

转移性结直肠癌抗 EGFR 治疗耐药机制的研究进展

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【摘要】 表皮生长因子受体(epidermal growth factor receptor, EGFR)是转移性结直肠癌(metastatic colorectal cancer, mCRC)的主要治疗靶点之一,然而抗 EGFR 治疗的耐药一直是亟待解决的临床难题。肿瘤细胞本身 EGFR 相关信号通路异常激活,基因组不稳定性等遗传学或表观遗传学改变是引发耐药最常见的机制,近期也有研究发现肿瘤微环境中细胞丰度和细胞因子的变化等也是引发抗 EGFR 治疗耐药的重要机制。我们将从肿瘤细胞和肿瘤微环境两个方面,对 mCRC 抗 EGFR 治疗的耐药机制进行综述。

【关键词】 转移性结直肠癌(mCRC); 表皮生长因子受体(EGFR); 耐药; 基因突变; 肿瘤微环境

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Research progress in the resistance mechanism of anti-EGFR therapy in metastatic colorectal cancer

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【Abstract】 Epidermal growth factor receptor (EGFR) is one of the primary therapeutic targets for metastatic colorectal cancer (mCRC). However, primary or acquired resistance to anti-EGFR therapy has long been a crucial problem to be solved urgently. Abnormal activation of EGFR-related signaling pathways in tumor cells, genomic instability and genetic or epigenetic changes are the most common mechanism of resistance to anti-EGFR therapy. Meanwhile, recent evidences showed that alterations of cell abundance and cytokines in the tumor microenvironment are also closely related to anti-EGFR therapy resistance. In this review, we will summarize the research progress about the mechanism of resistance to anti-EGFR therapy in CRC from the aspects of both the tumor cell and tumor microenvironment.

【Key words】 metastatic colorectal cancer (mCRC); epidermal growth factor receptor (EGFR); resistance; genetic mutations; tumor microenvironment

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结直肠癌(colorectal cancer, CRC)是全球第三大常见癌症,也是第三大癌症相关死亡原因^[1]。远处转移是导致 CRC 患者死亡最常见的原因,转移性

结直肠癌(metastatic colorectal cancer, mCRC)患者5年生存率仅为13.8%^[2]。长期以来,以化疗为基础的系统治疗在 mCRC 的综合治疗中占主导地位,患

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者中位总生存期在8~12个月^[3-4]。2004年,靶向表皮生长因子受体(epidermal growth factor receptor, EGFR)药物西妥昔单抗的出现,标志着mCRC进入分子靶向治疗的时代。EGFR属于表皮生长因子受体家族,与配体结合后形成同源或异源二聚体,进而激活下游通路,诱导细胞增殖^[5]。多项研究表明^[6-7],化疗联合抗EGFR治疗mCRC的总体生存(overall survival, OS)和无进展生存(progress free survival, PFS)均显著高于单纯化疗。

然而,抗EGFR治疗仅对部分RAS/RAF野生型的mCRC有效,RAS/RAF作为EGFR下游通路分子可介导EGFR的信号通路激活,引起对抗EGFR治疗耐药,初始RAS/RAF野生型mCRC在抗EGFR治疗的压力下,基因发生继发性突变可引起获得性耐药。最新的国内外指南已将KRAS、NRAS及BRAF状态作为指导抗EGFR治疗的重要标志物,也标志着mCRC的治疗理念向精准治疗转变。近期研究表明RAS和BRAF野生型患者依然可发生获得性抗EGFR耐药,有一半以上野生型患者不能从抗EGFR治疗中获益,仍存在抗EGFR

治疗耐药的其他机制^[8]。一方面,与mCRC发生发展相关的基因组学改变,使一部分RAS和BRAF野生型患者产生原发性耐药;另一方面,RAS和BRAF野生型患者在抗EGFR治疗过程中,其基因组发生改变可产生获得性耐药^[9];而最新研究表明治疗过程中肿瘤微环境(tumor microenvironment, TME)的重塑也可介导抗EGFR获得性耐药的发生^[10]。因此,精准筛选抗EGFR治疗受益患者尤为重要。本文将从肿瘤细胞和肿瘤微环境两个方面,对mCRC抗EGFR治疗的耐药机制进行综述,为临床预防和逆转耐药策略提供借鉴。

