·综　述·

FGFR信号通路在肿瘤中的作用机制与靶向治疗研究进展

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［摘　要］ 成纤维细胞生长因子（fibroblast growth factor，FGF）及成纤维细胞生长因子受体（fibroblast growth factor receptor，FGFR）信号通路是调控细胞增殖、分化、迁移和存活的关键分子枢纽，在胚胎发育、组织修复和代谢稳态等多种生理过程中扮演着核心角色。该通路的异常激活，特别是由FGFR家族基因（FGFR1~4）的突变、扩增或染色体重排等基因异常所驱动，已成为多种恶性肿瘤发生与发展的重要致癌因素。携带这类变异的患者总体生存预后较差。近年来随着精准医疗理念的深入和高通量测序技术的普及，针对FGFR变异的新药研发不断取得进展，已有多种小分子抑制剂获批用于治疗携带特定FGFR基因异常的肿瘤患者，显著改善了这类患者的预后。文章旨在探讨肿瘤患者中FGFR信号通路与肿瘤发生发展的相关性及存在FGFR信号通路变异的肿瘤患者的治疗方案，着重探讨了FGFR靶向治疗新进展。

［关键词］ 成纤维细胞生长因子受体；肿瘤；靶向治疗

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Research progress on the mechanism of FGFR signaling pathway in tumors and targeted therapy

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［**Abstract**］ Fibroblast growth factor（FGF）and fibroblast growth factor receptor（FGFR）signaling pathways are key molecular hubs that regulate cell proliferation，differentiation，migration，and survival. They play a central role in various physiological processes such as embryonic development，tissue repair，and metabolic homeostasis. Abnormal activation of this pathway，driven by genetic abnormalities such as mutations，amplification，or chromosomal rearrangements in FGFR family genes（FGFR1-4），has become an important oncogenic factor in the development of various malignant tumors. Patients carrying such variations generally have a poorer overall survival prognosis. In recent years，with the deepening of the concept of precision medicine and the popularization of high-throughput sequencing technology，new drug development targeting FGFR variations has made continuous progress. Various small molecule inhibitors have been approved for the treatment of tumor patients with specific FGFR gene abnormalities，significantly improving the prognosis of these patients. This article aims to explore the correlation between the FGFR signaling pathway and tumor occurrence and development in tumor patients，as well as the treatment options for tumor patients with FGFR signaling pathway variations，and focuses on the new progress in FGFR-targeted therapy.

［**Key words**］ fibroblast growth factor receptor；tumor；targeted therapy

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成纤维细胞生长因子受体（fibroblast growth factor receptor，FGFR）是一类带有胞内酪氨酸激酶结构域的跨膜受体，与成纤维细胞生长因子（fibroblast growth factor，FGF）共同组成FGF/FGFR信号通路，参与细胞增殖、分化、迁移和致癌过程[1]。该通路的

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异常激活已被证实是包括尿路上皮癌（urothelial carcinoma，UC）、胆管癌（cholangiocarcinoma，CCA）、肺癌等多种实体肿瘤及血液肿瘤的致癌驱动因素[2-3]。据统计，约7.1%的实体瘤患者存在FGFR基因突变，这使得FGFR成为肿瘤精准治疗的一个重要靶点[4]。近年来，随着厄达替尼（erdafitinib）、培米替尼（pemigatinib）和富替巴替尼（futibatinib）等多款FGFR抑制剂的研发不断取得进展，给携带有FGFR基因突变的患者带来了希望，特别是在既往接受过治疗的晚期UC和CCA患者中[5-7]。然而，FGFR抑制剂在临床应用中普遍面临着耐药性的产生和治疗不良反应（如高磷酸盐血症）等挑战，这些问题限制了药物的长期疗效和患者获益[8]。文章系统梳理了FGFR基因突变的分子特征、常用检测方法和治疗现状，并对相关药物研发和临床研究的最新数据进行了总结，旨在为临床诊断、治疗和药物研发提供参考。

