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Research progress of fibroblast growth factor receptor in gastric cancer

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Abstract: The incidence and mortality of gastric cancer are in the forefront of the tumor, and the prognosis is poor, especially in the middle and advanced stage. Even with comprehensive treatment, the 5-year survival is very low. The development of precision medicine has extended the survival of patients, and fibroblast growth factor receptor (FGFR) has gradually become a popular target for the treatment of gastric cancer. In this paper, the common FGFR alteration types in gastric cancer and the exploration of FGFR inhibitors in the field of gastric cancer in recent years were reviewed, and the challenges faced were analyzed.

Keyword: Fibroblast growth factor receptor; Gastric cancer; Fibroblast growth factor receptor inhibitor; Tyrosine kinase inhibitor; Ligand trap; Monoclonal antibody; Gene amplification; Genetic mutation; Gene rearrangement

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In 2020, there were over 1 million new cases of gastric cancer globally, with 769,000 deaths, ranking 5th in terms of incidence and 4th in terms of mortality among all cancers [1]. Due to the subtle early symptoms of gastric cancer, most patients are diagnosed at an advanced stage [2]. Advanced gastric cancer has limited treatment options and poor efficacy, with a median survival time of less than 1 year. The development of precision medicine for tumors has prolonged progression-free survival (PFS) and overall survival for patients. Human epidermal growth factor receptor 2 (HER2) is currently known as a target for targeted therapy in gastric cancer. Patients with HER2-positive advanced gastric cancer can benefit from anti-HER2 treatment. However, there are still fewer effective targeted treatment options for HER2-negative patients is still less, and new treatment targets need to be identified.

Fibroblast growth factor receptors (FGFR) belong to the family of receptor tyrosine kinases and consist of four subtypes, namely FGFR1, FGFR2, FGFR3, and FGFR4, and their 22 ligands. After binding to ligands, FGFR can activate a series of downstream signaling pathways, including the RAS/RAF/MEK/MAPK pathway, the PI3K/AKT/mTOR pathway, the JAK/STAT pathway, and the PLCγ pathway. The excessive activation of the RAS-RAF-MEK-MAPK pathway stimulates cell proliferation and differentiation. The excessive activation of the PI3K-AKT-mTOR pathway can inhibit cell apoptosis. Activation of the JAK-STAT pathway can promote tumor invasion, metastasis and immune escape. The PLCγ signaling pathway plays an important role in tumor metastasis [3].

The FGFR has become an important target for precision therapy in gastric cancer [4]. Previous studies have shown that FGFR plays an important/essential role in the treatment of tumors such as cholangiocarcinoma and urothelial carcinoma. The incidence of FGFR genomic alterations in gastric cancer ranges from 7% to 16.8% [5-6]. Research on this target in gastric cancer is increasing, and corresponding targeted drugs have become a new choice for the treatment of gastric cancer patients.

1 FGFR gene abnormalities

A multi-tumor study analyzing 4 853 solid tumor patients showed that 7.1% of patients had FGFR gene abnormalities, which is similar to a study in China [7]. The majority of these abnormalities were gene amplifications (66%), followed by mutations (26%) and rearrangements (8%). FGFR gene abnormalities were widely distributed in multiple tumor types, with the most common being urothelial carcinoma, followed by breast cancer, endometrial cancer, squamous cell lung cancer, ovarian cancer, and others. In the Chinese population, FGFR gene alterations were most common in colorectal cancer, followed by gastric cancer, breast cancer, and esophageal cancer [6]. Furthermore, the FGFR subtypes and types of gene alterations vary among different types of tumors. The most common FGFR variant in gastric cancer is FGFR2, followed by FGFR1 and FGFR3, and the most common alteration is amplification, followed by rearrangement and mutation, which may co-occur [8].

1.1 FGFR amplification/overexpression

FGFR2 amplification occurs in 4% to 9% of gastric cancers, especially in diffuse-type gastric cancer [9], and is associated with lymphatic vessel infiltration and poor prognosis [10]. FGFR1 amplification occurs in approximately 2% of gastric cancers, and the cases are similar to gastric cancer cases with FGFR2 amplification,

which are usually associated with low survival rates and distant metastasis [11]. FGFR3 and FGFR4 amplifications are rare. A study found that ctDNA sequencing is better at detecting FGFR2 amplification compared to traditional tissue testing (7.7% vs 2.6%-4.4%), which can complement tissue testing [12]. In addition to amplification, FGFR2 overexpression occurs in 40% to 60% of gastric cancer patients and is associated with depth of tumor infiltration and worse survival rates [13]. FGFR1 and FGFR4 overexpression are also significantly associated with gastric cancer progression, including invasion depth, lymph node metastasis, pathological stage, distant metastasis, and recurrence. Co-overexpression of two or more FGFRs can lead to exceptionally poor prognosis [14]. The frequency of FGFR3 and FGFR4 overexpression and their clinical significance are less studied, although one study reported FGFR3 overexpression in 64% of gastric cancer, which was not associated with overall survival [14].

1.2 FGFR mutations

FGFR mutations include single-nucleotide variations and insertion-deletion mutations. FGFR2 and FGFR3 mutations are more common compared to FGFR1 and FGFR4 mutations. FGFR2 mutations are most common in endometrial cancer, with an incidence of 10% to 12%, and are often associated with poor prognosis [15]. FGFR3 mutations are closely related to bladder cancer and can affect prognosis and response to immunotherapy [16-17]. The single nucleotide variation rate of FGFR in gastric cancer is 6.2% [7], mainly involving FGFR1 mutations. In gastric cancer, the G636C-FGFR4 mutation can activate FGFR4 protein and are carcinogenic [18].

1.3 FGFR rearrangements and fusions

FGFR2 and FGFR3 often fuse with other genes. FGFR2 fusion is more common in intrahepatic cholangiocarcinoma, with an incidence of 10% to 15%, and rarer in other tumors. The most common fusion partner of FGFR2 is BICC1, and others include CIT, CCDC6, and CCAR2 [19]. Professor Liu Baorui's team [20] detected the incidence of FGFR2 rearrangements (FGFR2/VTI1A and FGFR2/TACC2) in poorly cohesive gastric carcinoma is 3.1%, and were associated with poor prognosis. *In vitro* studies showed that gastric cancer cell lines transfected with TACC2-FGFR2 fusion were more sensitive to FGFR2 inhibitors, suggesting that FGFR2 may be a potential therapeutic target for poorly cohesive gastric carcinoma. FGFR3 fusion is relatively common in glioblastoma and bladder cancer, with the fusion partner gene being TACC3. FGFR3 fusion is rare in gastric cancer, and the reported incidence varies across different studies. A phase I study reported one case of FGFR3-TACC3 fusion in a gastric cancer patient, who achieved partial remission after receiving FGFR inhibitor treatment, with a duration of remission lasting 5.4 months [21].

