

肺鳞癌治疗新靶点FGFR的研究进展

《现代肿瘤医学》[ISSN:1672-4992/CN:61-1415/R] 期数: 2019年22期 页码: 4120-4124 栏目: 综述 出版日期: 2019-10-08

Title: Research progress in the treatment of new target FGFR for lung squamous cell carcinoma

作者: 罗洋冲¹; 刘晶晶²; 毛贵兵¹; 陶娥红¹; 王胜飞¹; 支蓉¹; 赵磊¹; 王周清¹

1.曲靖市第二人民医院心胸外科; 2.药剂科, 云南 曲靖 655000

Author(s): Luo Xiangchong¹; Liu Jingjing²; Mao Guibing¹; Tao Ehong¹; Wang Shengfei¹; Zhi Rong¹; Zhao Lei¹; Wang Zhouqing¹

1.Department of Cardiothoracic Surgery;2.Department of Pharmacy,Qujing Second People's Hospital,Yunnan Qujing 655000,China.

关键词: 肺鳞癌; 成纤维细胞生长因子; 成纤维细胞生长因子受体; 治疗靶点

Keywords: squamous cell lung cancer; FGF; FGFR; targeting

分类号: R734.2

DOI: 10.3969/j.issn.1672-4992.2019.22.042

文献标识码: A

摘要: 肺癌是目前全球发病率和死亡率均居前列的恶性肿瘤,其中肺鳞癌经手术、放化疗等综合治疗后,其疗效仍不满意。随着分子靶向治疗在肺腺癌中取得了令人瞩目的成果,而肺鳞癌患者中EGFR基因突变及ALK融合基因少见,急需探索新的靶点指导肺鳞癌患者的临床治疗。研究表明,FGFR家族(FGFR1-4)是肺鳞癌中突变频率较高的基因,FGFR基因的激活突变和扩增与肺鳞癌的发生和发展密切相关,同时许多小分子FGFR抑制剂在临床应用中已经取得较好的治疗效果。目前,许多FGFR抑制剂治疗肺鳞癌的临床试验也正在进行研究,针对FGFR靶点的基因治疗可为肺鳞癌的治疗提供一种新的策略。本文就FGFR在肺鳞癌的靶向治疗中的最新研究进展进行综述。

Abstract: Lung cancer is a malignant tumor with the highest morbidity and mortality in the world, and the curative effect of lung squamous cell carcinoma remains unsatisfactory after comprehensive treatment including surgery, radiotherapy and chemotherapy. As molecular targeted therapy in lung adenocarcinoma making remarkable achievements, and lung squamous carcinoma in patients with rare EGFR mutations and ALK fusion gene, so we need to explore new targets to guide the clinical treatment of patients with pulmonary squamous carcinoma. Studies have shown that FGFR (FGFR1-4) of the family is the gene mutation frequency in lung squamous carcinoma is higher, the activation of FGFR gene mutation and amplification is closely related to the occurrence and development of lung squamous carcinoma, and many small molecules FGFR inhibitor has good treatment effect in clinical applications. At present, many clinical trials of FGFR inhibition in the treatment of lung squamous cell carcinoma are also under study, and gene therapy for FGFR target may provide a new strategy for the treatment of lung squamous cell carcinoma. This article reviews the recent progress of FGFR in targeted therapy for lung squamous cell carcinoma.

参考文献/REFERENCES

- [1] Chen WJ, Tang RX, He RQ, et al. Clinical roles of the aberrantly expressed lncRNAs in lung squamous cell carcinoma: A study based on RNA-sequencing and microarray data mining [J]. *Oncotarget*, 2017, 8(37):61282-61304.
- [2] Trueb B. Biology of FGFR1, the fifth fibroblast growth factor receptor [J]. *Cell Mol Life Sci*, 2011, 68(6):951-964.
- [3] Trueb B, Amann R, Gerber SD. Role of FGFR1 and other FGF signaling proteins in early kidney development [J]. *Cell Mol Life Sci*, 2013, 70(14):2505-2518.
- [4] Lemmon MA, Schlessinger J. Cell Signaling by receptor tyrosine kinases [J]. *Cell*, 2010, 141(7):1117-1134.
- [5] Beenken A, Mohammadi M. The FGF family: Biology, pathophysiology and therapy [J]. *Nat Rev Drug Discov*, 2009, 8(3):235-253.
- [6] Wesche J, Haglund K, Haugsten EM. Fibroblast growth factors and their receptors in cancer [J]. *Biochem J*, 2011, 437(2):199-213.
- [7] Knights V, Cook SJ. De-regulated FGF receptors as therapeutic targets in cancer [J]. *Pharmacol*