1 FGFR基因突变的生物学基础与致癌机制

1.1 FGFR基因的结构、配体及下游通路

FGFR属于受体酪氨酸激酶（receptor tyrosine kinase，RTK）家族，其经典结构由包含3个免疫球蛋白样结构域（Ig Ⅰ~Ⅲ）的胞外配体结合区、单次跨膜区以及胞内酪氨酸激酶结构域组成。生理状态下，当FGFR胞外区与其配体FGF结合后，会诱导受体发生二聚化及胞内激酶结构域的自磷酸化，进而激活包括RAS-MAPK、PI3K-AKT、PLCγ和STAT在内的多条下游经典信号通路[9]，精密调控细胞的增殖、分化、迁移与凋亡等生物学过程（图1）。

然而，在肿瘤中该通路的异常调控往往具有强烈的致癌驱动作用。例如，在脑胶质瘤中，FGFR1的N546K和K656E两个热点突变通过改变与下游效应蛋白PLCγ的结合亲和力，不仅持续激活相关促癌信号网络，还能逃避正常的溶酶体降解途径，进而发挥强大的致癌功能[10]。此外，FGF/FGFR信号通路的异常激活还参与维持骨髓细胞瘤病毒癌基因同源物（cellular-myelocytomatosis oncogene，c-Myc）等关键原癌蛋白的稳定性[11]。上述机制充分阐明了FGF/FGFR信号轴在肿瘤发生发展中的核心作用，为其作为抗肿瘤靶向治疗的切入点提供了坚实的生物学基础。

1.2 泛癌种中的FGFR基因变异谱系

FGFR基因变异是多种癌症发生发展过程中的重要驱动因素，其变异类型包括融合、突变、扩增、过表达以及肿瘤微环境（tumor microenvironment，TME）紊乱等，在不同肿瘤中的分布具有显著的组织特异性。在非实体瘤中，多发性骨髓瘤（multiple myeloma，MM）的肿瘤细胞中普遍存在FGF配体的分泌和FGFR的自分泌激活，其中15%~20%的MM病例携带FGFR3基因组改变[11]。而在部分急性髓