肿瘤细胞自身基因组学改变介导的抗EGFR耐药

RTK-RAS信号通路 以EGFR为代表的受体酪氨酸激酶超家族及其下游的RAS-RAF信号通路是目前发现的最主要的抗EGFR治疗耐药机制(图1)。除了经典的RAS及BRAF突变,介导抗EGFR耐药的基因组学改变可发生于该通路各个环节,包括配体、膜受体及下游信号转导分子。

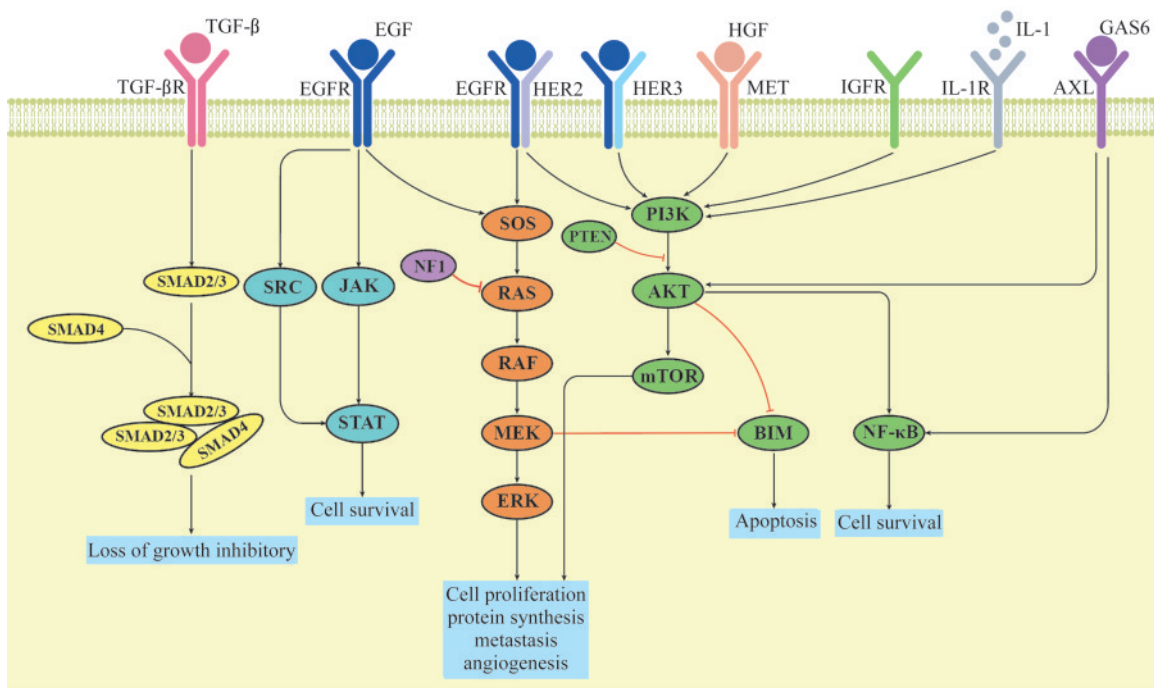


图1 表皮生长因子受体(EGFR)信号通路和可能耐药机制

Fig 1 Epidermal growth factor receptor (EGFR) signaling pathway and potential mechanism of resistance

AREG和EGF的低表达 双调蛋白(amphiregulin, AREG)和上皮调节蛋白(epiregulin, EREG)作为EGFR的配体,能诱导EGFR激活,进

而通过RAS-RAF-MAPK和PI3K-AKT-mTOR通路促进肿瘤的发生和发展。研究表明,AREG和EGF的表达水平与抗EGFR治疗疗效密切相关,

AREG和EREG高表达的患者预后更好^[11-12]。有学者尝试调节AREG和EREG的水平以改善抗EGFR疗效,降低AREG/EREG启动子和基因内CpGs甲基化,使AREG和EREG基因表达上调,以达到临床获益^[13]。