2 Progress in FGFR inhibitors for gastric cancer

2.1 Tyrosine kinase inhibitors (TKIs)

FGFR-TKIs include multi-targeted inhibitors of FGFR and selective FGFR inhibitors (pan-FGFR inhibitors, FGFR1-3 inhibitors, FGFR4 inhibitors).

2.1.1 Multi-targeted inhibitors of FGFR

Multi-targeted inhibitors of FGFR can target FGFR and other receptors such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), and relevant drugs include pazopanib, regorafenib, lenvatinib, sorafenib, and nintedanib. Multi-targeted inhibitors of FGFR have high activity but low selectivity and significant systemic toxicity, with common adverse reactions including hypertension, fatigue, gastrointestinal reactions, and hand-foot syndrome. Pazopanib combined with chemotherapy is currently used to treat advanced gastric cancer patients, especially those with FGFR3 amplification, and has achieved better therapeutic effects [22]. Regorafenib can dose-dependently inhibit FGFR2 signaling in cell and mouse experiments, suppressing the growth of gastric cancer cells with FGFR2 amplification, which can serve as a predictive marker for regorafenib sensitivity in gastric cancer treatment [23]. Nintedanib has shown certain anti-tumor activity in FGFR2-amplified gastric cancer cell lines [24].

2.1.2 Selective FGFR Inhibitors

Erdafitinib, pemigatinib, and infigratinib, which were approved by the FDA for the treatment of advanced urothelial carcinoma and cholangiocarcinoma with different FGFR family gene mutations, belong to selective FGFR inhibitors. Selective FGFR inhibitors have high sensitivity and relatively low systemic toxicity because they inhibit the FGFR pathway only and avoid the toxic effects of other targets. While the kinase domains of FGFR3 are highly similar, FGFR4 has a unique structure, thus most selective FGFR inhibitors can inhibit FGFR1-3 in different degrees, with a few TKIs exclusively inhibiting FGFR4. Infigratinib showed an objective response rate of 25.0% (n = 20) and a median duration of response of 3.8 months in locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma patients with FGFR2 gene amplification. Based on these trial data, infigratinib was granted breakthrough therapy designation by China's National Medical Products Administration (NMPA) for the treatment of FGFR2-amplified gastric cancer. AZD4547 is a highly active and selective FGFR1-3 inhibitor. A study showed that there was no statistically significant difference in PFS between AZD4547 and paclitaxel in the treatment of advanced gastric cancer patients with FGFR2 amplification after failed first-line chemotherapy. AZD4547 exhibited good tolerability, and the degree of response to AZD4547 positively correlated with FGFR2

amplification times, suggesting potentially better efficacy for patients with highly amplified FGFR2 gene [25]. The drug was granted orphan drug designation for the treatment of gastric cancer by the FDA in March 2022. Derazantinib is an oral FGFR1-3 inhibitor with strong efficacy in gastric cancer models and has a synergistic anti-tumor effect with paclitaxel [26]. LY2874455 is a pan-FGFR inhibitor, which was evaluated in a phase IB trial with 29 gastric cancer patients, with 1 achieving partial remission and 12 showing stable disease [27]. Futibatinib is an orally orally bioavailable, selective, irreversible FGFR inhibitor, with inhibitory effects on FGFR1-4. Futibatinib has broad-spectrum anti-tumor activity in cancer cell lines and xenograft models with FGFR genomic aberrations, including gastric cancer, and with a reduced risk of resistance compared to other FGFR inhibitors [28]. In two phase I clinical studies, objective response rates for gastric cancer patients treated with futibatinib were 22% and 36.4%, respectively, demonstrating a certain degree of anti-tumor activity [21, 29]. Common adverse reactions mainly included hyperphosphatemia, diarrhea, and nausea.

2.2 Monoclonal antibodies

FGFR monoclonal antibodies mainly exert anti-tumor effects by blocking ligand/receptor binding and/or receptor dimerization, or by conjugating with highly cytotoxic drugs [30-31]. Bemarituzumab is the first humanized monoclonal antibody targeting FGFR2b in the world, which can block the binding and activation of FGFs with FGFR2b, inhibit downstream pathways, and block tumor progression. Additionally, it can induce enhanced antibody-dependent cellular cytotoxicity and potentially achieve tumor cell killing by recruiting NK cells. In an exploratory phase II clinical trial of bemarituzumab combined with mFOLFOX6 in patients with advanced gastric or GEJ adenocarcinoma selected for FGFR2b expression and HER2-negativity, although there was no statistically significant improvement in PFS (9.5 months *vs.* 7.4 months, P=0.073), promising clinical efficacy was achieved [32]. Subgroup analysis showed that the higher the expression level of FGFR2b, the longer the survival. However, the combination therapy group observed 83% of grade 3 or higher adverse events, including neutropenia, corneal disorders, and oral mucositis. At the same time, the Phase Ib/III study of Bemarituzumab combined with mFOLFOX6 and nivolumab for first-line treatment of HER2-negative gastric /GEJ adenocarcinoma is currently underway. Some safety data from Phase Ib were released at the 2023 annual meeting of the European Society of Oncology (ESMO), and after 13 months of follow-up, no dose-limiting toxicity or new safety events were reported.

2.3 Fibroblast growth factor (FGF) ligand traps

FGF ligand traps can bind and isolate FGF ligands, preventing them from binding to FGFR. Unlike monoclonal antibodies that only target a single ligand, ligand trap FC-fusion proteins can bind to multiple ligands. Macromolecular FGF traps include FP-1039/GSK3052230, Ms FGFR2c, and sFGFR3, which originate from the extracellular space of FGFR1, FGFR2, and FGFR3, respectively. Micromolecular FGF traps include sm27 and NSC12 [33]. FP-1039 is well tolerated in non-selective advanced cancer patients, with some hyperphosphatemia and retinal changes observed, and no nail or dermal toxicity observed [34]. It also shows clinical efficacy in patients with pleural mesothelioma and non-small cell lung cancer [35-36]. NSC12 has certain anti-tumor activity in multiple myeloma and lung cancer models [37-38].

At present, the indications for FGFR inhibitors are mainly for cholangiocarcinoma and urothelial carcinoma, but there are still many preclinical studies and clinical trials of FGFR inhibitors for the treatment of gastric cancer in progress [39], hoping to achieve exciting results.