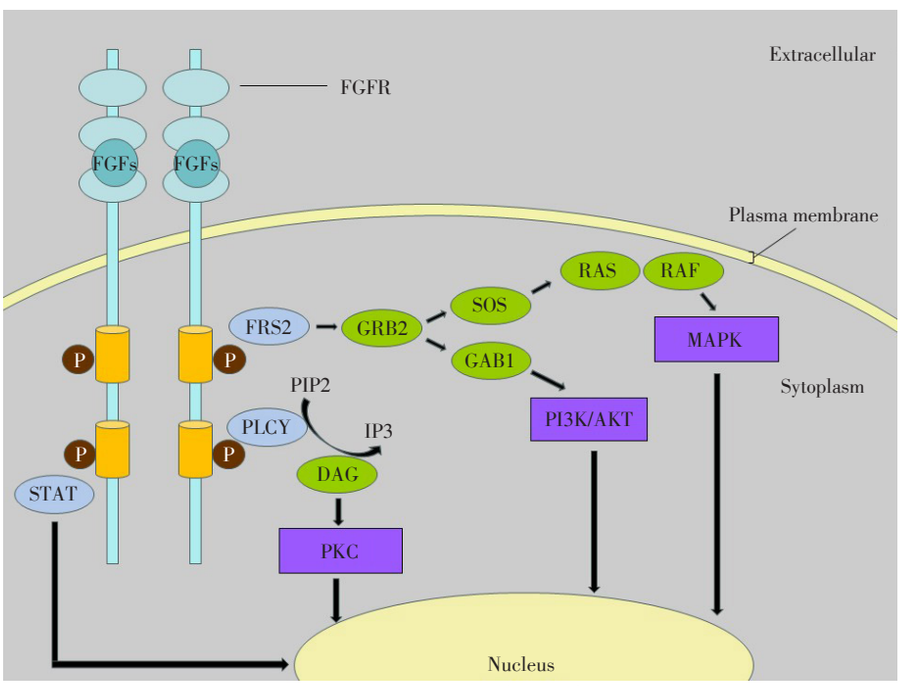

图1 FGF/FGFR信号通路

Figure 1 FGF/FGFR signaling pathway

系白血病(acute myeloid leukemia，AML)及骨髓/淋巴肿瘤(myeloid/lymphoid neoplasms，MLN)患者中常伴有FGFR1重排[12]。大规模基因组分析显示，FGFR1~4基因变异在实体瘤的总发生率为2.7%~4.2%[4]。其中，扩增是最常见的FGFR1改变，在结直肠癌(colorectal cancer，CRC)中发生率约为3.8%，并与预后不良相关[13]。FGFR2融合是CCA的标志性改变，发生率为10%~16%，并且在早发CCA中更为常见[14-15]。在UC中，FGFR3突变尤为普遍，在非肌层浸润性膀胱癌(non-muscle-invasive bladder cancer，NMIBC)中高达70%，肌层浸润性膀胱癌(muscle-invasive bladder cancer，MIBC)中约为15%[16-17]。此外，FGFR基因变异在儿童肿瘤中同样起着重要作用，特别是在低级别胶质瘤和横纹肌肉瘤中发生率接近9%[18-19]。除了常见的融合、突变，有研究还发现FGFR2可以通过基因突变、重排、扩增等多种方式产生外显子18截短(FGFR2ΔE18)这一新型致癌变异[20-21]。这种变异谱系的复杂性和组织特异性，凸显了在精准治疗中对FGFR变异进行精确分型的重要性。

1.3　FGFR信号通路在肿瘤微环境中的作用

FGF/FGFR信号通路不仅直接驱动肿瘤细胞的增殖与存活，还在塑造肿瘤微环境中发挥着关键作用，尤其是在免疫调控和血管生成方面[22-23]。既往多项研究表明，FGFR3基因突变与膀胱癌的“冷”免疫微环境或免疫豁免表型密切相关，其通过上调肿瘤细胞的丝氨酸合成，诱导巨噬细胞向免疫惰性表型转化，进而抑制T细胞的招募和活化，最终导致T细胞浸润减少和免疫抑制细胞如调节性T细胞(Treg)和M2型巨噬细胞的富集[24-27](图2)。在胆管癌中，FGFR融合阳性的肿瘤也表现出较低的程序性死亡配体1(programmed deathligand 1，PD-L1)水平和T细胞浸润，呈现“免疫沙漠”特征[28-29]。在血管生成方面，FGFR/血管内皮生长因子受体(vascular endothelial growth factor receptor，VEGFR)双重抑制剂(如仑伐替尼)通过破坏肿瘤结构和血管网络，而非直接杀伤肿瘤细胞诱导肿瘤消退[30]。在肝细胞癌(hepatocellular carcinoma，HCC)中，仑伐替尼等FGFR抑制剂能够将“冷”免疫微环境转变为“热”状态，增加$CD8^+$T细胞和颗粒酶B的浸润，为免疫治疗创造有利条件[31]。综上，FGFR信号通路通过复杂的机制调控肿瘤免疫微环境和血管生成，FGFR抑制剂不仅能直接抑制肿瘤，还能重塑微环境，增强其他疗法的疗效。

2　FGFR基因变异的检测方法

准确识别携带FGFR变异的患者是实施精准靶向治疗的先决条件。目前，临床上主要依赖组织或液体活检样本，运用多种分子诊断技术进行联合筛查[32]。基于组织样本的检测手段主要包括：用于评估基因扩增与重排的荧光原位杂交(FISH)、用于检测蛋白表达水平的免疫组织化学(immunohistochemistry，IHC)，以及能够全面解析基因突变、融合及拷贝数变异的二代测序(next-generation sequencing，

