能促进癌细胞增殖、血管生长, 同时调控血管内皮细胞生长因子分化, 而肿瘤生长和转移有赖于血管生成, 因此TNBC的转移风险增加^[19]。

TNBC患者常常对TNBC的标准化疗蒽环类药物产生耐药, 这也许归因于IL-8可以上调TNBC细胞表面的乳腺癌耐药蛋白(BCRP)数量。BCRP是一类72 kDa的跨膜蛋白, 它具有将蒽环类药物从肿瘤细胞表面移除的能力^[38-40]。一些体外试验的数据表明, TNBC细胞表面的BCRP呈高水平表达, 并且经过药物处理后能够进一步上调表达。值得注意的是, 在蒽环类药物作用于肿瘤细胞后, BCRP的上调仅维持短暂的数小时, 但IL-8将在接下来的几天内持续表达^[41-42]。Chen等^[36]进行的一项研究发现IL-8能够在不影响其他蛋白标记表达的情况下提升BCRP的表达, 这使得IL-8有可能成为一项潜在代理性生物标记物, 代替BCRP在TNBC中的表达水平, 也将提示TNBC对化疗药物的耐药程度。

5 GR

GR是由一段由9个外显子组成的DNA片段在染色体5p31q上编码的, 其配体——糖皮质激素, 则是肾上腺皮质兴奋状态下释放的一类血浆蛋白结合激素。配体激活状态下的糖皮质激素受体成为二聚物, 移动至细胞核内, 并增加糖皮质激素诱导基因的转录^[43-44]。这一过程将导致TNBC的抗凋亡作用被激活, 引起化疗药物的耐药^[45-46]。GR具体的作用机制还未有明确的定论, 已有临床前期证据提示, GR的抗凋亡作用可由BRCA1调节, BRCA1的活化可引起MAPK p38下游磷酸化^[44]。但另一些研究提示GR长时间活化将导致BRCA1表达下降, 而短时间游离的GR则上调BRCA1表达^[47-48]。要阐明GR的作用机制需要更多深入研究, 但GR仍能作为一个药效动力学生物标记物在TNBC诊治中发挥作用。

6 结 语

TNBC是所有乳腺癌类型中异质性高, 亚型众多的一种, 其复杂的生理生化特性导致其临床治疗困难重重, 生物标记物与TNBC的发生发展密切相关, 其在肿瘤细胞的增殖、抵抗凋亡、血管生成和转移中发挥了重要作用, 至今为止, 还没有已明确应用于TNBC的生物标记物, 因此对

分子靶标的深入、彻底的研究以及对分子水平的尖端技术钻研就显得更为重要, 对生物标记物作用机制的探索将提供对TNBC更具针对性的治疗路径, 为TNBC的治疗突破带来更多希望。

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