3 Challenges and dilemmas

The efficacy of FGFR inhibitors is limited by resistance mechanisms. To overcome resistance, Professor Chen Yongheng *et al.* [40] proposed the development of novel covalent FGFR inhibitors, the use of combination therapy, disruption of lysosomal structure to release sequestered TKIs, and the utilization of FGFR ligands or FGFR-specific monoclonal antibodies to bypass TKI resistance, and other corresponding strategies. The team led by Chen Lingfeng [41] has developed a novel orally effective FGFR2-selective degrader (LC-MB12) that can circumvent mutation-related resistance. Combination therapy can simultaneously block multiple activation pathways, inhibit the activation of bypass signals, overcome acquired resistance, and MEK inhibitors can overcome resistance to FGFR inhibitors in FGFR-driven gastric cancer [42]. When FGFR is inhibited, a well-defined MAPK-ERK signaling pathway in gastric cancer will be activated [19], and the combination therapy with MEK inhibitors may enhance the inhibitory effect of FGFR, and improve treatment benefits. The resistance mechanism of FGFR1 inhibitors can regulate cellular autophagy mainly through the activation of the TAK1/AMPK signaling pathway. TAK1 inhibitors can synergistically inhibit resistance induced by FGFR inhibitors [43]. The FGF/FGFR signaling pathway is involved in regulating the tumor microenvironment, including immune cells, angiogenesis, and epithelial-mesenchymal transition. FGFR inhibitors can enhance the response to immune checkpoint inhibitors by affecting various stages of cancer immune regulation [44]. The expression of FGFR1 in gastric cancer models has been shown to enhance the efficacy of immunotherapy

[45].

4 Conclusion and outlook

Currently, approved targeted therapies for gastric cancer mainly focus on HER2, VEGFR, and PD-1 targets in clinical practice. However, these options still fall short of meeting the complete therapeutic needs of patients. Increasingly, new targets are being gradually explored, and more targeted drugs are tested by clinical trials. The exploration of FGFR inhibitors for gastric cancer is predominantly in the pre-clinical or small-sample clinical research stage. However, the efficacy of FGFR inhibitors is limited by acquired drug resistance and adverse effects, posing challenges to their therapeutic potential. Broadening the indications, exploring the potential of combination therapies with other treatment approaches, and implementing sequential treatments require collective efforts in the field of medicine.

Conflict of Interest None

Reference

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021, 71(3): 209-249.

[2] Zeng HM, Ran XH, An L, et al. Disparities in stage at diagnosis for five common cancers in China: a multicentre, hospital-based, observational study[J]. Lancet Public Health, 2021, 6(12): e877-e887.

[3] Du SC, Zhang Y, Xu JM. Current progress in cancer treatment by targeting FGFR signaling[J]. Cancer Biol Med, 2023, 20(7): 490-499.

[4] Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group[J]. Ann Oncol, 2020, 31(11): 1491-1505.

[5] Helsten T, Elkin S, Arthur E, et al. The FGFR landscape in cancer: analysis of 4, 853 tumors by next-generation sequencing[J]. Clin Cancer Res, 2016, 22(1): 259-267.

[6] Sun Y, Li G, Zhu W, et al. A comprehensive pan-cancer study of fibroblast growth factor receptor aberrations in Chinese cancer patients[J]. Ann Transl Med, 2020, 8(20): 1290.

[7] Zuo W, He Y, Li W, et al. Landscape of *FGF*/*FGFR* alterations in 12, 372 Chinese cancer patients[J]. J Cancer, 2020, 11(22): 6695-6699.

[8] Helsten T, Schwaederle M, Kurzrock R. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: biologic and clinical implications[J]. Cancer Metastasis Rev, 2015, 34(3): 479-496.

[9] Matsumoto K, Arao T, Hamaguchi T, et al. *FGFR2* gene amplification and clinicopathological features in gastric cancer[J]. Br J Cancer, 2012, 106(4): 727-732.

[10] Su X, Zhan P, Gavine PR, et al. FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study[J]. Br J Cancer, 2014, 110(4): 967-975.

[11] Schäfer MH, Lingohr P, Sträßer A, et al. Fibroblast growth factor receptor 1 gene amplification in gastric adenocarcinoma[J]. Hum Pathol, 2015, 46(10): 1488-1495.

[12] Jogo T, Nakamura Y, Shitara K, et al. Circulating tumor DNA analysis detects *FGFR2* amplification and concurrent genomic alterations associated with FGFR inhibitor efficacy in advanced gastric cancer[J]. Clin Cancer Res, 2021, 27(20): 5619-5627.

[13] Tokunaga R, Imamura Y, Nakamura K, et al. Fibroblast growth factor receptor 2 expression, but not its genetic amplification, is associated with tumor growth and worse survival in esophagogastric junction adenocarcinoma[J]. Oncotarget, 2016, 7(15): 19748-19761.

[14] Murase H, Inokuchi M, Takagi Y, et al. Prognostic significance of the co-overexpression of fibroblast growth factor receptors 1, 2 and 4 in gastric cancer[J]. Mol Clin Oncol, 2014, 2(4): 509-517.

[15] Jeske YW, Ali S, Byron SA, et al. FGFR2 mutations are associated with poor outcomes in endometrioid endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study[J]. Gynecol Oncol, 2017, 145(2): 366-373.

[16] Ascione CM, Napolitano F, Esposito D, et al. Role of FGFR3 in bladder cancer: treatment landscape and future challenges[J]. Cancer Treat Rev, 2023, 115: 102530.

[17] Xu PH, Chen SY, Wang YH, et al. FGFR3 mutation characterization identifies prognostic and immune-related gene signatures in bladder cancer[J]. Comput Biol Med, 2023, 162: 106976.

[18] Futami T, Kawase T, Mori K, et al. Identification of a novel oncogenic mutation of FGFR4 in gastric cancer[J]. Sci Rep, 2019, 9(1): 14627.

[19] Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer[J]. Nat Rev Cancer, 2017, 17(5): 318-332.

[20] Wang Y, Shi T, Wang X, et al. FGFR2 alteration as a potential therapeutic target in poorly cohesive gastric carcinoma[J]. J Transl Med, 2021, 19(1): 401.

[21] Meric-Bernstam F, Bahleda R, Hierro C, et al. Futibatinib, an irreversible FGFR1-4 inhibitor, in patients with advanced solid tumors harboring *FGF*/*FGFR* aberrations: a phase I dose-expansion study[J]. Cancer Discov, 2022, 12(2): 402-415.

[22] Limaye S, Patil D, Akolkar D, et al. Response to pazopanib-based combination regimen in a case of FGFR3 amplified gastric adenocarcinoma[J]. Clin Case Rep, 2021, 9(11): e04986.

[23] Cha YJ, Kim HP, Lim Y, et al. FGFR2 amplification is predictive of sensitivity to regorafenib in gastric and colorectal cancers *in vitro*[J]. Mol Oncol, 2018, 12(7): 993-1003.

[24] Hilberg F, Tontsch-Grunt U, Baum A, et al. Triple angiokinase inhibitor nintedanib directly inhibits tumor cell growth and induces tumor shrinkage via blocking oncogenic receptor tyrosine kinases[J]. J Pharmacol Exp Ther, 2018, 364(3): 494-503.

