doi: 10.3978/j.issn.2095-6959.2022.05.035
**View this article at:** https://dx.doi.org/10.3978/j.issn.2095-6959.2022.05.035

# 肿瘤细胞耐药分子机制的研究进展

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**[摘　要]** 临床上肿瘤患者在接受化疗和靶向治疗后体内形成耐药的肿瘤细胞。这类细胞具有增殖缓慢、细胞代谢调节性强、表型可塑性高和对肿瘤微环境的适应性强等特征。这些特征背后的分子机制与肿瘤细胞产生耐药相关。耐药细胞的减速机制可以发生在细胞内，也可以通过微环境介导。耐药细胞可以通过线粒体呼吸，调控蛋白质合成，和增强抗氧化途径的方式来调节细胞代谢。耐药细胞通过上皮间质转化和转分化来改变细胞表型。耐药细胞通过和肿瘤微环境中的肿瘤相关巨噬细胞、肿瘤相关成纤维细胞等其他细胞相互作用，增强其对微环境的适应能力。结合临床现状，开发可靠的临床前肿瘤耐药细胞模型对进一步研究肿瘤耐药细胞的特性和寻找临床治疗新策略具有重要意义。

**[关键词]** 肿瘤耐药细胞；治疗耐药；特征；机制

# Research progress in persistent cancer cells in molecular mechanisms

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**Abstract** Cancer patients with receiving chemotherapy and targeted therapy have persistent cancer cells remaining in their bodies. These cells are labelled by their slow proliferation, high metabolic plasticity, high phenotypic plasticity, and strong adaptability to the tumor microenvironment. The molecular mechanisms of these characteristics promote the development of drug resistance in persistent cancer cells. The slow proliferation mechanism of persistent cancer cells can occur intracellularly or be triggered by microenvironment. Cell metabolism is regulated by mitochondrial respiration, protein synthesis, and antioxidant pathways in persistent cancer cells. The phenotype of persistent cancer cells is changed by epithelial-to-mesenchymal transition and transdifferentiation. Tumor-associated macrophages, cancer-associated fibroblasts and other cells in the microenvironment interact with persistent cancer cells to enhance their adaptability to the microenvironment. At the present clinical situation, the development of a reliable preclinical cancer models is of great significance to further study the characteristics of persistent cancer cells so that new clinical strategies targeting persistent cancer cells for doctors to carry out.

**Keywords** persistent cancer cells; therapy resistance; characteristics; mechanisms

**收稿日期 (Date of reception)**：2021–04–09

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肿瘤的异质性是肿瘤患者对化疗和靶向治疗临床获益不同的原因之一。肿瘤细胞的基因异质性会导致不同程度的药物敏感性，对化疗药敏感性低的肿瘤细胞可能引起药物解离出现原发性耐药[1]。有研究[2]发现体内耐药的肿瘤细胞，在没有发生基因突变的情况下处于一种低增殖的状态，这种状态与细菌对抗生素的耐药反应极为相似。肿瘤细胞的耐药可以通过2种理论来解释：其一是治疗前可能已经存在单个耐药细胞的假设，在治疗时普通的肿瘤细胞被杀死，而耐药细胞可以存活；另一种理论是拉马克的适应学说，即个别肿瘤细胞可能在接触药物后发生耐药，所以细胞发生耐药是由药物导致的。本文基于各种类型的肿瘤在采用化疗和靶向治疗后发生耐药的大量实验研究，总结耐药细胞的特征，讨论肿瘤细胞的耐药机制和治疗方法，其耐药机制涉及表观遗传的改变、转录和翻译的调控以及复杂的细胞间作用，这些过程对治疗靶点的研究有重要意义。

## 1 耐药机制

肿瘤耐药细胞主要以这4种生物分子机制产生耐药：1)减慢细胞增殖；2)调节细胞代谢；3)转变细胞表型；4)调控肿瘤微环境。下文将围绕这4种机制详细介绍肿瘤细胞的耐药机制。

### 1.1 减慢细胞增殖

肿瘤细胞对表观遗传的重新编辑，可以改变耐药细胞的基因表达，从而诱导细胞进入缓慢增殖状态。在该状态下，细胞通过提高基因突变率，诱导细胞产生耐药性。下文从细胞内的内在机制和微环境介导的外在机制2个方面进一步阐明细胞的减速机制。

