

吉非替尼在非小细胞肺癌治疗中获得性耐药机制的研究进展

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摘要: 该文围绕吉非替尼在非小细胞肺癌治疗中获得性耐药机制新进展, 指出当今吉非替尼获得性耐药机制的热点和难点, 从依赖或非依赖表皮生长因子受体(EGFR)信号通路、激活EGFR下游靶标、组织学的变化等方面进行了评述, 为临床克服获得性吉非替尼耐药提供新的治疗策略。

关键词: 非小细胞肺癌; 吉非替尼; 获得性耐药; 综述文献

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Advances in mechanisms of acquired resistance to gefitinib in the treatment of non-small cell lung cancer

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Abstract: This paper focuses on the latest advance in the acquired resistance of gefitinib in the treatment of non-small cell lung cancer, points out current hotspots and difficulties in the acquired resistance of gefitinib and reviews them in terms of EGFR-dependent or EGFR-independent signaling pathways, activation of EGFR downstream targets, and histological changes, providing new treatment strategies for overcoming the acquired resistance of gefitinib in clinical practice.

Key words: non-small cell lung cancer; gefitinib; acquired resistance; review

肺癌是我国死亡率第一的恶性肿瘤, 其中非小细胞肺癌(NSCLC)约占肺癌发病率的85%。表皮生长因子酪氨酸激酶受体抑制剂(EGFR-TKIs)靶向药物用于治疗转移性非小细胞肺癌EGFR外显子19缺失或外显子21点突变(L858R)患者, 吉非替尼是首个EGFR-TKIs药物, 在临床前研究中, 吉非替尼已证明对多种表达EGFR的人类癌细胞系具有抗肿瘤活性, 包括肺癌、卵巢癌、乳腺癌和结肠癌^[1-2]。2008年美国国立综合癌症网络(NCCN)肺癌诊疗指南指出对有EGFR突变、无鼠类肉瘤病毒癌基因(KRAS)突变、东方人、腺癌、女性和不吸烟的晚期非小细胞肺癌是EGFR-TKIs药物治疗的优势人群, 有效性可升至40%以上。自获批用于一线治疗以来, 约80%携带EGFR阳性突变的NSCLC患者经EGFR-TKIs治疗后无进展生存期显著延长^[3], 多项III期临床研究表明, 吉非替尼在无进展生存率和应答率方面优于化

疗^[4], 但大部分的患者在治疗后6~12个月出现吉非替尼的获得性耐药^[5], 因此, 研究并总结其耐药机制十分有必要, 现综述如下。

1 依赖EGFR通路产生吉非替尼获得性耐药

1.1 Thr790Met(T790M)突变

2005年, Kobayashi等^[6]对吉非替尼获得性耐药的患者的EGFR基因进行测序后首次发现T790M突变, 即EGFR外显子20的790位氨基酸(T790M)处的苏氨酸被蛋氨酸取代, 其增加ATP对EGFR的亲和力, 从而减弱吉非替尼的结合功效^[7], 导致吉非替尼耐药的发生。临幊上相关的T790M耐药性细胞可以原发性存在, 也可以从长期服用吉非替尼导致耐药形成, 说明T790M并不仅仅存在于获得性耐药机制^[8]。

EGFR T790M突变是导致NSCLC分子靶向治疗失败的主要原因。奥西替尼作为第三代EGFR-TKIs, 是具有EGFR T790M突变的非小细胞肺癌患者的标准治疗方法^[9]。重编程肿瘤相关的巨噬细胞, 通过双靶向联合给药吉非替尼/伏立诺他逆转了EGFR T790M耐药, 从而使EGFR T790M阳性细胞对吉非

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替尼重新敏感^[10]。Yin等^[11]发现细胞程序式死亡-配体1(Programmed cell death-ligand 1, PD-L1)纳米抗体也有逆转此类耐药的作用，辛伐他汀/吉非替尼联合PD-L1纳米抗体药物可以实现逆转耐药。Li等^[12]发现紫草素显著抑制EGFR的磷酸化并导致EGFR降解，进而促进T790M和L858R激活突变吉非替尼耐药的NSCLC细胞恢复敏感性。因此EGFR T790M突变虽然容易发生，但仍然可通过其他药物治疗解决。