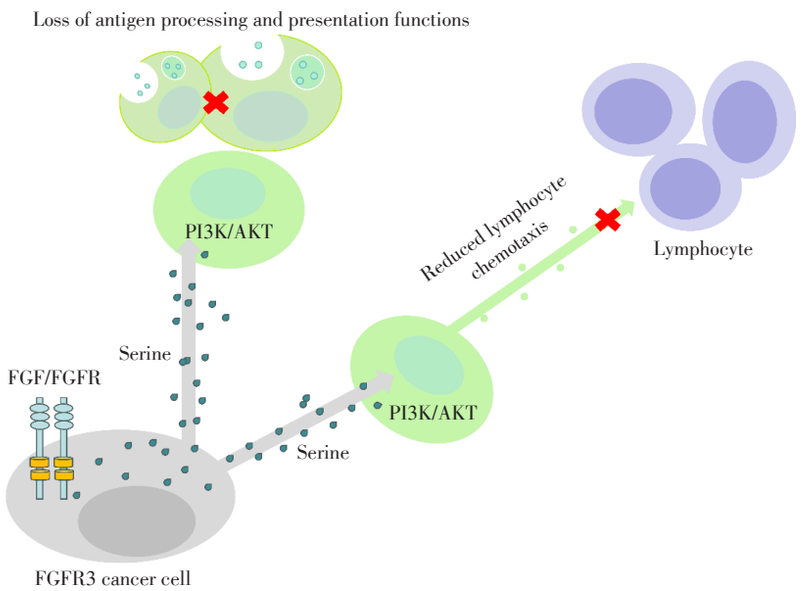

图2　FGFR信号通路在肿瘤微环境中的作用

Figure 2　The role of the FGFR signaling pathway in the tumor microenvironment

NGS）技术[33-34]。NGS已被国内外权威指南推荐为FGFR变异检测的“金标准”。然而，传统组织活检存在创伤性大、晚期取材困难以及难以克服肿瘤空间异质性等固有局限。例如，在UC中，原发灶与转移灶之间FGFR3突变状态的不一致率高达26%，提示仅依赖原发灶的基因测序可能无法准确反映转移病灶的真实靶点状态[35-36]。鉴于此，当组织样本获取受限或无法满足NGS检测需求时，以循环肿瘤DNA（circulating tumor DNA，ctDNA）为代表的液体活检技术，凭借其微创性及能更全面反映全身肿瘤异质性的优势，正日益成为一种不可或缺的重要补充诊断手段。

3 FGFR靶向药物的研究进展

3.1 已获批泛FGFR抑制剂的临床疗效与安全性评估

近年来，多款泛FGFR抑制剂获批上市标志着FGFR靶向治疗进入了临床实践的新纪元。厄达替尼是一种口服选择性泛FGFR酪氨酸激酶抑制剂（tyrosine kinase inhibitor，TKI），已获批用于携带FGFR2/3变异的经治晚期UC。BLC2001研究显示其客观缓解率（objective response rate，ORR）达40%，中位无进展生存期（median progression free survival，mPFS）和中位总生存期（median overall survival，mOS）分别为5.5个月和13.8个月，且长期随访显示疗效持久[37]。THOR研究进一步证实，其对免疫检查点抑制剂（immune checkpoint inhibitors，ICI）治疗后进展的FGFR变异UC患者的OS显著优于化疗（12.1个月*vs* 7.8个月）[38]。培米替尼获批用于携带FGFR2融合/重排的晚期、转移性或不可手术切除的经治CCA患者[39]。在FIGHT-202研究中，培米替尼治疗的ORR为37%，中位PFS和OS分别为7.0个月和17.5个月[40]。后续的多中心回顾性研究同样证实了培米替尼在临床实践中的有效性和安全性[41]。富替巴替尼是一种不可逆的FGFR1~4抑制剂，同样获批用于FGFR2融合/重排的经治iCCA[42]。在FOENIX-CCA2研究中，ORR为42%，mPFS和mOS分别为9.0个月和21.7个月，显示出持久的临床获益[43]。已获批泛FGFR抑制剂的临床研究见表1。

表1 FGFR抑制剂研究汇总

Table 1 Summary of FGFR inhibitor research

Study title	Phase	Drug name	Target	ORR（%）	mPFS（months）	mOS（months）
BLC2001	Ⅱ	Erdafitinib	FGFR2/3	40.0	5.5	13.8
THOR	Ⅲ	Erdafitinib	FGFR	45.6	5.6	12.1
FIGHT-202	Ⅱ	Pemigatinib	FGFR2	37.0	7.0	17.5
FOENIX-CCA2	Ⅱ	Futibatinib	FGFR2	42.0	9.0	21.7