EGFR突变 EGFR胞外区域突变也是抗EGFR治疗耐药的潜在机制之一, Montagut等^[14]发现EGFR ECD的S492R突变与抗EGFR治疗耐药相关,由于492位氨基酸的丝氨酸被精氨酸取代,位于EGFR胞外结构域的冗长侧链可干扰EGFR与西妥昔单抗的结合。与此同时,S492R突变只在经抗EGFR治疗的mCRC患者中检测到,可能是由于靶向治疗导致EGFR胞外区域的突变而引起获得性耐药^[15]。陆续有研究发现并确定了许多其他ECD突变(I462, S464, G465, K467, K489, I491),这些突变同样介导mCRC抗EGFR治疗的耐药^[16-17]。一些新型抗EGFR疗法(Sym004和MM-151)可通过靶向EGFR ECD的不同位点来克服EGFR ECD突变引起的耐药^[18-19]。

HER2扩增 人表皮因子生长受体(human epidermal growth factor receptor, HER2)是由HER2基因编码的一种酪氨酸激酶受体,与细胞增殖分化有关。HER2基因扩增发生于3%~5%的RAS野生型mCRC中,是抗EGFR治疗耐药的重要机制之一^[20-21]。抗EGFR治疗耐药的KRAS野生型患者中,部分存在HER2扩增,且扩增个体肺转移率较高^[20,22]。多项研究揭示应用HER2抑制剂对该类患者疗效甚佳^[23-24]。2016年HERACLES研究^[23]结果显示,对经化疗联合抗EGFR治疗无效,KRAS野生型且HER2扩增的患者进行双靶向治疗(曲妥珠单抗+拉帕替尼),客观应答率(objective response rate, ORR)达30%且无严重不良反应。在MyPathway的研究^[25]中,37例HER2扩增的转移性结直肠癌患者,经双靶向治疗(曲妥珠单抗+帕妥珠单抗)后取得部分缓解(partial response, PR)的有14例(38%; 95%CI: 23%~55%)。最近DESTINY-CRC01研究^[26]显示,DS-8201(一种由曲妥珠单抗和拓扑异构酶I抑制剂组成的抗体耦联药物)用于既往接受过标准治疗的HER2阳性的转移性CRC患者,取得临床获益且ORR达45.3%。HER2状态的评估为临床治疗决策提供了重要依据,HER2联合EGFR靶向治疗可能作为抗EGFR耐药患者的潜在

治疗方案,但仍需要更多的临床试验进一步验证。

MET扩增 MET基因编码肝细胞生长因子(hepatocyte growth factor, HGF)的酪氨酸激酶受体(c-MET), c-MET可绕过RAS直接激活其下游MAPK和AKT通路,在多种肿瘤中均有致癌作用且与不良预后相关^[27-28]。在未经治疗的mCRC患者中,仅有约1%存在MET扩增,与KRAS/BRAF突变以及HER2扩增呈互斥关系,且MET扩增的异种移植瘤对抗EGFR治疗无应答^[29]。Bardelli等^[29]发现MET扩增与KRAS野生型患者抗EGFR治疗的获得性耐药性有关,且体内体外实验证明抗EGFR治疗联合MET抑制剂可以逆转耐药,显著诱导肿瘤消退。

KRAS扩增 除热点突变外,KRAS扩增也是致癌机制之一。近期发现一小部分mCRC患者存在KRAS扩增,可能是导致患者耐药的原因^[30]。有研究证实,KRAS扩增个体对抗EGFR治疗不敏感,与患者不良预后相关^[30-31]。Favazza等^[32]发现KRAS扩增的患者几乎均有炎症性肠病病史,8例接受了抗EGFR治疗,在治疗过程中均出现疾病进展,4例扩增且RAS/BRAF/PIK3CA野生型患者在接受西妥昔单抗治疗后均未获益。因此,KRAS扩增可能是EGFR抑制剂的潜在耐药机制。