#### 1.1.1 细胞减速的内在机制

诸多实验[3-5]已经验证了肿瘤耐药细胞可通过表观遗传的甲基化或去甲基化过程，调控DNA的表达来减慢细胞增殖。有研究[6]发现：在化疗后的胶质母细胞瘤中观察到耐药细胞的*Notch1*基因表达上调，去甲基酶KDM6A/B被激活[7]，细胞处于缓慢增殖状态。去甲基酶降低了组蛋白的甲基化水平，抑制了与细胞周期相关基因的表达[4]。敲除*KDM6A/B*基因观察到耐药细胞的增殖速率显著加快，说明表观遗传的重新编辑与细胞的缓慢增殖状态有关。除了胶质母细胞瘤，在黑色素瘤和非小细胞肺癌的耐药细胞中也观察到去甲基酶的激活。除了组蛋白的去甲基化，组蛋白的三甲基化通过抑制长穿插重复元件1(long interspersed repeat element 1，LINE 1)的转录[8]，也使耐药细胞增殖减慢[9]。有研究[10]显示：在化疗后的结肠癌中观察到，转录因子E2F相关的细胞增殖通路受到抑制，细胞处于缓慢增殖状态。在化疗后的基底细胞癌中，耐药细胞通过激活WNT信号诱导细胞缓慢增殖[11]。在化疗后的黑色素瘤中观察到，耐药细胞的黏着斑激酶(focal adhesion kinase，FAK)磷酸化增加，FAK可以导致转录因子c-Jun磷酸化，进而激活转录激活蛋白 1(activator protein 1，AP1)的活性，诱导细胞缓慢增殖[12]。

肿瘤耐药细胞可以通过转录负反馈影响细胞膜上受体的表达，进而诱导细胞缓慢增殖。在化疗后的非小细胞肺癌中观察到，细胞膜上的受体酪氨酸激酶AXL上调[13]，AXL与生长停滞特异性蛋白6(growth arrest-specific gene 6，GAS6)特异性结合诱导细胞缓慢增殖[14]。同样，作用于细胞膜受体的厄洛替尼通过YAP1-TEAD信号介导丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)通路失活[15]，诱导耐药细胞进入缓慢增殖状态[16]。

#### 1.1.2 微环境介导减速的外在机制

肿瘤微环境中多种细胞间的相互作用均对细胞增殖产生重要影响。肿瘤耐药细胞可以通过调控肿瘤微环境诱导细胞缓慢增殖。在化疗后的黑色素瘤中观察到，肿瘤相关成纤维细胞中的纤连蛋白基质通过整合素β1-FAK-Src信号通路介导耐药细胞缓慢增殖[17]。

细胞可以通过激活c-Jun氨基末端激酶(c-Jun N-terminal kinase，JNK)信号通路介导细胞自噬。而在肿瘤耐药细胞中观察到JNK的激活和干细胞标志物NANOG和SOX2上调[18]，干细胞标志物的上调可能是滞育和肿瘤耐药性增加的标志[19-22]。滞育是指物种处于休眠状态或在不利于生存条件下会暂停正常的胚胎发育，并且只有在消除压力因素后才会恢复的现象[23]。在化疗后的胰腺癌小鼠中观察到，$CD4^+$T细胞可以通过TNFR1-IFN-γ信号通路诱导肿瘤生长停滞[24]，表明肿瘤微环境中免疫细胞分泌的炎症因子可以诱导细胞缓慢增殖。

处于缓慢增殖状态的肿瘤耐药细胞通过基因突变获得耐药性[5,25-26]。在人类微卫星稳定(microsatellite-stable，MSS)的结直肠癌中观察到，耐药细胞从错配修复(mismatch repair，MMR)和同源重组(homologous recombination，HR)修复转变为由DNA聚合酶介导的DNA损伤修复[27]。这种转变导致碱基配对错误率增加，可能在基因组

中掺入异常的DNA片段，导致耐药细胞的突变率提高。并且DNA中的胸腺嘧啶易水解脱氨，由于DNA聚合酶的修复能力弱，无法修复胸腺嘧啶水解导致的T:G错配[28]，导致基因的突变率增加。此外DNA低甲基化或羟基化会增加基因组的不稳定性[10]，从而提高耐药细胞的适应性突变。