3.2 新一代及选择性FGFR抑制剂的研究进展

尽管目前已获批的泛FGFR抑制剂取得了成功，但其疗效常因获得性耐药突变和不良反应而受限[44-45]。其中最常发生的是与FGFR1抑制相关的高磷酸盐血症[46]及与FGFR4抑制相关的腹泻[47]。为了克服这些挑战，新一代高选择性FGFR抑制剂的研究正在进行。Lirafugratinib（RLY-4008）是一款高选择性的不可逆FGFR2抑制剂，其对FGFR2的选择性比FGFR1高约250倍，比FGFR4高5 000倍以上[48]。这种高选择性使其在临床试验中能够在有效诱导肿瘤消退的同时，不引起明显的不良反应，并且对多种FGFR2原发变异及耐药突变均有活性，在晚期CCA患者中，ORR为45.6%，mPFS和mOS分别达到了11.3个月和22.8个月。此外，不良事件主要为皮肤黏膜毒性和眼部事件，多数为1~2级且可逆[49]。另一款在研药物ISM7594（ABSK061）是一种选择性的双重FGFR2/3抑制剂，它能有效避开FGFR1/4，同样旨在减轻高磷酸盐血症等不良反应，并对多种耐药突变保持活性。截至2023年12月，Ⅰ期剂量爬坡试验中携带FGFR变异的8例患者，在接受ISM7594治疗后，3例达到了部分缓解（partial response，PR），ORR为37.5%，3例达到了疾病稳定（stable disease，SD），疾病控制率（disease control rate，DCR）为75%[50-51]。TYRA-300则是一种选择性FGFR3抑制剂，不仅用于治疗FGFR3变异的UC，还用于治疗由FGFR3胚系突变引起的软骨发育不全等非恶性疾病。在接受TYRA-300治疗的携带FGFR3变异的UC患者中，DCR为100%，且与FGFR1、FGFR2相关的不良反应极少出现[52-53]。此外，一些新型化合物在克服特定耐药突变方面显示出优势。Tinengotinib在临床前和临床研究中证实对FGFR抑制剂治疗后进展的FGFR2融合CCA具有活性。在FGFR2变异的CCA患者中，mPFS为7.26个月，mOS为15.93个月。安全性方面，无5级AE发生，最常见

3级（54.1%）和4级（2.8%）AE为高血压、口腔炎、手足综合征，与其他晚期实体瘤人群观察到的AE一致[54]。这些新一代抑制剂通过提升亚型选择性和减少不良反应，有望为FGFR靶向治疗带来更优的疗效和安全性。

3.3 新兴疗法的研究进展

为了突破传统小分子抑制剂的局限性，多种新型FGFR靶向治疗模式正在积极探索中，主要包括靶向蛋白降解剂（proteolysis targeting chimera，PROTAC）、抗体药物和DNA适配子等。

PROTAC是一种利用细胞内泛素-蛋白酶体系统特异性降解目标蛋白的双功能分子。针对FGFR的PROTAC旨在通过降解FGFR蛋白而非仅仅抑制其激酶活性，来提供更持久和彻底的信号通路阻断，并有望克服因激酶结构域突变引起的耐药[55]。LC-MB12和28e是高效的选择性FGFR2降解剂，在胃癌和CCA模型中显示出强大的抗肿瘤活性，并能克服看门人突变[56-57]。LC-MF-4是首个被报道的高效FGFR3选择性降解剂，在FGFR3-TACC3融合阳性的异种移植模型中展现了强大的抗肿瘤活性[58]。

抗体药物与小分子抑制剂不同，其靶向受体的胞外域具有高特异性和长半衰期。Bemarituzumab是一种靶向FGFR2b的单克隆抗体，目前正在胃癌中进行临床试验[59]。为解决传统双价抗体可能引起的受体激动效应，研究人员开发了双特异性抗体和四价抗体。例如，靶向FGFR2胞外域不同表位的双特异性抗体不仅能有效阻断FGFR2融合蛋白的信号，还能与FGFR抑制剂产生协同作用，并对激酶区突变保持活性[60]。类似地，一种四价FGFR3×FGFR3双特异性抗体能有效抑制多种FGFR3致癌突变体（包括TKI耐药突变）驱动的肿瘤生长[61]。此外，将抗人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）的Affibody与FGFR2融合构建的双特异性蛋白偶联药物（peptide-drug conjugate，PDC）也显示出对HER2和FGFR共阳性肿瘤细胞的强效杀伤作用[62]。