1.2 EGFR其他突变

其他EGFR突变包括L792X、G796S、L718Q、G724S^[13]和外显子20插入突变等^[14]。外显子20插入通过在EGFR的N端添加残基来抑制吉非替尼与其结合位点的结合。Eck等^[15]发现在吉非替尼敏感和耐药的细胞系中，用天然化合物244-MPT处理可以减少EGFR磷酸化，还可以抑制其下游信号通路包括蛋白激酶B(protein kinase B, AKT)和细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)的激活，所以244-MPT可以ATP竞争的方式与野生或突变EGFR相互作用并抑制活性。Wu等^[16]发现一种新型的EGFR和肝细胞生长因子受体(cMET)双重抑制剂即N19，其通过泛素蛋白酶体同时降解两种蛋白质，有效克服EGFR突变NSCLC细胞中吉非替尼的抗性。

虽然EGFR的突变位点多变，但是只要能降解EGFR蛋白或者抑制其磷酸化就可以解决依赖EGFR信号通路产生的吉非替尼获得性耐药。

2 非依赖EGFR通路 / 激活旁路信号通路导致吉非替尼获得性耐药

2.1 跨膜络氨酸激酶受体(MET)扩增/肝细胞生长因子(HGF)过表达

吉非替尼获得性耐药最常见的替代途径是MET扩增，其占获得性吉非替尼耐药患者的5%~10%^[17]。MET基因编码MET酪氨酸激酶受体，肝细胞生长因子(HGF)作为MET受体的配体激活MET，激活的MET诱导MET的自身磷酸化并与ERBB3(人表皮生长因子受体3型)结合，ERBB3通过激活PI3K/AKT信号通路来促进肺癌吉非替尼获得性耐药^[18]。HGF通过PI3K/AKT途径激活MET并诱导耐药性^[19]。HGF结合和激活MET受体，以EGFR非依赖性途径来刺激PI3K信号通路的激活，即通过旁路激活导致获得性吉非替尼耐药。研究发现，利用PC-9吉非替尼耐药细胞系在体外建立脑膜癌转移的小鼠模型，发现

脑膜癌中癌细胞EGFR T790M阴性，其耐药性与MET激活引起的MET拷贝数增加有关，吉非替尼与MET抑制剂克唑替尼联合治疗，可消退对吉非替尼耐药的脑膜癌^[20]。Capmatinib(INC280)是一种有效的选择性MET抑制剂，Wu等^[21]通过Ib/II期研究调查发现，对于EGFR突变MET失调的NSCLC，特别是MET扩增的患者，capmatinib与吉非替尼的联合治疗是一种很有效的治疗方法。Gemmell等^[22]发现了神经纤维网蛋白2b(NRP2b)特异性促进HGF诱导的AKT激酶磷酸化，敲低NRP2b，减弱了NSCLC细胞对吉非替尼的耐药性。因此关于MET扩增或HGF过表达所导致的吉非替尼获得性耐药可通过联用相关抑制剂达到逆转耐药的效果。

2.2 胰岛素样生长因子1受体(IGF1R)

IGF1R是一种跨膜异四聚体蛋白，在促进癌细胞存活等方面发挥作用^[23]。IGF1R激活两种信号转导途径，即RAS/RAF/MEK/ERK和PI3K/AKT途径。在没有EGFR T790M突变的情况下，IGF1R可在吉非替尼耐药中发挥作用^[24]。另有人发现细胞核中高表达IGF1R有助于肺癌吉非替尼耐药^[25]。Choi等^[26]发现在吉非替尼敏感的HCC827细胞中，跨膜4 L6家族成员5(TM4SF5)和IGF1R高表达，它们通过促进ERK、Akt和S6激酶(S6K)的活性来促进吉非替尼耐药^[26]。依托泊苷诱导的蛋白质同源物2.4(EI24)是p53反应基因，在肿瘤抑制中起重要作用。其下调表达通过诱导IGF-1R途径赋予NSCLC细胞中耐药性^[27]。

上述结果表明减少IGF1R的表达可与EGFR激酶抑制剂组合使用，以增强对NSCLC的功效。另外一些lncRNA，比如GAS5(生长停滞特异蛋白5)可通过下调IGF1R来增加吉非替尼耐药细胞的敏感性^[28]。最近纳米医学的应用也为逆转这类耐药提供了可能，在IGF1R旁路激活诱导的吉非替尼耐药性肿瘤中，近红外激光照射后硫化铜(CuS)纳米颗粒局部升高了肿瘤细胞中的活性氧(ROS)水平，导致IGF1R及其下游AKT/ERK/NF-κB信号级联反应被阻断进而可以使患者对这一类吉非替尼治疗敏感^[29]。