MAP2K1突变 丝裂原活化蛋白激酶激酶1(mitogen-activated protein kinase kinase, MAP2K1)又称MEK1,是RAS和RAF下游的一种蛋白激酶,在细胞增殖和分化中起重要作用^[33]。MAP2K1在mCRC患者中突变率为1%~2%,其中最常见突变类型包括K57E/N/T和Q56P,可导致MAP2K1结构性激活^[34-35]。前期有研究表明,MAP2K1突变是mCRC患者对EGFR抑制剂产生原发和继发耐药的潜在机制^[9,36]。Russo等^[37]对接受抗EGFR治疗长期有效后发生肝转移的患者进行活检穿刺,发现该基因第57位密码子的赖氨酸被苏氨酸取代,且给予帕尼单抗联合曲美替尼治疗后取得疗效。Chuang等^[38]发现联合MEK抑制剂可提高抗肿瘤疗效,但之后有2名患者经抗EGFR联合MEK抑制剂治疗后仍发生疾病进展。因此,MAP2K1突变通过激活下游通路,介导抗EGFR治疗耐药,而抗EGFR联合MEK抑制剂治疗可能对该类患者有效。

除上述耐药机制外,RTK-RAS通路中其他分子近年来也被证明与抗EGFR治疗耐药相关,有研

究表明膜受体 AXL 过表达、EPHA2 过表达以及 NF1 抑癌基因突变等与治疗耐药相关,均有可能成为潜在治疗靶点,但仍需进一步证实^[10,39-41]。

PI3K-AKT 信号通路 在 EGFR 下游通路中,除了 RAF-RAF-MEK 通路外,PIK3/PIK3CA 通路也参与了抗 EGFR 治疗的耐药(图 1)。

PIK3CA 突变 PIK3CA 突变在 CRC 中的发生率为 10%~20%,主要发生在外显子 9 和 20,引起 PI3K 下游的 AKT/mTOR 信号的激活^[42]。研究表明,PIK3CA 外显子 20 的突变与抗 EGFR 治疗低应答率有关^[43]。PIK3CA 外显子 20 突变与接受抗 EGFR 治疗的 KRAS 野生型 mCRC 患者的 PFS 和 OS 显著相关,KRAS/NRAS/BRAF/PIK3CA 野生型的肿瘤患者的总有效率为 64.4%,mPFS 为 11.3 个月,任一基因发生突变都会使这两项指标降低(ORR 47.4%,mPFS 7.7 个月)^[44]。以上研究结果表明 PIK3CA 外显子 20 突变可以作为抗 EGFR 治疗耐药的潜在生物标志物,而外显子 9 与抗 EGFR 治疗耐药的相关性尚不明确。

PTEN 缺失/突变 在 PI3K-PTEN-AKT 通路中,PTEN 作为肿瘤抑制基因在肿瘤发生发展中发挥重要作用,PTEN 缺失导致细胞内 PI3K/AKT 信号的持续激活^[45]。PTEN 缺失存在于 30% 的 CRC 患者中,且与抗 EGFR 治疗耐药有关^[46]。Loupakis 等^[47]发现治疗有效患者的转移灶中 PTEN 阳性显著,提示 PTEN 状态可能是预测抗 EGFR 治疗疗效的指标。增强 PTEN 的功能可以通过增强其转录来实现,而转录的表现遗传沉默是由于启动子或组蛋白甲基化所致。早期研究报道了 DNA 甲基转移酶抑制剂地西他滨联合帕尼单抗治疗 KRAS 野生型患者的安全性^[48-49]。

TGF- β 通路

SMAD4 突变 抑癌基因 SMAD4 是转化生长因子 β (transforming growth factor- β , TGF- β)信号通路的关键分子,其失活突变可引起 TGF- β 通路的异常激活,约有 10% 的结直肠癌患者发生 SMAD4 基因突变且与预后不良相关^[34,50]。抗 EGFR 单抗的低反应性是由于 TGF- β 引起的 MAPK/JNK 信号通路过度激活而导致^[51-52]。FIRE-3 研究表明,SMAD4 突变是预后不良的标志物之一,且 SMAD4 野生型个体经西妥昔单抗治疗的 ORR 更高,SMAD4 突变可能为西妥昔单抗耐药提供依据^[51,53]。