### 1.2 调节细胞代谢

#### 1.2.1 利用线粒体呼吸

肿瘤耐药细胞的一个共同特征是通过线粒体呼吸最大程度地减少葡萄糖消耗。在诸多实验中观察到肿瘤耐药细胞中与线粒体相关的生物学过程处于激活或强化状态。在化疗后的胰管腺癌中观察到，耐药细胞通过上调线粒体中生物合成的调节因子促进线粒体的氧化磷酸化过程[29]。在化疗后的急性髓系白血病中观察到，耐药细胞的线粒体处于高氧化磷酸化状态，其合成ATP的效率高[30-31]，以及耐药细胞的线粒体合成ATP的酶表达上调[32]。有趣的是，有实验[33-34]表明肿瘤耐药细胞能量生成的方式更接近于正常细胞而并非一般的肿瘤细胞。

此外，不同类型的肿瘤代谢葡萄糖的方式可能存在差异。在化疗后的淋巴瘤小鼠中观察到，耐药细胞将葡萄糖代谢为柠檬酸盐，而不生成乳酸。随着丙酮酸激酶的增加，进入线粒体三羧酸循环(tricarboxylic acid，TCA)的葡萄糖含量增加[35]。除了淋巴瘤中观察到耐药细胞是TCA和线粒体呼吸的混合代谢，在乳腺癌中观察到的耐药细胞也是混合代谢表型，其磷酸戊糖途径和线粒体呼吸都被激活[36]。

肿瘤耐药细胞可以利用其他的营养物质进行代谢，其代谢还与自噬等生物过程相关。在肺癌小鼠模型中观察到，耐药细胞可通过自噬回收代谢底物促进能量生成[37]。在人黑色素瘤中发现化疗药可以通过调控转录，导致自噬相关的耐药[38-39]。通过实验观察到耐药细胞代谢的新途径，在化疗后的胰管腺癌小鼠中观察到，耐药细胞可以利用过氧化物酶体进行脂肪酸β氧化分解(fatty acid oxidation，FAO)[29]。在人三阴性乳腺癌(triple-negative breast cancer，TNBC)中观察到，耐药细胞通过FAO保持高水平的ATP生成[40]。乳腺癌、黑色素瘤的耐药细胞中的代谢过程有脂肪酸转运体白细胞分化抗原36参与[41-42]。在肝细胞癌和肺癌中发现，棕榈酸去饱和为不寻常的脂肪酸sapienate[43]，这种细胞内脂肪酸去饱和途径表明肿瘤耐药细胞的代谢途径具有高度可塑性[44]。

#### 1.2.2 调控蛋白质合成

细胞大约一半以上的能量用于蛋白质合成，所以对于肿瘤耐药细胞必须尽量减少其蛋白质合成[45]。对不同肿瘤的全基因组研究[46]表明：增殖减慢在很大程度上与蛋白质合成减少有关。在白血病、黑色素瘤中发现，N6-甲基腺嘌呤(N6-methyladenosine，m6A)的转录后修饰降低了肿瘤耐药细胞的翻译效率[5,47]。

#### 1.2.3 增强抗氧化途径

线粒体有氧呼吸产生的超氧化物可以导致肿瘤细胞发生氧化应激[48]。因此，肿瘤耐药细胞需要一个强有力的抗氧化过程来应对超氧化物。其抗氧化途径之一是谷胱甘肽过氧化物酶4(glutathione peroxidase 4，GPX4)催化谷胱甘肽的还原反应，通过谷胱甘肽减少细胞内脂质过氧化物以降低氧化应激反应。GPX4一旦减少可以引起细胞铁死亡[49]，另外在乳腺癌、肺癌和黑色素瘤耐药细胞中观察到GPX4的上调，表明耐药细胞通过上调GPX4诱导细胞耐药[50]。另一抗氧化途径是通过醛脱氢酶(aldehyde dehydrogenase，ALDH)保护耐药细胞免受活性氧的毒性作用[51]。除此之外，耐药细胞中核因子E2相关因子2(NF-E2-related factor 2，NRF2)的激活可以提高谷胱甘肽/氧化谷胱甘肽(GSH/GSSG)的比率和瞬时受体电位阳离子通道亚家族A(transient receptor potential cation channel subfamily A，TRPA1)的表达，从而起到抗凋亡作用[52-53]。