2.3 人类表皮生长因子受体2(HER2)

HER2/ERBB2是ERBB家族的成员，NSCLC患者中约2%发生HER2突变，在女性、不吸烟、腺癌与东方种族中明显更为常见^[30]。几乎所有的HER2突变都位于外显子20，即编码HER2的激酶结构域^[31]。与其他家族成员不同，HER2具有很强的激酶活性，但没有确定的配体结合域。因此，它必须与其他家

族成员(包括活化的EGFR)形成异二聚体才能进行磷酸化^[32]。HER2和EGFR相互结合可以不依赖EGFR间接激活PI3K,因此HER2的扩增,突变或者过表达与吉非替尼耐药息息相关。基于这一特点,逆转HER2相关耐药必须还要抑制与HER2形成二聚体的其他相关RTKs,这样才能更好地达到恢复吉非替尼敏感性的效果。

2.4 酪氨酸激酶受体(AXL)

AXL是一种细胞表面受体酪氨酸激酶,是TAM家族激酶的一部分,生长停滞特异蛋白6(GAS6)是AXL的配体。AXL/GAS6激活会导致MEK/ERK和PI3K/AKT途径激活和吉非替尼的获得性耐药^[33]。此外,GAS6/AXL激活通常伴有EMT。Bae等^[34]研究发现AXL在吉非替尼获得性耐药细胞系(H292-Gef)中过表达,元胺化胺(YD)通过水解膜内蛋白导致AXL的下调,来克服吉非替尼获得性的耐药。

2.5 白细胞介素-6(IL-6)

肿瘤及周围的炎性因子通过提供多种促进癌变的细胞因子和趋化因子,为肿瘤的生长提供了有利的环境。白细胞介素6(IL-6)被发现与炎症驱动的癌症有关,并且在获得性吉非替尼耐药中也起着至关重要的作用。Ray等^[35]发现EGFR和IL-6信号通路可通过多种媒介和下游信号通路以多种方式发生串扰,从而驱动耐药性。最近一项研究确定ERK激活是通过细胞因子(如IL-6)的功能发生的,具体机制为E3泛素-蛋白连接酶(RNF25)介导细胞中的NF-κB激活,诱导ERK信号的激活以引起耐药性^[36]。抗IL6抗体MEDI1117,联合吉非替尼治疗方案可逆转肺癌吉非替尼耐药,增强吉非替尼的抗肿瘤的能力^[37]。

上述所有机制均不经过EGFR,而是通过其他受体酪氨酸激酶激活下游相关信号通路导致吉非替尼耐药的发生。因此发现更多与获得性吉非替尼耐药相关的RTKs,将为吉非替尼未知的耐药机制提供新的思路。

3 激活EGFR下游靶标导致获得性吉非替尼耐药

3.1 磷酸酯酶与张力蛋白同源物(PTEN)下调

PTEN是抑癌基因,可以将活性磷脂酰肌醇(3,4,5)-三磷酸(PIP3)转换为非活性磷酸化磷脂酰肌醇(4,5)-双磷酸酯(PIP2),从而使PI3K/AKT信号失活。Maeda等^[38]研究发现携带EGFR突变的肺癌PC-9细胞中PTEN表达下降导致AKT的磷酸化增加进而获得对吉非替尼的抗性。在另有研究报道H1975吉非替尼天然耐药H1975和HCC827获得性耐药细胞中致癌线

粒体膜相关蛋白-腺嘌呤核苷酸转位酶-2(ANT2)的表达升高,当抑制miR-221/222水平和恢复PTEN可以导致ANT2减少,PI3K/Akt信号通路失活,增加了吉非替尼的敏感性^[39],因此对于PTEN下调的非小细胞肺癌耐药患者,恢复PTEN的表达或者抑制Akt信号通路可以作为一种逆转耐药的有效方式。

