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·综 述·

# 曲妥珠单抗在HER2阳性胃癌中耐药机制研究进展

# Research progress on resistance mechanisms of trastuzumab in HER2-positive gastric cancer

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[摘 要] 曲妥珠单抗是晚期人表皮生长因子受体2(HER2)阳性胃癌患者治疗的一线用药,耐药问题是曲妥珠单抗治疗中面临的主要挑战。曲妥珠单抗治疗的耐药机制除了与HER2自身状态有关外,也与PI3K/AKT、MEK/ERK等经典信号通路以及有丝分裂相关的非经典信号通路的异常激活有关,胃癌肿瘤微环境中代谢及免疫调控的改变也会导致患者对曲妥珠单抗耐药,目前抗体药物偶联物等新型治疗方案可以克服并改善曲妥珠单抗的耐药性。本文聚焦曲妥珠单抗在HER2阳性胃癌中的耐药机制及其克服曲妥珠单抗耐药新型疗法的研究进展,为临床优化曲妥珠单抗治疗HER2阳性胃癌提供了新思路。

[关键词] 人表皮生长因子受体2(HER2);胃癌;曲妥珠单抗;耐药;抗耐药
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胃癌是全球第五大恶性肿瘤,由于多数胃癌患者在确诊时常处于晚期,其病死率极高,位居恶性肿瘤相关死亡原因的第四位[1]。随着精准医疗的发展,胃癌的分子靶向治疗越来越受到关注,其中抗人表皮生长因子受体2(human epidermal growth factor receptor 2, HER2)的临床意义较明确,应用较广泛[2]。HER2属于表皮生长因子受体家族,该家族成员还包括HER1、HER2、HER3和HER4,HER2可以与家族的其他成员构成异二聚体,以调节细胞增殖、分化、迁移和肿瘤发生[3-4]。全球胃癌患者中HER2平均阳性率为17.5%,中国胃癌患者的HER2阳性率为8.8%[5-6]。曲妥珠单抗(trastuzumab)是首个针对HER2开发的人源化单克隆抗体,其与HER2的细胞外结构域结合,抑制细胞内HER2信号通路,抑制细胞周期停滞并介导抗体依赖的细胞毒性[7]。近年来,曲妥珠单抗治疗胃癌的耐药机制研究逐渐深入,主要有HER2自身的突变、下游信号通路的异常激活,以及肿瘤微环境(tumor microenvironment, TME)和代谢的改变等[8-9]。本文就HER2阳性胃癌对曲妥珠单抗治疗耐药机制及克服耐药性的研究进展进行综述,为指导胃癌治疗及优化胃癌治疗策略提供参考依据。

## 1 曲妥珠单抗治疗的耐药机制

新的中国临床肿瘤学会胃癌临床指南和美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)指南均将曲妥珠单抗列为晚期HER2阳性胃癌患者的一线用药[6, 10]。然而,这种个体化治疗仍然面临着敏感性不足及耐药性的问题。探索曲妥珠单抗治疗耐药的机制并克服其耐药性可以为晚期胃癌患者提供新的治疗策略。

### 1.1 HER2表达异常

HER2结构的改变或者继发突变都会导致曲妥珠单抗治疗耐药的发生,曲妥珠单抗治疗后HER2表达的变化在胃癌中尚不明确。有学者[5]在测定曲妥珠单抗治疗晚期HER2阳性胃癌患者的HER2状态后发现,在接受曲妥珠单抗治疗的胃癌患者中有60.6%的患者发生了HER2的表达缺失,这种继发性的HER2表达缺失是胃癌患者治疗效果不明显的原因之一。另一项研究[11]也证实,在接受曲妥珠单抗治疗的患者中,有29.1%的晚期胃癌患者HER2阳性转为阴性,这种HER2状态的改变使得曲妥珠单抗的靶向性减弱,从而产生耐药问题。

### 1.2 HER配体及其下游信号通路调控

曲妥珠单抗耐药的主要机制之一是HER2下游信号通路的失调。SAMPERA等[12]通过研究曲妥珠单抗治疗耐药胃癌细胞的变化后发现,耐药细胞中表皮生长因子(EGF)、双调蛋白、转化生长因子α和肝素结合EGF样生长因子在内的HER家族配体在耐药细胞中过表达。过表达的HER配体会引起下游MAPK/ERK和PI3K/AKT等通路的异常激活,这与曲妥珠单抗的敏感性密切相关[13-14]。