### 1.3 改变细胞表型

#### 1.3.1 上皮 - 间质转化

上皮-间质转化(epidermal-mesenchymal transition，EMT)是上皮细胞失去极性和细胞间黏附能力，转化为间质细胞获得迁移和增殖能力的过程，间质细胞抵抗细胞死亡的能力更强，更有利于产生耐药性[54]。EMT与胚胎发育、伤口愈合、组织纤维化、肿瘤侵袭和转移等生物学过程相关[55]。在实验中发现肺癌的耐药细胞发生了EMT，在化疗后的肺癌中观察到成纤维细胞生长因子受体3 (fibroblast growth factor receptor，FGFR3)被激活，激活的FGFR3激活ERK信号诱导EMT[56]。在化疗后的肺鳞癌中观察到，耐药细胞上调EMT的标志物，包括N钙黏蛋白、波形蛋白和Slug蛋白[57]。除了肺癌，其他肿瘤的耐药细胞也可以发生EMT[51]，比如人基底样乳腺癌耐药细胞被证明是通过EMT产生的[58]。EMT还可以

使肿瘤耐药细胞逃避免疫监视。对肺腺癌的大数据分析[59]表明：EMT促进多种免疫抑制的膜蛋白表达包括程序性死亡受体-配体1(programmed cell death-ligand 1，PD-L1)、T细胞免疫球蛋白黏蛋白-3(T-cell immunoglobulin and mucin domain-containing protein 3，TIM3)和淋巴细胞活化蛋白3(lymphocyte-activation gene 3，LAG3)，这些免疫检查点的高表达促进免疫逃逸。

1.3.2 转分化

转分化是指细胞从一个成熟的谱系转化为另一个成熟的谱系，失去多能分化潜力[60]。在实验中观察到细胞转分化可能与耐药有关，并且通过实验验证了此耐药机制。在化疗后的基底细胞癌中观察到，耐药细胞转分化后形成混合细胞表型[61-62]，然而在未经治疗的基底细胞癌中没有观察到这种混合表型，提示药物诱导肿瘤细胞转分化是耐药细胞的耐药机制[63]。在前列腺癌中观察到药物诱导肿瘤细胞发生神经内分泌转分化，用雄激素剥夺疗法治疗人去势抵抗性前列腺癌(castration-resistant prostate cancer，CRPC)，CRPC细胞不依赖雄激素发生转分化，分化后的细胞在组织学上类似于神经内分泌前列腺癌(neuroendocrine prostate cancer，NEPC)细胞，并表达神经内分泌免疫组织化学标志物[64-65]。经检测这些NEPC样细胞保留了最初CRPC的基因特征，例如跨膜丝氨酸蛋白酶 2(transmembrane serine protease 2，TMPRSS2)与成红细胞病毒E26致癌物(E26 oncogene，ERG)融合基因[66]，表明这些细胞确实是从最初的肿瘤细胞中转分化而来[67]。耐药细胞转分化后的细胞表型存在差异。黑色素瘤细胞通过转分化为神经嵴样干细胞产生耐药[68]。非小细胞肺癌中发现耐药细胞转分化为小细胞肺癌表型[69]。在一个罕见的非小细胞肺癌病例中，耐药细胞在组织学上转分化为神经内分泌样细胞[70]。

### 1.4 调控肿瘤微环境

1.4.1 肿瘤细胞共生

肿瘤细胞的共生关系是指肿瘤细胞为了更好地利用能量与其他细胞形成共同作用的整体。有研究[71]发现：在小鼠胰腺神经内分泌瘤中，位于血管远端的肿瘤细胞通过表达单羧酸转运体(monocarboxylate transporter，MCT)，特别是MCT4乳酸转运体转运糖无氧酵解产生的乳酸。而位于血管近端的肿瘤细胞通过表达MCT1乳酸转运体摄取血管远端肿瘤细胞产生的乳酸[72]，乳酸分子可以激活哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)信号，导致肿瘤细胞耐药[73]。另有研究[72-74]发现在乳腺癌、胰腺癌和肾细胞癌中肿瘤耐药细胞与其他肿瘤细胞存在共生关系。