3.2 无鼠类肉瘤病毒癌基因(KRAS)突变

KRAS就像一个分子开关,与癌细胞异常增殖及耐药都有关系。在最近的一项研究中,研究者开发了精氨酸九聚体肽融合蛋白s-9R作为siRNA载体。其有效沉默了靶基因KRAS的表达,恢复了NSCLC细胞对吉非替尼的敏感性,并且处理后的细胞的凋亡率显著高于对照组^[40]。鉴于当前尚无直接的抗KRAS治疗方法。现已出现了部分针对KRAS下游信号传导的新策略。帕比司他,一种组蛋白脱乙酰基酶抑制剂,其可通过抑制KRAS下游信号传导使KRAS突变体/EGFR野生型NSCLC对吉非替尼敏感^[41]。

3.3 磷脂酰肌醇-3-激酶催化亚基(PIK3CA)的突变

PIK3CA是I类PI3K同种型之一^[42]。在37例(占3%)EGFR-TKIs获得性耐药患者中被发现^[43]。Sun等^[44]研究发现PI3K/mTOR的双重抑制剂NVP-BEZ235通过下调PI3K/AKT/mTOR磷酸化可有效抑制吉非替尼耐药非小细胞肺癌的生长。

3.4 β-连环蛋白(β-catenin)的激活

β-catenin是一种双功能蛋白,参与监管和协调信息粘附和基因转录等生物过程。依赖ATP的RNA解旋酶(DDX17)激活β-catenin来促进获得性吉非替尼耐药,在NSCLC患者中抑制DDX17可能是克服吉非替尼获得性耐药的一种有前途的策略^[45]。因此增强的β-catenin途径可作为对EGFR靶向药物有抗药性患者的新靶标^[46]。

3.5 信号转导和转录激活剂3(STAT3)增加

STAT3是STAT蛋白家族的成员的细胞因子和生长因子,STAT3被受体相关的受体相关Janus激酶(JAK)磷酸化,形成同型或异型二聚体,并易位至细胞核,充当转录激活因子的角色。Cui等^[47]发现STAT3信号传导可能参与吉非替尼耐药的发生。据报道,环孢霉素A(CsA)通过抑制STAT3途径促进吉非替尼诱导的细胞凋亡,促进吉非替尼对肺癌细胞的抗癌活性^[48]。多元茶碱I(PPI)使STAT3信号通路失活而抑制了增殖,并诱导其对吉非替尼耐药的NSCLC的凋亡^[49]。因此,PPI可以作为治疗吉非替尼耐药的NSCLC有前途的药物。

上述所有机制均是通过EGFR下游相关信号通路上某蛋白突变或异常增加而导致信号通路异常激活，因此抑制相关信号通路或蛋白的异常激活即可有效逆转吉非替尼的耐药。

4 组织学变化导致吉非替尼获得性耐药

4.1 上皮-间充质转化(EMT)

EMT是上皮细胞失去细胞极性和细胞间粘附，获得迁移和侵袭性成为间充质干细胞的过程。Weng等^[50]发现对吉非替尼具有耐药性的NSCLC细胞表现出EMT功能，E-钙黏着蛋白减少，波形蛋白和干性增加，而没有任何EGFR二次突变。E-钙黏着蛋白在亲本细胞中的敲除增加了吉非替尼的耐药性和干性，而在耐药细胞中波形蛋白的敲除则产生了相反作用。研究表明，miRNA通过EMT来参与肺癌吉非替尼获得性耐药。在NSCLC中，由TGF-β1诱导的miR-134和miR-487b诱导EMT可以促进吉非替尼耐药性^[51]。由TGF-β1诱导的miR-23a通过抑制E-钙黏着蛋白促进EMT^[52]。miR-19A也通过EMT促进了吉非替尼的耐药^[53]。而miR-1-3p和miR-206可以逆转吉非替尼耐药，通过抑制c-Met下游Akt和Erk通路，并阻断HGF诱导的上皮-间质转化(EMT)^[54]。miRNA对EMT具有双向调控作用，除此之外某些蛋白的变化也会导致EMT的发生，例如F-盒/WD重复蛋白7(FBXW7)敲低极大地促进NSCLC细胞的上皮-间质转化，迁移和侵袭^[55]。最近研究显示连接蛋白26(Cx26)与吉非替尼耐药性EMT表型的变化相关，并且已经证实Cx26与PI3K/Akt信号传导在功能上相互作用，从而促进NSCLC细胞中的EMT和吉非替尼耐药^[56]。Sakuma等^[57]发现脯氨酰异构酶Pin1蛋白在经历过EMT并获得了对EGFR TKIs的抗性的EGFR突变型肺癌组织中表达，但在其原发性肿瘤中没有表达。表明抑制Pin1活性可以是肺癌治疗中的新策略。同时，高CD44表达与间充质表型有关，Cd44敲低逆转了EMT变化^[58]。实际上，香烟烟雾提取物暴露通过介导NSCLC中的Src激活和EMT诱导吉非替尼耐药^[59]，因此吸烟不仅可以导致肺癌的发生，还会导致吉非替尼耐药的发生。La等^[60]研究发现吉非替尼和培美曲塞的同时治疗防止了PC9和HCC827细胞中T790M突变或上皮-间充质转化(EMT)介导的吉非替尼耐药性的出现，如果在临幊上也切实有效，将会为延缓患者出现相关耐药做贡献。