#### 1.2.1 PI3K/AKT信号通路

PI3K/AKT通路是HER2调控胃癌进展的重要信号通路,也是曲妥珠单抗治疗HER2阳性胃癌后改变较为明显的信号通路,该通路与曲妥珠单抗的治疗

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耐药性密切相关。研究[15]表明，PI3K激酶α的突变及磷酸酶和张力蛋白同源物（phosphatase and tensin homolog, PTEN）的失活均会导致PI3K/AKT的过度激活。PTEN的缺失与曲妥珠单抗治疗后的反应不佳有关，PTEN可以负调控PI3K/AKT信号通路，从而影响曲妥珠单抗的治疗敏感性，PTEN的下调与miR-21相关，miR-21能够负调控PTEN而上调PI3K/AKT信号通路导致曲妥珠单抗耐药[16]。PI3K/AKT也与肿瘤血管生成密切相关，6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶可以调控HER2促进CXCL8向TME分泌，从而促进肿瘤血管生成，这种作用与PI3K/AKT/NF-κB通路相关，并且使得曲妥珠单抗治疗产生耐药[17]。

1.2.2 MEK/ERK信号通路

类固醇受体共激活因子（steroid-receptor coactivator, SRC）是一种非受体酪氨酸激酶，参与HER2调节的下游信号通路，在曲妥珠单抗耐药细胞中SRC的磷酸化会上调，SRC能够与黏附斑激酶（focal adhesion kinase, FAK）相互作用影响MEK/ERK信号通路调控曲妥珠单抗的治疗敏感性[18]。β-半乳糖苷α2,6-唾液酸转移酶Ⅰ与胃癌的转移和不良预后相关，其下游信号的调控也是通过提高ERK的磷酸化水平，从而促进曲妥珠单抗治疗耐药[19]。此外，其他药物或激素也有可能改变ERK信号通路而使得曲妥珠单抗治疗耐药，如儿茶酚胺也能够激活ERK信号通路并可在转录水平上诱导黏蛋白4表达上调，从而降低曲妥珠单抗治疗胃癌的敏感性[20]。

1.2.3 Wnt/β-catenin信号通路

β-连环素（β-catenin）可以与HER2直接结合并促进HER2在Y877和Y1248位点的磷酸化，还能够通过促进HER2与SRC的相互作用使曲妥珠单抗治疗耐药[21]。研究[22]表明，Wnt/β-catenin信号通路介导的上皮钙黏素（E-cadherin）缺失与转移性的HER2阳性胃癌患者低生存率有关，曲妥珠单抗会使E-cadherin表达减少，从而抑制Wnt/β-catenin信号通路。研究[23]表明，在曲妥珠单抗耐药的胃癌细胞中Wnt/β-catenin信号异常激活，并且当胃癌细胞在含有Wnt受体Wnt3a的条件培养基中培养时，Wnt信号通路活性及对曲妥珠单抗耐药性增加，通过进一步实验发现，在胃癌中Wnt/β-catenin通路能够通过调控胃癌细胞的干性和上皮间质转化（EMT）表型促进胃癌细胞耐药。

1.2.4 PLK1/MISP信号通路

研究[24]表明，曲妥珠单抗的治疗耐药与保罗样激酶1（Polo-like kinase 1, PLK1）的下游信号通路相关，靶向PLK1可以改善曲妥珠单抗治疗乳腺癌的敏感性。但是，关于PLK1信号通路与胃癌治疗敏感性的研究较为缺乏。研究[25]发现，SHC-转化蛋白1（SHC-transforming protein 1, SHC1）的结合蛋白SHC结合和纺锤体相关1（SHC binding and spindle associated 1, SHCBP1）在HER2激活后会与SHC1分离，释放后的SHCBP1会易位到细胞核中响应HER2的级联反应，通过与PLK1结合并促进PLK1错义互作蛋白（missense-interactor of PLK1, MISP）的磷酸化，从而调节细胞有丝分裂，SHCBP1及PLK1的信号异常激活会降低曲妥珠单抗治疗胃癌的敏感性。