DNA适配子作为一种新兴的靶向工具同样展现了潜力。研究发现，DNA适配子VZ23能够特异性结合FGFR1b/c，而不影响FGFR2~4，从而有效抑制FGFR1介导的信号通路，为治疗FGFR1相关的疾病提供了TKI之外的新选择[63]。这些新型治疗策略通过不同的作用机制，为克服FGFR抑制剂的耐药和毒性问题开辟了新的途径。

4 FGFR变异相关血液肿瘤的临床治疗现状

t（4；14）（p16；q32）易位在MM患者中发生率为15%~20%，是最常见的IgH易位之一，可导致FGFR3和多发性骨髓瘤SET（multiple myeloma SET，MMSET）结构域蛋白基因的过表达。携带t（4；14）的MM患者常表现为缓解期短、复发更具侵袭性，常伴肾功能衰竭、血细胞减少和髓外病变，预后不良。尽管新型药物如硼替佐米和来那度胺在一定程度上改善了这部分患者的预后，但t（4；14）仍是MM的高危遗传学标志，靶向FGFR3的治疗策略具有重要临床价值[11]。对于伴有FGFR1重排的MLN，异基因造血干细胞移植（allogeneic hematopoietic stem cell transplantation，allo-HCT）是目前唯一公认的潜在治愈性疗法。然而，疾病复发仍然是移植后面临的主要挑战，约23%的患者经历了复发/进展。针对移植后复发的困境，靶向FGFR的TKI展现了重要的挽救治疗价值。一项针对22例接受allo-HCT治疗的FGFR1重排MLN患者的回顾性研究显示，2例复发患者分别接受了泊那替尼（ponatinib）或培米替尼治疗后均达到了完全缓解，并在复发后分别存活了34.5个月和37个月。这提示了一种新的治疗策略：在allo-HCT后，特别是在移植后仍能检测到微小残留病灶的患者中，使用TKI进行维持治疗可能成为预防复发、巩固疗效的一种极具前景的方法[64]。

5 FGFR抑制剂的耐药机制与应对策略

5.1 靶内继发突变与旁路激活

尽管FGFR抑制剂在临床上取得了成功，但获得性耐药的产生限制了其长期疗效[65]。耐药机制主要分为靶内继发突变和旁路激活两大类。

靶内耐药的形成主要归因于激酶结构域内出现的新发突变，这些改变可通过影响药物结合位点的空间构象，或促使受体维持持续活化状态，从而削弱FGFR抑制剂的结合效能[66-67]。继发突变位点中最常见的包括“看门人”残基和“分子刹车”残基[68]。以FGFR2为例，V565（看门人）与N550（分子刹车）2个位点的突变最为常见，二者合计占所有继发突变事件的60%以上[69-70]。在接受富替巴替尼治疗的患者中，耐药突变谱相对较窄，主要集中在V565和N550位点；而在接受可逆性抑制剂治疗的患者中，耐药突变谱更为广泛，涉及14个不同残基[68]。值得注意的是，靶向共价抑制剂结合的半胱氨酸残基（如FGFR2 C492）的突变虽然能导致耐药，但其发生频