[25] Van Cutsem E, Bang YJ, Mansoor W, et al. A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with FGFR2 polysomy or gene amplification[J]. Ann Oncol, 2017, 28(6): 1316-1324.

[26] McSheehy PMJ, Forster-Gross N, El Shemerly M, et al. The fibroblast growth factor receptor inhibitor, derazantinib, has strong efficacy in human gastric tumor models and synergizes with paclitaxel *in vivo*[J]. Anticancer Drugs, 2023, 34(4): 532-543.

[27] Michael M, Bang YJ, Park YS, et al. A Phase 1 Study of LY2874455, an Oral Selective pan-FGFR Inhibitor, in Patients with Advanced Cancer[J]. Target Oncol, 2017, 12(4): 463-474.

[28] Sootome H, Fujita H, Ito K, et al. Futibatinib is a novel irreversible FGFR 1-4 inhibitor that shows selective antitumor activity against FGFR-deregulated tumors[J]. Cancer Res, 2020, 80(22): 4986-4997.

[29] Doi T, Shitara K, Kojima T, et al. Phase I study of the irreversible fibroblast growth factor receptor 1-4 inhibitor futibatinib in Japanese patients with advanced solid tumors[J]. Cancer Sci, 2023, 114(2): 574-585.

[30] Kim SB, Meric-Bernstam F, Kalyan A, et al. First-in-human phase I study of aprutumab ixadotin, a fibroblast growth factor receptor 2 antibody-drug conjugate (BAY 1187982) in patients with advanced cancer[J]. Target Oncol, 2019, 14(5): 591-601.

[31] Catenacci DV, Tesfaye A, Tejani M, et al. Bemarituzumab with modified FOLFOX6 for advanced FGFR2-positive gastroesophageal cancer: fight Phase III study design[J]. Future Oncol, 2019, 15(18): 2073-2082.

[32] Wainberg ZA, Enzinger PC, Kang YK, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study[J]. Lancet Oncol, 2022, 23(11): 1430-1440.

[33] Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder[J]. Pharmacol Res, 2020, 151: 104567.

[34] Tolcher AW, Papadopoulos KP, Patnaik A, et al. A phase I, first in human study of FP-1039 (GSK3052230), a novel FGF ligand trap, in patients with advanced solid tumors[J]. Ann Oncol, 2016, 27(3):

526-532.
[35] van Brummelen EMJ, Levchenko E, Dómine M, et al. A phase Ib study of GSK3052230, an FGF ligand trap in combination with pemetrexed and cisplatin in patients with malignant pleural mesothelioma[J]. Invest New Drugs, 2020, 38(2): 457-467.
[36] Morgensztern D, Karaseva N, Felip E, et al. An open-label phase IB study to evaluate GSK3052230 in combination with paclitaxel and carboplatin, or docetaxel, in FGFR1-amplified non-small cell lung cancer[J]. Lung Cancer, 2019, 136: 74-79.
[37] Castelli R, Giacomini A, Anselmi M, et al. Synthesis, structural elucidation, and biological evaluation of NSC12, an orally available fibroblast growth factor (FGF) ligand trap for the treatment of FGF-dependent lung tumors[J]. J Med Chem, 2016, 59(10): 4651-4663.
[38] Castelli R, Taranto S, Furiassi L, et al. Chemical modification of NSC12 leads to a specific FGF-trap with antitumor activity in multiple myeloma[J]. Eur J Med Chem, 2021, 221: 113529.
[39] Lengyel CG, Hussain S, Seeber A, et al. FGFR pathway inhibition in gastric cancer: the golden era of an old target?[J]. Life, 2022, 12(1): 81.
[40] Yue ST, Li YK, Chen XJ, et al. FGFR-TKI resistance in cancer: current status and perspectives[J]. J Hematol Oncol, 2021, 14(1): 23.
[41] Ma L, Li YY, Luo RX, et al. Discovery of a selective and orally bioavailable FGFR2 degrader for treating gastric cancer[J]. J Med Chem, 2023, 66(11): 7438-7453.
[42] Lau DK, Luk IY, Jenkins LJ, et al. Rapid resistance of FGFR-driven gastric cancers to regorafenib and targeted FGFR inhibitors can be overcome by parallel inhibition of MEK[J]. Mol Cancer Ther, 2021, 20(4): 704-715.
[43] Peng R, Chen Y, Wei LN, et al. Resistance to FGFR1-targeted therapy leads to autophagy via TAK1/AMPK activation in gastric cancer[J]. Gastric Cancer, 2020, 23(6): 988-1002.
[44] Ruan RW, Li L, Li X, et al. Unleashing the potential of combining FGFR inhibitor and immune checkpoint blockade for FGF/FGFR signaling in tumor microenvironment[J]. Mol Cancer, 2023, 22(1): 60.
[45] Yang CC, Song DL, Zhao FY, et al. Comprehensive analysis of the prognostic value and immune infiltration of *FGFR* family members in gastric cancer[J]. Front Oncol, 2022, 12: 936952.

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· 研究进展 ·

成纤维细胞生长因子受体在胃癌中的研究进展

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摘要：胃癌发病率及死亡率均位于肿瘤前列，且预后差，尤其是中晚期胃癌，即便采取了综合治疗，5 年生存率也很低。精准医疗的发展延长了患者的生存期，成纤维细胞生长因子受体（FGFR）已逐渐成为胃癌治疗的热门靶点。本文就胃癌中常见的 FGFR 改变类型和近年 FGFR 抑制剂在胃癌领域中的探索进行综述，并对面临的挑战进行分析。

关键词：成纤维细胞生长因子受体；胃癌；成纤维细胞生长因子抑制剂；酪氨酸激酶抑制剂；配体陷阱；单克隆抗体；基因扩增；基因突变；基因重排
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Research progress of fibroblast growth factor receptor in gastric cancer

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Abstract: The incidence and mortality of gastric cancer are in the forefront of the tumor, and the prognosis is poor, especially in the middle and advanced stage. Even with comprehensive treatment, the 5-year survival is very low. The development of precision medicine has extended the survival of patients, and fibroblast growth factor receptor (FGFR) has gradually become a popular target for the treatment of gastric cancer. In this paper, the common FGFR alteration types in gastric cancer and the exploration of FGFR inhibitors in the field of gastric cancer were reviewed, and the challenges were analyzed.