1.3 肿瘤代谢及微环境改变

CHANG等[26]敲减胃癌耐药细胞中GATA6基因后，进行代谢组学分析发现，GATA6参与胃癌耐药细胞的三羧酸循环、糖代谢、氨基酸及核苷酸代谢，导致胃癌细胞代谢重编程，从而促进曲妥珠单抗的耐药性。研究[27]表明，胃癌细胞中的糖酵解活跃是曲妥珠单抗耐药的关键因素，与曲妥珠单抗敏感细胞相比，曲妥珠单抗耐药细胞会导致具有昼夜节律的糖酵解相关基因表达增加，伴随着规律的己糖激酶2依赖性节律。与曲妥珠单抗耐药相关的代谢研究除了糖酵解，还有谷氨酰胺代谢。最近的一项研究[28]发现，曲妥珠单抗耐药的HER2阳性胃癌细胞中所有谷氨酰胺分解代谢相关的转运蛋白和代谢酶均增加，谷氨酰胺酶1（glutaminase 1, GLS1）的过表达最为明显，因此，耐药细胞中谷氨酰胺代谢水平明显升高。TME由多种免疫细胞和蛋白质组成，主要作用为促进肿瘤的进展[29]。TME内的免疫细胞具有双重作用，既抑制肿瘤，又通过细胞因子分泌参与肿瘤血管生成、免疫抑制和细胞增殖等过程[30]。TME中免疫细胞的这些复杂的多重作用往往会促进肿瘤进展，增强对药物治疗的耐受性。研究[31]表明，HER2信号转导可能参与胃癌TME中免疫细胞活化的调节，HER2信号转导通过抑制胃癌细胞中干扰素基因刺激因子信号转导来抑制胃癌TME中的免疫细胞活化，从而产生耐药。TME中巨噬细胞与肿瘤的进展密切相关。研究[28]显示，胃癌细胞会通过CDC42/NF-κB信号通路促进GLS1表达并促进GLS1微囊泡释放至TME中，这些微囊泡具有促进巨噬细胞极化为M2型和促血管生成功能，导致HER2阳性胃癌细胞产生获得性曲妥珠单抗耐药。

## 2 克服曲妥珠单抗耐药性的新策略

随着对曲妥珠单抗耐药机制研究的不断深入，针对其耐药机制的新策略不断丰富，增加曲妥珠单抗对晚期胃癌的治疗敏感性成为临床研究的热点[32]。泛人类表皮生长因子受体（pan-human epidermal

growth factor receptor, pan-HER）抑制剂是一类新型的针对HER家族受体的抑制药物，能够与曲妥珠单抗联合提高曲妥珠单抗的治疗效果[33]。除了抑制HER2，pan-HER抑制剂还可以作用于HER家族的其他受体，从而克服曲妥珠单抗的耐药性[34]。近年来，许多pan-HER抑制剂，如波西替尼（poziotinib）、拉帕替尼（lapatinib）等，已经在胃癌治疗的临床试验中不断被评估[35-36]。此外，抗体-药物偶联物可以弥补曲妥珠单抗治疗敏感性低的问题[37]。目前，最常见的曲妥珠单抗-药物偶联物分别为曲妥珠单抗-美坦新（emtansine）和曲妥珠单抗-德曲妥珠单抗（trastuzumab deruxtecan）。最近的一项Ⅱ期临床试验结果[38-39]显示，与曲妥珠单抗标准疗法相比，曲妥珠单抗-德曲妥珠单抗治疗可显著改善HER2阳性胃癌患者的预后。研究[40]表明，曲妥珠单抗和二甲双胍联合治疗可以提高HER2阳性胃癌患者的临床疗效。在曲妥珠单抗耐药胃癌细胞中，糖酵解随着昼夜节律的振荡而波动，基于二甲双胍的时间疗法会破坏该昼夜节律振荡并部分克服曲妥珠单抗治疗胃癌的耐药问题[27]。此外，曲妥珠单抗和免疫疗法联合治疗是治疗HER2阳性胃癌患者的一种有前景的策略。除了联合其他疗法外，最新的研究[41]发现，新的药物递送技术也可逆转曲妥珠单抗的耐药性，一种新的TME中pH响应型mRNA递送的纳米平台能将PTEN等治疗性的mRNA递送至TME中，从而逆转曲妥珠单抗的耐药性。

## 3　结　语

曲妥珠单抗在治疗晚期胃癌中具有良好的临床疗效，已经被美国FDA批准为晚期HER2阳性胃癌的一线标准疗法，但是由于胃癌异质性较高，较长时间的曲妥珠单抗治疗会导致继发性耐药，曲妥珠单抗耐药的问题仍然是晚期胃癌患者治疗面临的巨大挑战。曲妥珠单抗耐药的机制十分复杂，涉及到多种基因、信号通路及代谢和肿瘤免疫微环境的改变[42]。改善药物递送途径、联合免疫治疗、抗体-药物偶联物及同时阻断HER2和其他靶点是克服曲妥珠单抗耐药的潜在治疗策略。有学者[43]指出，曲妥珠单抗与其他药物联用克服曲妥珠单抗耐药性仍然是目前临床试验的主要研究方向。目前，许多新型的靶向HER2的药物可用于克服曲妥珠单抗治疗的耐药性[44]。未来可以开展更多靶点药物联合手术治疗的探索改善曲妥珠单抗等一线治疗的耐药问题，从而提高晚期胃癌患者的生存率并减轻症状，克服曲妥珠单抗耐药性的新型策略研究具有广阔的前景。

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