1.4.2 肿瘤相关成纤维细胞

研究[75-76]发现黑色素瘤、结直肠癌、胶质母细胞瘤和乳腺癌中的肿瘤相关成纤维细胞(cancer-associated fibroblasts，CAFs)参与诱导肿瘤耐药。CAFs诱导耐药的相关机制是通过分泌肝细胞生长因子(hepatocyte growth factor，HGF)激活受体间质表皮转化因子(mesenchymal to epithelial transition factor，MET)[77]，MET激活下游PI3K-AKT信号通路，肿瘤细胞通过这一信号通路介导细胞耐药[75]。

在黑色素瘤、肺癌和结肠腺癌中发现CAFs可以通过多种途径诱导肿瘤细胞产生免疫耐受。HGF招募免疫抑制性的中性粒细胞到肿瘤微环境中，抑制T细胞发挥作用[78]。CAFs还可以分泌微小RNA转移到肿瘤细胞上。CAFs分泌的微小RNA与凋亡蛋白酶激活因子1(apoptotic protease activating factor 1，APAF1)直接结合，抑制肿瘤细胞凋亡[79-80]。不同部位的CAFs的作用方式不同，比如在胰腺癌近端的CAFs与肿瘤细胞直接进行细胞间作用，胰腺癌远端的CAFs通过分泌细胞因子作用于其他肿瘤细胞[81]。除CAFs的异质性之外，特殊类型的CAFs可以表达白细胞分化抗原10(cluster of differentiation，CD10)和G蛋白偶联受体77 (G protein coupled receptor 77，GPR77)诱导肿瘤耐药[82]。

1.4.3 肿瘤相关巨噬细胞

肿瘤相关巨噬细胞(tumour-associated macrophages，TAMs)分泌生长因子、促血管生成因子和免疫抑制因子促进肿瘤进展[83-86]。TAMs分泌多种细胞因子进入肿瘤微环境，包括白细胞介素-6 (interleukin-6，IL-6)、肿瘤坏死因子(tumor necrosis factor，TNF)、趋化因子CCL5[87]和CCL18促进肿瘤发生耐药。

## 2 治疗模式探索

治疗耐药性肿瘤的关键是使耐药的肿瘤细胞重新对药物敏感，使化疗或靶向治疗达到更好的疗效[88]。肿瘤耐药细胞可以提供一个治疗的潜在靶点。细胞内在的耐药机制和与耐药细胞所处微环境也可以提供潜在的药物治疗靶点。我们推测增强肿瘤耐药细胞的氧化应激可能会抑制抗氧化反应，避免细胞耐药。使用只对耐药细胞转

录和翻译产生影响的药物来根除耐药细胞具有极大的临床意义。除此以外，Kris Wood团队利用CRISPRi(基因抑制/沉默)技术筛选提出化疗诱导进化陷阱的治疗策略[89]。研究[5,90]发现联合使用化疗药也可以阻止耐药的发生。

另一种策略是针对肿瘤耐药细胞转变后的细胞表型进行靶向治疗。在黑色素瘤、肺鳞癌中，靶向治疗转分化后的细胞可以阻止耐药群体的出现，延缓肿瘤复发[4,68,91]。在临床前模型中通过干预肿瘤微环境影响转分化的过程也提示了新的治疗靶点[75,92]。

## 3 结语

肿瘤耐药细胞能在化疗和靶向治疗后存活，攻击宿主并最终导致临床进展。目前的研究可以从多个方面解释肿瘤耐药的发生。本文虽然分析了许多针对肿瘤耐药细胞的治疗方法，但目前大多方法还没有转化为临床应用。并且迄今为止还没有整合多种耐药机制的治疗方法，因此迫切需要新的治疗策略来打破耐药的天花板。

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**本文引用：** 汪润坤, 金燕, 许斌. 肿瘤细胞耐药分子机制的研究进展[J]. 临床与病理杂志, 2022, 42(5): 1239-1246. doi: 10.3978/j.issn.2095-6959.2022.05.035

***Cite this article as:*** WANG Runkun, JIN Yan, XU Bin. Research progress in persistent cancer cells in molecular mechanisms[J]. Journal of Clinical and Pathological Research, 2022, 42(5): 1239-1246. doi: 10.3978/j.issn.2095-6959.2022.05.035