4.2 小细胞肺癌(SCLC)的转化

EGFR-TKIs获得性抗性的患者中约5%患者发生

了SCLC的转化^[43]。最近的一项实验分析表明，在100%的SCLC转化病例中，发生了视网膜母细胞瘤(RB)丢失，神经内分泌标记物增加，EGFR表达降低等^[61]。在发生小细胞转化的吉非替尼耐药后由于异质性的存在，免疫标记基因的表达有许多的不确定性通过一份小细胞肺癌转化病例分析发现^[62]，程序性死亡配体1(PD-L1)蛋白在具有EGFR T790M的肿瘤细胞中部分表达，但在SCLC转化的肿瘤细胞中不表达。SCLC转化的肝转移显示无PD-L1表达且肿瘤浸润淋巴细胞少，而其他病变则显示PD-L1表达和CD8阳性T细胞浸润，因此PD-L1可能成为获得性吉非替尼发生SCLC转化的一个重要标志物，为临床克服此类耐药提供线索。

4.3 癌症相关的成纤维细胞(CAFs)

CAF_s可以诱导HCC827和PC9细胞的EMT表型，并伴随上皮向间充质转化标志物表达的变化。因此CAF_s可以促进吉非替尼的抗性，并且可能成为EGFR激活突变的NSCLC的治疗靶点^[63]。当然CAF_s不仅促进耐药方面发挥作用，科学家发现CAF_s在治疗肿瘤耐药中也起着重要作用。存在一个CAF_s的特殊亚群，CD200阳性CAF_s，该亚群在与EGFR突变阳性的肺癌细胞共培养时，通过增强凋亡增强了EGFR基因突变阳性肺癌对吉非替尼的敏感性^[64]。而在没有吉非替尼的情况下，它们也不影响肺癌细胞的生存能力，因此在体外肺癌细胞与CAF_s共培养，可以延缓吉非替尼相关耐药的出现时间。

上述所有机制都是由恶性程度较低预后较好向恶性程度更高预后更差转化的组织学改变，抑制相关组织学改变即可有效逆转吉非替尼耐药。

5 其他机制促进获得性吉非替尼耐药

5.1 自噬

吉非替尼可以促进轻链蛋白3(LC3)表达，这是自噬的标志。并且获得性耐药细胞也发生了自噬，因此获得性耐药性可能与自噬有关。氯喹作为自噬溶酶体形成的抑制剂可以克服耐药细胞中的自噬^[65]。Zhu等^[66]发现自噬促进的衰老有助于对吉非替尼产生抗性，自噬抑制作用增强了细胞凋亡并消除了衰老。另外Mao等^[67]发现砷可以促进NSCLC细胞中EGFR的自噬降解，这些都为自噬引起的获得性耐药提供了一种可能的方案。

5.2 表观遗传学

在恶性肿瘤中某些癌基因、抑癌基因、增殖相关和凋亡相关的信号通路改变可通过表观遗传上调

或者下调相关基因导致耐药。已知PTEN的表达降低可以导致获得性吉非替尼耐药, Maeda等^[38]发现PTEN启动子CpG的高甲基化就会导致PTEN的表达降低。已知miR-483-3p的强制表达通过抑制增殖和促进细胞凋亡, 有效提高了对吉非替尼耐药的肺癌细胞对吉非替尼的敏感性, Yue等^[68]发现在耐吉非替尼的肺癌细胞中, miR-483-3p自身启动子的高度甲基化可自身沉默。Terai等^[69]发现在吉非替尼耐药细胞中640个基因的DNA甲基化增加, 说明了DNA甲基化也与获得性吉非替尼耐药关系密切。