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2020 年全球新发胃癌病例超过 100 万例，死亡病例达 76.9 万例，发病率和死亡率在所有癌症中分别位居第 5 位和第 4 位[1]。由于胃癌早期症状较隐蔽，大部分的胃癌患者确诊时已经是中晚期[2]，晚期胃癌治疗手段有限，疗效欠佳，生存时间常不足 1 年。肿瘤精准医学的发展延长了患者的无进展生存期（PFS）和总生存期，人类表皮生长因子受体 2（human epidermalgrowth factor receptor-2, HER2）是胃癌目前已知的靶向治疗的靶点，HER2 阳性晚期胃癌患者可从抗 HER2 治疗中获益，但对于 HER2 阴性的患者仍缺乏有效的靶向治疗方案，需要寻找新的治疗靶点。

成纤维细胞生长因子受体（fibroblast growth factor receptors, FGFR）属于酪氨酸激酶受体，有 4 种亚型，即 FGFR1、FGFR2、FGFR3 和 FGFR4，以及 22 个配体，FGFR 与配体结合可激活下游一系列的信号通路：鼠肉瘤病毒/鼠肉瘤病毒致癌基因同源物/线粒体活性蛋白激酶/丝裂原活化蛋白激酶（rat sarcoma viral/rat sarcoma viral oncogene homolog/mitogen-activated protein kinases kinase/mitogen-activated protein

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kinases, RAS/RAF/MEK/MAPK)、磷脂酰肌醇 3-激酶/蛋白激酶 B/哺乳动物雷帕霉素靶蛋白(phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin, PI3K/AKT/mTOR)、非受体酪氨酸激酶/信号传导和转录激活因子(janus kinase/signal transducer and activator of transcription, JAK/STAT)和磷脂酶 C-γ(phospholipaseC-γ, PLC-γ)。RAS-RAF-MEK-MAPK 通路的过度激活刺激细胞增殖和分化;PI3K-AKT-mTOR 通路的过度激活能够抑制细胞凋亡;JAK-STAT 通路可以促进肿瘤侵袭转移,增强肿瘤免疫逃逸;PLC-γ 信号通路在肿瘤转移中具有重要作用[3]。

FGFR 已成为胃癌精准治疗的重要靶点[4]。既往研究,FGFR 在胆管癌及尿路上皮癌等肿瘤的治疗中发挥着重要作用,FGFR 的基因改变在胃癌中发生率占 7%~16.8%[5-6],针对这一靶点在胃癌领域的研究也越来越多,相应的靶向药物也成为胃癌患者治疗的新选择。

1　FGFR 基因异常

一项纳入 4 853 例实体肿瘤患者的多瘤种研究分析显示,7.1%的患者存在 FGFR 基因异常[5],这与中国的一项研究结果相似[7],其中大多数是基因扩增(66%),其次是突变(26%)和重排(8%)。FGFR 基因异常表达广泛分布于多个瘤种中,最常见的是尿路上皮癌,其次是乳腺癌、子宫内膜癌、肺鳞癌、卵巢癌等。而在中国人群中,FGFR 基因改变最常见于结直肠癌,其次是胃癌、乳腺癌和食管癌[6]。且不同瘤种常见的 FGFR 亚型和基因改变类型均有所不同,胃癌中常见的 FGFR 变异亚型是 FGFR2,其次是 FGFR1、FGFR3,改变的类型大多数是扩增,其次是重排、突变,这些改变有时可能同时发生[8]。

1.1　FGFR 扩增/过表达　FGFR2 扩增存在于 4%~9%的胃癌中,特别是弥漫型胃癌中[9],并与患者的淋巴管浸润和预后不良相关[10]。FGFR1 扩增发生在约 2%的胃癌中,与 FGFR2 扩增的胃癌病例类似,通常与生存率低和远处转移相关[11]。而 FGFR3 和 FGFR4 的扩增很少见。有研究发现,ctDNA 测序相较于传统的组织检测可以更好的发现 FGFR2 扩增(7.7% *vs* 2.6%~4.4%),可以对组织检测进行查漏补缺[12]。

除了扩增外,FGFR2 的过表达发生在 40%~60%的胃癌患者中,且与肿瘤浸润深度和更差的生存率相关[13]。FGFR1 和 FGFR4 过表达也与胃癌进展显著相关,包括侵袭深度、淋巴结转移、病理分期、远处转移和复发,并且两个或多个 FGFR 的共同过表达会导致预后差[14]。FGFR3 和 FGFR4 过表达的频率和临床研究较少,尽管一项研究报告了 FGFR3 在 64%的胃癌中过表达,但这与总生存期的差异无关[14]。

1.2　FGFR 突变　FGFR 的突变包括单核苷酸变异和插入/缺失突变。相对于 FGFR1 和 FGFR4,FGFR2 和 FGFR3 的突变较为常见。FGFR2 突变最常见于子宫内膜癌,发生率为 10%~12%,且往往与预后差相关[15]。FGFR3 突变与膀胱癌的发生密切相关[16],并可影响预后及对免疫治疗的反应[17]。胃癌中 FGFR 的单核苷酸变异率为 6.2%[7],主要为 FGFR1 的突变。在胃癌中,FGFR4 基因 G636C 突变可导致 FGFR4 蛋白激活产生致癌作用[18]。

1.3　FGFR 重排和融合　常与其他基因发生融合的 FGFR 亚型为 FGFR2 和 FGFR3。FGFR2 融合在肝内胆管癌中比较常见,发生率为 10%~15%,在其他肿瘤中比较罕见。FGFR2 最常见的融合伴侣是 BICC1,其他还有 CIT、CCDC6、CCAR2 等[19]。刘宝瑞教授团队在低黏附性胃癌患者中检测到 FGFR2/VTI1A 和 FGFR2/TACC2 融合/重排率为 3.1%,且与预后不良相关。在体外试验中 TACC2-FGFR2 融合胃癌细胞系对 FGFR2 抑制剂更敏感[20],表明 FGFR2 可能是低黏附性胃癌的潜在治疗靶点,填补了这一领域的治疗空缺。FGFR3 融合在胶质母细胞瘤和膀胱癌中相对常见,FGFR3 的融合伴侣基因是 TACC3。FGFR3 融合在胃癌中很罕见,不同文献报道的在胃癌中的发生率不同,一项 I 期研究中报道了 1 例 FGFR3-TACC3 融合的胃癌患者,接受 FGFR 抑制剂治疗后达到了部分缓解,缓解持续时间为 5.4 个月[21]。

2　FGFR 抑制剂在胃癌中的研究进展

2.1　酪氨酸激酶抑制剂(TKIs)　靶向 FGFR 的酪氨酸激酶抑制剂包括多靶点 FGFR 抑制剂和选择性 FGFR 抑制剂(pan-FGFR 抑制剂、FGFR1-3 抑制剂、FGFR4 抑制剂)。

2.1.1　多靶点 FGFR 抑制剂　多靶点 FGFR 抑制剂在靶向 FGFR 的同时可以靶向血管内皮生长因子受体(VEGFR)和血小板源性生长因子受体(PDGFR)等其他靶点,比如帕唑帕尼、瑞戈非尼、仑伐替尼、索拉非尼、尼达尼布等。多靶点 FGFR 抑制剂具有广泛的活性,但是选择性低、全身毒性大,常见的不良反应有高血压、乏力、胃肠道反应、手足综合征等。帕唑帕尼联合化疗目前已被用于治疗晚期胃癌患者,尤其是伴有 FGFR3 扩增的患者[22],并取得了良好的治疗效果。瑞戈非尼在细胞和小鼠试验中可以剂量依赖性地抑制 FGFR2 信号传导,抑制 FGFR2 扩增的胃癌细胞生长,FGFR2 扩增可以作为预测瑞戈非尼对胃癌治疗敏感性的指标[23]。尼达尼布在 FGFR2 扩增的胃癌细胞系中显示出一定的抗肿瘤活性[24]。