非编码 RNA 肿瘤细胞介导的抗 EGFR 耐药机制中,除了经典信号通路的基因组学改变外,以非编码 RNA 为代表的表观遗传学改变也是近年来发现的重要机制。

micro-RNA micro-RNAs(miRs)是在转录后水平控制基因表达的短链非编码 RNA,参与细胞的发育和各项生理过程,并在肿瘤或炎症等病理条件下失调^[54]。结直肠癌中,miRs 的失调促进了肿瘤的发生、发展以及治疗耐药^[55-56]。miRs 不仅可作为肠癌早期诊断生物标志物,也是早期 mCRC 对抗 EGFR 单抗耐药的潜在决定因素^[57]。

在 mCRC 中,miR-31 通过抑制 RAS-p21-GTP 酶激活蛋白 1 来激活 RAS 信号通路,从而促进癌细胞的发生和生长,miR-31 高表达与 mCRC 的疾病进展和不良预后相关,而 miR-31-3p 低表达患者在 FOLFIRI 联合西妥昔单抗治疗中获益^[58-61]。Mosakhani 等^[62]检测了接受抗 EGFR 治疗的 KRAS/BRAF 野生型患者中原发灶的 miRNA 表达,发现 miR-31、miR-140-5p 上调和 miR-592、miR-1224-5p 下调与不良预后相关,miRNA 图谱可以有效筛选患者进行个体化治疗。研究发现,miR-100 和 miR-125b 的过表达与西妥昔单抗耐药有关,可协同抑制 Wnt/ β -catenin 负调控因子,引起 Wnt 信号通路激活,且抑制 Wnt 信号通路可恢复对西妥昔单抗的反应^[63]。

lncRNA 长链非编码(lncRNA)是长度大于 200 个核苷酸的非编码 RNA,可通过结合 miRs 和蛋白质来影响 mRNA 翻译和基因的表达。研究表明,lncRNAs 的失调与人类癌症相关^[64-66]。lncRNA SNHG6 通过与 miR-26a、miR-26b 和 miR-214 相互作用并调节它们共同的靶点 EZH2,促进肠癌细胞的生长、迁移和侵袭^[67]。体外实验表明,lncRNA CRNDE 通过调控 miR-181a-5p 促进肠癌细胞的增殖和化疗耐药^[68]。Peng 等^[69]发现 9 种 lncRNA 在疾病控制组和治疗无应答组之间表达存在差异,其中 5 种与患者 PFS 显著相关,进一步研究发现 lncRNA POU5F1P4 在获得性耐药细胞中和患者体内均下调,证明此基因下调促进了 mCRC 患者对西妥昔单抗的耐药性。lncRNA LINC00973 在西妥昔单抗耐药细胞中的表达显著上调,敲低可改善 H508 细胞对西妥昔单抗的耐药性^[70]。Yang 等^[71]研究发现,具有 3 个外显子的 lncRNA 尿路上皮癌相关 1(UCA1)在西妥昔单抗耐药肠癌细胞及外泌体中表

达明显增加,进展期患者UCA1表达明显高于病情缓解个体,且该lncRNA可通过外泌体传递至敏感细胞使其获得耐药性。lncRNA CRART16过表达可以下调miR-371a-5p来诱导西妥昔单抗耐药,进而负性调控V-Erb-B2红系白血病病毒同源基因3(ERBB3)的表达^[72]。虽然介导抗EGFR治疗耐药的lncRNA被陆续发现,但是其耐药机制仍不明确。

其他机制

Src Src基因编码非受体酪氨酸激酶,约80%的CRC患者Src基因过表达,且与mCRC的发生密切相关^[73]。有研究发现Src的激活介导了抗EGFR耐药的发生,耐药细胞株DiFi5存在Src介导的信号激活,Src抑制剂PP2可以对抗其耐药性^[74]。但一项Ⅱ期临床试验研究显示FOLFOX与西妥昔单抗和达沙替尼联合使用对mCRC患者无明显获益,可能因为达沙替尼不能完全消除Src引起的磷酸化^[75]。在肺癌和乳腺癌中Src抑制剂和抗EGFR联合治疗的临床试验在进行中且取得一定疗效,但是在mCRC中有待进一步证实。