5.3 癌症干细胞(CSC)

CSC是导致化疗失败的重要原因, 具有对多种化疗药物耐药的特点, 近些年来, 靶向药物耐药也出现了CSC的身影。胚胎干细胞转录因子(Oct4)参与多种癌症的CSC特性。Kobayashi等^[70]发现在吉非替尼耐药的小鼠肿瘤中, Oct4和CD133高表达, 表明其耐药性与癌症干细胞有关。同时Chiu等^[71]研究结果表明, 叉形头转录因子的O亚型(Forkhead box O3, FOXO3a)也与非EGFR依赖突变的吉非替尼耐药性和肺癌肿瘤干性有关。Liu等^[72]研究发现IL-8也增加了肿瘤干细胞样特性, IL-8的敲低导致吉非替尼耐药细胞中干细胞样特征的丧失, 暗示IL-8是克服吉非替尼耐药性的潜在治疗靶标。Yu等^[73]发现miR-124a可增强NSCLC细胞的吉非替尼敏感性通过靶向泛素特异性蛋白酶14(USP14)来抑制癌症干细胞。因此MicroRNA也可通过直接调节癌症干细胞(CSC), 诱导NSCLC对吉非替尼的敏感。

5.4 微小RNA(miRNA)

miRNA是一类小非编码RNA, 通常在人类癌症中失调, 并且与治疗耐药性有关^[68]。如果miRNA在转录水平上负调节其基因靶标, 则可推测miRNA可能会降低EGFR的表达、活性和PI3K/Akt信号转导, 从而使肿瘤对吉非替尼诱导的细胞毒性敏感^[74]。Jin等^[75]发现抑制miR-873通过上调GLI1增加NSCLC细胞的吉非替尼耐药性。这些结果表明miR-873-GLI1信号传导参与NSCLC中的吉非替尼抗性。另外Baumgartner等^[76]研究发现miR-19b在NSCLC致癌过程中增强了细胞增殖和细胞抗凋亡能力, 也导致了耐药的发生。Wu等^[77]发现miR-155高表达和miR-630的低表达也导致了吉非替尼耐药性的增加。Jiao等^[54]证明了miR-1-3p和miR-206可以在体内异种移植小鼠模型中提高吉非替尼敏感性, 因此miRNA是一把双刃剑, 一部分miRNA可以促进耐药, 另一

部分可以抑制耐药。

5.5 长链非编码RNA(LncRNA)

LncRNAs是长度大于200个核苷酸的非编码RNA, 在基因表达调控中发挥基础性作用, 在获得性吉非替尼耐药中也发挥着重要作用, Li等^[78]发现敲低lncRNA RHPN1-AS1会赋予吉非替尼耐药性。Cheng等^[79-81]研究发现, 长非编码RNA UCA1(与尿路上皮癌1)和lncRNA BC087858也可促进吉非替尼耐药。Dong等^[28]发现GAS5能够逆转A549细胞对吉非替尼的耐药, 主要机制是减少了P-EGFR、P-ERK、P-Akt、P-IGFIR的表达。LncRNA既可以是促进耐药, 也可以逆转耐药, 因此研究LncRNA对于获得性吉非替尼耐药也是十分必要的。

6 总结与展望

近年来, 随着对吉非替尼耐药的深入研究, 不断有新的耐药机制被挖掘, 研究耐药机制逐渐成为吉非替尼治疗不可或缺的一部分。吉非替尼获得性耐药机制大致包括经过EGFR、不经过EGFR、激活下游信号通路相关靶标、组织学变化等, 不同的机制之间也可以发生串扰, 相互影响, 但是仍然有20%的耐药机制尚不清楚, 由于临床耐药样本获取难度很大, 也为研究这些未知耐药机制增加了难度。必须注意的是, 关于获得性吉非替尼耐药在表观遗传学方面以及物质代谢方面的研究还很少, 本课题组将结合前人研究基础深入研究并探讨与物质代谢和表观遗传相关的耐药机制, 进一步揭开未知耐药机制的神秘面纱。

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