2.1.2　选择性 FGFR 抑制剂　目前已上市的厄达替尼(erdafitinib)、佩米替尼(pemigatinib)、英菲格拉替尼(infigratinib)三款 FGFR 抑制剂均属于选择性 FGFR 抑制剂,FDA 获批用于治疗不同的 FGFR 家族基因变异的晚期尿路上皮癌、胆管癌的患者。选择性 FGFR 抑制剂靶向性更好,因仅抑制 FGFR 通路,从而避免了其他靶点的毒性作用,全身毒性相对较小。FGFR3 激酶结构域高度相似,而 FGFR4 具有独特的结构,大多数选择性 FGFR 抑制剂都可以不同程度地抑制 FGFR1-3,此外还有少数仅抑制 FGFR4 的 TKIs。Infigratinib 在经治的、携带 FGFR2 基因扩增的局部晚期或转移性胃癌或胃食管交界处(GEJ)腺癌患者的客观缓解率为 25.0%(n = 20),中位缓解持续时间为 3.8 个月。基于上述试验数据,infigratinib 被中国国家药品监督管理局授予用于 FGFR2 扩增胃癌治疗的

突破性疗法认定。AZD4547 是一种高活性及选择性的 FGFR1-3 抑制剂。一项对比 AZD4547 与紫杉醇治疗一线化疗失败后 FGFR2 扩增的晚期胃癌患者的有效性研究，结果显示，两组的无进展生存期（PFS）无统计学差异，AZD4547 耐受性良好，AZD4547 的反应程度与 FGFR2 扩增倍数成正相关，提示对于 FGFR2 高度扩增的患者，AZD4547 可能效果更好[25]。该药于 2022 年 3 月获 FDA 授予的用于治疗胃癌的孤儿药认定。德拉替尼（derazantinib）是一种口服的 FGFR1-3 抑制剂，在胃癌模型中具有较强疗效，同时与紫杉醇具有一定的协同抗肿瘤作用[26]。LY2874455 是一种泛 FGFR 抑制剂，在一项Ⅰ B 期试验中共纳入 29 例胃癌患者，其中 1 例达到部分缓解，12 例评估稳定[27]。福巴替尼（futibatinib）是一种口服生物利用度高、选择性强、不可逆的 FGFR 抑制剂，对 FGFR1-4 均有抑制作用，在包含胃癌在内的 FGFR 变异的细胞系和异种移植模型中具有广谱的抗肿瘤活性，并较其他 FGFR 抑制剂发生耐药风险降低[28]。在 2 项Ⅰ期临床研究中，接受福巴替尼治疗的胃癌患者客观缓解率分别为 22% 和 36.4%，显示出一定的抗肿瘤活性[21, 29]，常见的不良反应主要是高磷血症、腹泻、恶心等。

2.2　*单克隆抗体*　FGFR 单抗主要通过阻断配体/受体结合，和/或受体的二聚化或者与高细胞毒性药物偶联[30-31]等途径发挥抗肿瘤作用。贝玛妥珠单抗（bemarituzumab）是全球首个靶向 FGFR2b 的人源化单克隆抗体，可以阻断 FGFs 与 FGFR2b 的结合和激活，抑制下游通路，阻断肿瘤的进展。此外，也可诱导增强的抗体依赖性细胞介导的细胞毒性，并有可能通过 NK 细胞的募集达到潜在的肿瘤细胞杀伤作用。Bmarituzumab 联合 mFOLFOX6 对 FGFR2b 选择的、HER2 非阳性的晚期胃癌或 GEJ 腺癌患者，PFS 无统计学意义的显著改善（9.5 个月 *vs* 7.4 个月，$P=0.073$），但显示出有希望的临床疗效，亚组分析显示 FGFR2b 表达水平越高，生存期越长[32]。然而联合用药组观察到 83% 的 3 级以上不良事件，包括中性粒细胞减少、角膜病变、口腔炎等。同时 Bemarituzumab 联合 mFOLFOX6 和纳武利尤单抗一线治疗 HER2 阴性胃/GEJ 癌的Ⅰb/Ⅲ期研究目前也在进行中，2023 年的欧洲肿瘤内科学会年会上公布了部分Ⅰb 期安全性数据，经过 13 个月的随访，无剂量限制性毒性和新的安全性事件发生。

2.3　*FGF 配体陷阱*　FGF 配体陷阱可以结合并隔离 FGF 配体，阻止它们与 FGFR 结合。不同于单克隆抗体只针对单个配体，配体陷阱-FC 融合蛋白可以结合多个配体。大分子 FGF 陷阱包括 FP-1039/ GSK3052230、Ms FGFR2c 和 sFGFR3，分别来源于 FGFR1、FGFR2 和 FGFR3 的胞外，小分子 FGF 陷阱包括 sm27 和 NSC12[33]。FP-1039 在非选择性晚期癌症患者中耐受性良好，观察到一些高磷酸盐血症和视网膜改变，没有观察到指甲和皮肤毒性[34]，且在胸膜间皮瘤、非小细胞肺癌患者中显示出临床疗效[35-36]。NSC12 在多发性骨髓瘤及肺癌模型中具有一定的抗肿瘤活性[37-38]。

目前 FGFR 抑制剂的适应症主要是胆管癌和尿路上皮癌，但仍有很多 FGFR 抑制剂治疗胃癌的临床前研究及临床试验在进行中[39]，期待能取得令人振奋的结果。

3　挑战与困境

FGFR 抑制剂的疗效受到耐药性的限制，为了克服耐药，陈永恒团队提出开发新的 FGFR 共价抑制剂、采用联合疗法、破坏溶酶体结构以释放隔离的 TKI、利用 FGFR 配体或 FGFR 特异性单抗绕过 TKI 耐药等相应策略[40]。陈凌峰团队研发了一种新型口服有效的 FGFR2 选择性降解剂（LC-MB12），可以避免与突变相关的耐药性[41]。联合用药可以同时阻断多种激活途径，抑制旁路信号的激活，克服获得性耐药，MEK 抑制剂可以克服 FGFR 抑制剂在 FGFR 驱动的胃癌的耐药性[42]，当 FGFR 受到抑制时，胃癌中一个已明确的 MAPK-ERK 信号通路会被激活[19]，MEK 抑制剂联合治疗可能增强 FGFR 抑制作用，改善治疗获益。FGFR1 抑制剂的耐药机制主要是通过 TAK1/AMPK 信号激活调节细胞自噬，TAK1 抑制剂可以协同抑制 FGFR 抑制剂引起的耐药[43]。FGF/FGFR 信号通路参与调节肿瘤微环境，包括免疫细胞、血管发生和上皮-间质转化，FGFR 抑制剂可以通过影响癌症免疫调节的各个阶段来提高对免疫检查点抑制剂的反应[44]。FGFR1 在胃癌模型中的表达提高了免疫治疗效果[45]。