FBXW7突变 抑癌基因FBXW7编码Skp1-Cullin1-F-box蛋白泛素E3连接酶复合物的底物识别成分^[76]。E3连接酶复合体负向调节细胞内一系列关键致癌蛋白,因此,FBXW7功能缺失会引起胞内致癌蛋白积累,促进癌症发生发展^[77]。在肠癌中,FBXW7突变发生率为6%~10%,其缺失与RAS激活和抗EGFR单抗耐药的基因表达谱相关^[78]。研究表明,接受抗EGFR和化疗方案治疗的mCRC患者中耐药个体可发生FBXW7突变且治疗效果差^[79-80]。在CAPRI-GOIM研究中,1例FBXW7突变患者PFS为18个月,另2例FBXW7突变患者对FOLFIRI联合西妥昔单抗治疗无应答,部分从靶向联合化疗方案中获益的FBXW7突变个体均存在GAS6基因扩增,可能因为GAS6过表达与良好预后相关^[81-82]。

PRSS 丝氨酸蛋白酶由PRSS基因编码,可以断裂大分子蛋白质中的肽键。Tan等^[83]研究发现,肠癌细胞自身分泌PRSS,降解西妥昔单抗从而介导耐药。西妥昔单抗耐药细胞中PRSS1表达上调,敲低PRSS1可以抑制PI3K/AKT和MEK/ERK信号的激活。SNINK1是一种胰蛋白酶抑制剂,体内外可显著抑制PRSS1对西妥昔单抗的降解,SPINK1与西妥昔单抗联合治疗比单用更能有效抑

制癌细胞生长和p-ERK水平。mCRC患者血清中PRSS高水平与西妥昔单抗治疗无效密切相关,且PRSS1和PRSS3低表达个体PFS更长。因此PRSS高表达可能与抗EGFR治疗耐药相关,靶向治疗联合PRSS抑制剂是可行的选择。

基因组不稳定性 基因组不稳定性(genomic instability,GI)是指获得性基因突变率增加,与癌症发生发展密切相关^[84]。Russo等^[85]研究发现EGFR抑制剂可以下调耐药细胞中错配修复和同源重组修复基因,同时诱导低保真DNA聚合酶的合成,从而导致获得性耐药,且靶向治疗后患者肿瘤组织中MMR相关蛋白表达水平降低;同时发现,EGFR抑制剂可能通过增加癌细胞中活性氧的水平引起DNA损伤,微卫星不稳定性增加。另一项研究发现错配修复基因MLH1下调与不良预后相关,体外实验证明MLH1过表达可以增强耐药细胞的敏感性;进一步研究发现,MLH1缺失通过激活HER2/PI3K/AKT通路介导西妥昔单抗耐药,且阻断HER2信号增加微卫星不稳定型的敏感性,并在队列研究中得到验证^[86]。综上所述,可利用药物或遗传干扰来抑制癌细胞发生药物驱动的适应性突变,以减少新变异的产生,增加靶向治疗的临床疗效。

肿瘤微环境重塑介导的抗EGFR耐药 尽管基因检测能筛查出抗EGFR治疗有效的患者,但大部分获得性耐药的患者中并未发现遗传驱动耐药的因子,近年来肿瘤微环境的改变成为耐药机制的研究热点^[10,87]。2015年国际结直肠癌分型联盟^[88]提出了共识分子模型,根据不同病理特征将结直肠癌分为4种亚型:CMS1为微卫星不稳定型,又称为高突变型,表现为错配基因修复的改变;CMS2为经典型,与WNT和MYC信号通路异常激活有关;CMS3为代谢型,表现为KRAS突变程度高,代谢失调;CMS4为TGF- β 信号通路异常激活。

肿瘤相关成纤维细胞介导 肿瘤相关的成纤维细胞(tumor associated fibroblasts,CAF)通过分泌生长因子和炎症介质,重塑细胞外基质,参与调解肿瘤细胞代谢及功能。Woolston等^[10]研究发现转录组亚型的改变与获得性耐药关系密切,指出大部分出现疾病进展的患者从抗EGFR敏感的CMS2亚型转变为CMS4亚型。CMS4亚型富含CAF,是TGF- β 和生长因子的主要来源。在CMS4中,TGF- β 1和TGF- β 2 RNA水平显著增加,且CAF条