率较低，这可能与这些突变本身会降低受体的信号活性有关[69]。

旁路信号通路激活是另一种重要的耐药机制，即肿瘤细胞通过激活其他平行的信号通路来绕过被抑制的FGFR信号，维持其增殖和存活[71]。在CCA和UC中，KRAS、BRAF、NRAS等丝裂原活化蛋白激酶（mitogenactivated protein kinase，MAPK）通路上游基因的继发突变，或TSC1/2、PIK3CA、PTEN等PI3K通路相关基因的变异，是常见的旁路激活[72]。此外，其他RTK的激活也能介导耐药，如间质上皮转化因子（mesenchymalepithelial transition factor，MET）基因扩增或肝细胞生长因子（hepatocyte growth factor，HGF）诱导的MET激活可导致对厄达替尼的耐药[73]，而表皮生长因子受体（epidermal growth factor receptor，EGFR）信号的反馈性激活也限制了FGFR抑制剂的疗效[74]。在膀胱癌中，由脂肪前体细胞分泌的神经调节蛋白1（neuregulin 1，NRG1）通过激活人表皮生长因子受体3（human epidermal growth factor receptor 3，HER3）信号通路，同样可介导对厄达替尼的耐药[75]。这些复杂的耐药机制，尤其是多种机制（如靶内突变和旁路激活）的共存，对临床治疗提出了严峻挑战。

5.2 克服耐药的治疗策略研究进展

为克服FGFR抑制剂的单药耐药挑战，开发合理的联合治疗策略已成为研究核心。针对代偿性旁路激活引发的耐药，多项研究证实了双靶向联合的优势。例如，针对MAPK或PI3K通路激活介导的耐药，分别联合MAPK抑制剂（如曲美替尼）[76]或哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）抑制剂（如伊维莫司）[69]展现出显著的协同抗肿瘤作用。类似地，当耐药由MET或EGFR信号驱动时，联合相应的抑制剂（如吉非替尼）能有效恢复肿瘤细胞对FGFR靶向药物的敏感性[77]。除了阻断旁路信号，调节肿瘤微环境以联合免疫治疗也是极具前景的破局策略。FGFR抑制剂能重塑微环境，为联合ICI提供了理论基础。Ⅱ期NORSE研究表明，在不耐受顺铂的转移性UC患者中，厄达替尼联合抗PD-1抗体cetrelimab较单药显著提升了ORR（54.5% *vs*. 44.2%）和mOS（20.8个月 *vs*. 16.2个月），且该方案在PD-L1低表达人群中疗效尤为显著[44]。此外，干预肿瘤代谢与表观遗传状态为克服耐药提供了新维度。在FGFR突变的膀胱癌中，靶向亚精胺合成酶（spermidine synthase，SRM）或外被体蛋白复合物α亚基（coatomer protein complex subunit alpha，COPA）可显著增强厄达替尼的疗效[78]。同时，组蛋白去乙酰化酶（histone deacetylase，HDAC）抑制剂能够通过下调FGFR3的翻译水平，与FGFR抑制剂产生强烈的协同效应[79-80]。综上所述，这些多元化联合策略的不断验证，为破解FGFR抑制剂的耐药困局提供了切实可行的方案，进一步推动了肿瘤个体化精准治疗的发展。

6 结论和展望

FGFR信号通路异常激活是驱动多种恶性肿瘤的重要致癌因素。近年来，厄达替尼、培米替尼等泛FGFR抑制剂在UC、CCA等实体瘤及伴有FGFR1重排的髓系/淋巴系肿瘤中获批上市，显著改善了患者预后；Lirafugratinib、TYRA-300等新一代高选择性抑制剂及PROTACs、双特异性抗体等新兴疗法，为克服不良反应和耐药提供了新路径。然而，FGFR靶向治疗仍面临挑战：一是NGS与液体活检的联合应用虽提升了检测可及性，但标准化和规范化有待完善；二是高磷酸盐血症等不良反应及获得性耐药限制了长期疗效，耐药机制涉及靶内突变、旁路激活及微环境重塑等多维度；三是血液肿瘤中FGFR靶向治疗尚处早期，MLN-FGFR1患者的治疗策略需要进一步验证，FGFR3在MM中的价值也有待确证。展望未来，基于ctDNA动态监测的适应性治疗、FGFR抑制剂与免疫检查点抑制剂或MEK/mTOR抑制剂的联合策略、新型靶向降解技术的成熟，以及血液肿瘤与实体瘤治疗经验的跨瘤种整合，将推动FGFR靶向治疗向更精准、更安全、更持久的方向发展，为携带FGFR基因变异的患者带来更多临床获益。

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Lin Yixiang and Sun Ao were responsible for the topic selection，literature search，and writing；Zhang Meiling was responsible for writing guidance，paper revision and review.

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