4　结论与展望

胃癌目前临床获批适应症的靶向药物主要集中在 HER2、VEGFR、PD-1 靶点，但这仍不能完全满足患者的治疗需求。越来越多的新靶点被逐渐探索出来，越来越多的靶向药物也逐渐进入临床试验。目前针对 FGFR 抑制剂在胃癌中的探索很多还处于临床前或小样本临床研究，且药物获得性耐药和毒副作用限制了 FGFR 抑制剂的疗效，拓宽适应症、挖掘与其他治疗方案联合用药应用潜力及序贯治疗等需要医药领域一起努力。

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参考文献

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021, 71(3): 209-249.

[2] Zeng HM, Ran XH, An L, et al. Disparities in stage at diagnosis for five common cancers in China: a multicentre, hospital-based, observational study[J]. Lancet Public Health, 2021, 6(12): e877-e887.

[3] Du SC, Zhang Y, Xu JM. Current progress in cancer treatment by targeting FGFR signaling[J]. Cancer Biol Med, 2023, 20(7): 490-499.

[4] Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group[J]. Ann Oncol, 2020, 31(11): 1491-1505.

[5] Helsten T, Elkin S, Arthur E, et al. The FGFR landscape in canc-

er: analysis of 4, 853 tumors by next-generation sequencing[J]. Clin Cancer Res, 2016, 22(1): 259-267.

[6] Sun Y, Li G, Zhu W, et al. A comprehensive pan-cancer study of fibroblast growth factor receptor aberrations in Chinese cancer patients[J]. Ann Transl Med, 2020, 8(20): 1290.

[7] Zuo W, He Y, Li W, et al. Landscape of *FGF/FGFR* alterations in 12, 372 Chinese cancer patients[J]. J Cancer, 2020, 11(22): 6695-6699.

[8] Helsten T, Schwaederle M, Kurzrock R. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: biologic and clinical implications[J]. Cancer Metastasis Rev, 2015, 34(3): 479-496.

[9] Matsumoto K, Arao T, Hamaguchi T, et al. *FGFR*2 gene amplification and clinicopathological features in gastric cancer[J]. Br J Cancer, 2012, 106(4): 727-732.

[10] Su X, Zhan P, Gavine PR, et al. FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study[J]. Br J Cancer, 2014, 110(4): 967-975.

[11] Schäfer MH, Lingohr P, Sträßer A, et al. Fibroblast growth factor receptor 1 gene amplification in gastric adenocarcinoma[J]. Hum Pathol, 2015, 46(10): 1488-1495.

[12] Jogo T, Nakamura Y, Shitara K, et al. Circulating tumor DNA analysis detects *FGFR*2 amplification and concurrent genomic alterations associated with FGFR inhibitor efficacy in advanced gastric cancer [J]. Clin Cancer Res, 2021, 27(20): 5619-5627.

[13] Tokunaga R, Imamura Y, Nakamura K, et al. Fibroblast growth factor receptor 2 expression, but not its genetic amplification, is associated with tumor growth and worse survival in esophagogastric junction adenocarcinoma [J]. Oncotarget, 2016, 7(15): 19748-19761.

[14] Murase H, Inokuchi M, Takagi Y, et al. Prognostic significance of the co-overexpression of fibroblast growth factor receptors 1, 2 and 4 in gastric cancer[J]. Mol Clin Oncol, 2014, 2(4): 509-517.

[15] Jeske YW, Ali S, Byron SA, et al. FGFR2 mutations are associated with poor outcomes in endometrioid endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study[J]. Gynecol Oncol, 2017, 145(2): 366-373.

[16] Ascione CM, Napolitano F, Esposito D, et al. Role of FGFR3 in bladder cancer: treatment landscape and future challenges[J]. Cancer Treat Rev, 2023, 115: 102530.

[17] Xu PH, Chen SY, Wang YH, et al. FGFR3 mutation characterization identifies prognostic and immune-related gene signatures in bladder cancer[J]. Comput Biol Med, 2023, 162: 106976.

[18] Futami T, Kawase T, Mori K, et al. Identification of a novel oncogenic mutation of FGFR4 in gastric cancer[J]. Sci Rep, 2019, 9(1): 14627.

[19] Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer[J]. Nat Rev Cancer, 2017, 17(5): 318-332.

[20] Wang Y, Shi T, Wang X, et al. FGFR2 alteration as a potential therapeutic target in poorly cohesive gastric carcinoma[J]. J Transl Med, 2021, 19(1): 401.

[21] Meric-Bernstam F, Bahleda R, Hierro C, et al. Futibatinib, an irreversible FGFR1-4 inhibitor, in patients with advanced solid tumors harboring *FGF/FGFR* aberrations: a phase I dose-expansion study [J]. Cancer Discov, 2022, 12(2): 402-415.

[22] Limaye S, Patil D, Akolkar D, et al. Response to pazopanib-based combination regimen in a case of FGFR3 amplified gastric adenocarcinoma[J]. Clin Case Rep, 2021, 9(11): e04986.

[23] Cha YJ, Kim HP, Lim Y, et al. FGFR2 amplification is predictive of sensitivity to regorafenib in gastric and colorectal cancers *in vitro* [J]. Mol Oncol, 2018, 12(7): 993-1003.

[24] Hilberg F, Tontsch-Grunt U, Baum A, et al. Triple angiokinase inhibitor nintedanib directly inhibits tumor cell growth and induces tumor shrinkage via blocking oncogenic receptor tyrosine kinases [J]. J Pharmacol Exp Ther, 2018, 364(3): 494-503.

[25] Van Cutsem E, Bang YJ, Mansoor W, et al. A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with FGFR2 polysomy or gene amplification[J]. Ann Oncol, 2017, 28(6): 1316-1324.

[26] McSheehy PMJ, Forster-Gross N, El Shemerly M, et al. The fibroblast growth factor receptor inhibitor, derazantinib, has strong efficacy in human gastric tumor models and synergizes with paclitaxel *in vivo*[J]. Anticancer Drugs, 2023, 34(4): 532-543.

[27] Michael M, Bang YJ, Park YS, et al. A Phase 1 Study of LY2874455, an Oral Selective pan-FGFR Inhibitor, in Patients with Advanced Cancer[J]. Target Oncol, 2017, 12(4): 463-474.