件培养基(CAF medium, CM)培养CRC干细胞可以使其获得耐药性,用重组FGF1、FGF2和HGF处理,在西妥昔单抗暴露下癌细胞正常生长,且西妥昔单抗、FGFRi和MET抑制剂三药联用可有效抑制癌细胞生长,证实了CAF介导基质重塑在非遗传性耐药中的重要作用。另两项研究表明,在使用西妥昔单抗治疗后,CAF分泌的EGF和HGF增加,分别激活MAPK、MET信号通路,且双靶点治疗有助于克服耐药性^[89-90]。因此,在抗EGFR过程中,肿瘤微环境中CAF丰度增加,导致其分泌生长因子增加,从而引起获得性耐药,调节微环境中CAF丰度或其分泌的细胞因子可能成为新的治疗策略。

炎症细胞介导 体外研究显示,耐药细胞系中外周血单个核细胞产生的炎症因子,包括IL-1A、IL-1B和IL-8,均与EGFR治疗耐药相关。当肿瘤微环境中IL-1增加,IL-1与肿瘤细胞表面相应受体结合,继发性激活EGFR通路,来维持胞内ERK和AKT的信号^[91-92]。抑制该类细胞因子的产生可能是EGFR单抗耐药患者的有效治疗策略。研究表明,高水平表达IL-1受体(IL-1R)的患者对西妥昔单抗治疗无效^[92]。此外,接受西妥昔单抗联合化疗

的患者在治疗后外周血发生细胞因子改变(IL-2、IFN- γ 、IL-12和IL-18增加,IL-4和IL-10减少),提示与治疗反应相关,表明监测外周免疫系统可作为预测患者治疗疗效的参考^[93-94]。

结语 肿瘤基因组的高度异质性和不稳定性,是引起mCRC抗EGFR治疗耐药的重要原因。而传统的RAS和BRAF基因检测已无法满足肿瘤精准治疗的要求。下一代测序技术(next generation sequencing, NGS)的逐渐普及,有利于检出低突变频率的耐药基因突变;而液体活检技术的不断发展,可在抗EGFR治疗期间对ctDNA进行监测,及时发现耐药基因突变。针对耐药突变进行多靶点联合的个体化治疗策略显示了广阔的前景。近年来,EGFR单抗联合其他靶向治疗的临床研究取得了积极进展(表1),已有部分临床试验通过尝试联合其他靶点治疗从而克服抗EGFR治疗耐药,且取得了阳性结果。另一方面,肿瘤微环境的重塑与抗EGFR治疗耐药之间也存在密切关系,靶向微环境中细胞因子有望成为治疗抗EGFR耐药患者的新策略。

表1 抗EGFR治疗联合其他靶向治疗临床研究

Tab 1 Anti-EGFR treatment combined with other target therapy clinical trial

Study	NCT number	Recruitment Details	Treatment	Phase	Status
BEACON ^[95]	NCT02928224	BRAF V600E-mutant mCRC	Dabrafenib+trametinib+panitumumab	III	Completed
SWOG S1406 ^[96]	NCT02164916	BRAF V600E-mutant mCRC	Irinotecan+cetuximab+vemurafenib	II	Completed
KRYSTAL-1	NCT03785249	KRAS G12C-mutant mCRC	Adagrasib+cetuximab	I / II	Active
Codebreak101	NCT04185883	KRAS G12C-mutant mCRC	Sotorasib+ panitumumab	I / II	Active
— ^[97]	NCT01287130	KRAS mutant mCRC	Selumetinib+cetuximab	I	Completed
— ^[98]	NCT02205398	MET positive mCRC	Capmatinib+cetuximab	I	Terminated
— ^[99]	NCT01075048	MET positive mCRC	Tivantinib+cetuximab	II	Completed

作者贡献声明 韩佳滢 文献收集,绘图,论文撰写和修订。王祥宇 论文撰写和审阅,制表。张冲 论文写作指导。陈进宏 论文修订和审校。

利益冲突声明 所有作者均声明不存在利益冲突。

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