[28] Sootome H, Fujita H, Ito K, et al. Futibatinib is a novel irreversible FGFR 1-4 inhibitor that shows selective antitumor activity against FGFR-deregulated tumors [J]. Cancer Res, 2020, 80(22): 4986-4997.

[29] Doi T, Shitara K, Kojima T, et al. Phase I study of the irreversible fibroblast growth factor receptor 1-4 inhibitor futibatinib in Japanese patients with advanced solid tumors[J]. Cancer Sci, 2023, 114(2): 574-585.

[30] Kim SB, Meric-Bernstam F, Kalyan A, et al. First-in-human phase Ⅰ study of aprutumab ixadotin, a fibroblast growth factor receptor 2 antibody-drug conjugate (BAY 1187982) in patients with advanced cancer[J]. Target Oncol, 2019, 14(5): 591-601.

[31] Catenacci DV, Tesfaye A, Tejani M, et al. Bemarituzumab with modified FOLFOX6 for advanced FGFR2-positive gastroesophageal cancer: fight Phase Ⅲ study design[J]. Future Oncol, 2019, 15(18): 2073-2082.

[32] Wainberg ZA, Enzinger PC, Kang YK, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study [J]. Lancet Oncol, 2022, 23(11): 1430-1440.

[33] Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder[J]. Pharmacol Res, 2020, 151: 104567.

[34] Tolcher AW, Papadopoulos KP, Patnaik A, et al. A phase I, first in human study of FP-1039 (GSK3052230), a novel FGF ligand

trap, in patients with advanced solid tumors[J]. Ann Oncol, 2016, 27(3): 526-532.

[35] van Brummelen EMJ, Levchenko E, Dómine M, et al. A phase Ⅰb study of GSK3052230, an FGF ligand trap in combination with pemetrexed and cisplatin in patients with malignant pleural mesothelioma [J]. Invest New Drugs, 2020, 38(2): 457-467.

[36] Morgensztern D, Karaseva N, Felip E, et al. An open-label phase IB study to evaluate GSK3052230 in combination with paclitaxel and carboplatin, or docetaxel, in FGFR1-amplified non-small cell lung cancer[J]. Lung Cancer, 2019, 136: 74-79.

[37] Castelli R, Giacomini A, Anselmi M, et al. Synthesis, structural elucidation, and biological evaluation of NSC12, an orally available fibroblast growth factor (FGF) ligand trap for the treatment of FGF-dependent lung tumors [J]. J Med Chem, 2016, 59(10): 4651-4663.

[38] Castelli R, Taranto S, Furiassi L, et al. Chemical modification of NSC12 leads to a specific FGF-trap with antitumor activity in multiple myeloma[J]. Eur J Med Chem, 2021, 221: 113529.

[39] Lengyel CG, Hussain S, Seeber A, et al. FGFR pathway inhibition in gastric cancer: the golden era of an old target? [J]. Life, 2022, 12(1): 81.

[40] Yue ST, Li YK, Chen XJ, et al. FGFR-TKI resistance in cancer: current status and perspectives[J]. J Hematol Oncol, 2021, 14(1): 23.

[41] Ma L, Li YY, Luo RX, et al. Discovery of a selective and orally bioavailable FGFR2 degrader for treating gastric cancer[J]. J Med Chem, 2023, 66(11): 7438-7453.

[42] Lau DK, Luk IY, Jenkins LJ, et al. Rapid resistance of FGFR-driven gastric cancers to regorafenib and targeted FGFR inhibitors can be overcome by parallel inhibition of MEK[J]. Mol Cancer Ther, 2021, 20(4): 704-715.

[43] Peng R, Chen Y, Wei LN, et al. Resistance to FGFR1-targeted therapy leads to autophagy via TAK1/AMPK activation in gastric cancer[J]. Gastric Cancer, 2020, 23(6): 988-1002.

[44] Ruan RW, Li L, Li X, et al. Unleashing the potential of combining FGFR inhibitor and immune checkpoint blockade for FGF/FGFR signaling in tumor microenvironment[J]. Mol Cancer, 2023, 22(1): 60.

[45] Yang CC, Song DL, Zhao FY, et al. Comprehensive analysis of the prognostic value and immune infiltration of *FGFR* family members in gastric cancer[J]. Front Oncol, 2022, 12: 936952.

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[29] Hayashi K, Jutabha P, Endou H, et al. LAT1 is a critical trans porter of essential amino acids for immune reactions in activated human T cells[J]. J Immunol, 2013, 191(8): 4080-4085.

[30] Sinclair LV, Rolf J, Emslie E, et al. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation[J]. Nat Immunol, 2013, 14(5): 500-508.

[31] Wu G, Jr Morris SM. Arginine metabolism: nitric oxide and beyond [J]. Biochem J, 1998, 336 (Pt 1): 1-17.

[32] Ban H, Shigemitsu K, Yamatsuji T, et al. Arginine and Leucine regulate p70 S6 kinase and 4E-BP1 in intestinal epithelial cells[J]. Int J Mol Med, 2004, 13(4): 537-543.

[33] Rebsamen M, Pochini L, Stasyk T, et al. SLC38A9 is a component of the lysosomal amino acid sensing machinery that controls mTORC1 [J]. Nature, 2015, 519(7544): 477-481.

[34] Wang S, Tsun ZY, Wolfson RL, et al. Metabolism. Lysosomal amino acid transporter SLC38A9 signals arginine sufficiency to mTORC1[J]. Science, 2015, 347(6218): 188-194.

[35] Carroll B, Maetzel D, Maddocks OD, et al. Control of TSC2-Rheb signaling axis by arginine regulates mTORC1 activity[J]. eLife, 2016, 5: e11058.

[36] Chantranupong L, Scaria SM, Saxton RA, et al. The *CASTOR* proteins are arginine sensors for the mTORC1 pathway[J]. Cell, 2016, 165(1): 153-164.

[37] Chen CL, Hsu SC, Ann DK, et al. Arginine signaling and cancer metabolism[J]. Cancers, 2021, 13(14): 3541.

[38] Bogdan C. Regulation of lymphocytes by nitric oxide[J]. Methods Mol Biol, 2011, 677: 375-393.

[39] Nanthakumaran S, Brown I, Heys SD, et al. Inhibition of gastric cancer cell growth by arginine: molecular mechanisms of action[J]. Clin Nutr, 2009, 28(1): 65-70.

[40] Pavlova NN, Hui S, Ghergurovich JM, et al. As extracellular glutamine levels decline, asparagine becomes an essential amino acid [J]. Cell Metab, 2018, 27(2): 428-438.e5.

[41] Bishnupuri KS, Alvarado DM, Khouri AN, et al. IDO1 and kynurenine pathway metabolites activate PI3K-akt signaling in the neoplastic colon epithelium to promote cancer cell proliferation and inhibit apoptosis[J]. Cancer Res, 2019, 79(6): 1138-1150.

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