Ther,2010,125(1):105-117.

- [8] Mohammadi M,Olsen SK,Ibrahimi OA.Structural basis for fibroblast growth factor receptor activation [J] .Cytokine Growth factor Rev,2005,16(16):107-137.
- [9] Tiseo M,Gelsomino F,Alfieri R,et al.FGFR as potential target in the treatment of squamous non small cell lung cancer [J] .Cancer Treat Rev,2015,41(6):527-539.
- [10] Kohler LH,Mireskandari M,Knosel T,et al.FGFR1 expression and gene copy numbers in human lung cancer [J] .Virchows Arch,2012,461(1):49-57.
- [11] Dutt A,Ramos AH,Hammerman PS,et al.Inhibitor-sensitive FGFR1 amplification in human non-small cell lung cancer [J] .PloS One,2011,6(6):e20351.
- [12] Weiss J,Sos ML,Seidel D,et al.Frequent and focal FGFR1 amplification with therapeutically tractable FGFR1 dependency in squamous cell lung cancer [J] .Sci Transl Med,2010,2(62):62-93.
- [13] Zhang J,Zhang L,Su X,et al.Translating the therapeutic potential of AZD4547 in FGFR1-amplified non-small cell lung cancer through the use of patient derived tumor xenograft PDX models [J] .Clin Cancer Res,2012,18(24):6658-6667.
- [14] Heist RS,Mino-Kenudson M,Sequist LV,et al.FGFR1 amplification in squamous cell carcinoma of the lung [J] .J Thoracic Oncol,2012,7(12):1775-1780.
- [15] Seo AN,Jin Y,Lee HJ,et al.FGFR1 amplification is associated with poor prognosis and smoking in non small cell lung cancer [J] .Virchows Arch,2014,465(5):547-558.
- [16] Kim HR,Kim DJ,Kang DR,et al.Fibroblast growth factor receptor 1 gene amplification is associated with poor survival and cigarette smoking dosage in patients with resected squamous cell lung cancer [J] .J Clin Oncol,2013,31(6):731-737.
- [17] Miao JL,Liu RJ,Zhou JH,et al.Fibroblast growth factor receptor 1 gene amplification in non small cell lung cancer [J] .Chin Med J (English),2016,129(23):2868-2872.
- [18] Adachi Y,Watanabe K,Kita K,et al.Resistance mediated by alternative receptor tyrosine kinases in FGFR1-amplified lung cancer [J] .Carcinogenesis,2017,38(11):1063-1072.
- [19] Weeden CE,Holik AZ,Yong RJ,et al.Cisplatin increases sensitivity to FGFR inhibition in patient-derived xenograft models of lung squamous cell carcinoma [J] .Molecular Cancer Therapeutics,2017,16(8):1610-1622.
- [20] Cihoric N,Savic S,Schneider S,et al.Prognostic role of FGFR1 amplification in early-stage non-small cell lung cancer [J] .Br J Cancer,2014,110(12):2914-2922.
- [21] Nagatsuma AK,Aizawa M,Kuwata T,et al.Expression profiles of HER2,EGFR,MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma [J] .Gastric Cancer,2015,18(2):227-238.
- [22] Lee SY,Na YJ,Jeong YA,et al.Upregulation of EphB3 in gastric cancer with acquired resistance to a FGFR inhibitor [J] .Int J Biochem Cell Biol,2018(102):128-137.
- [23] Dutt A,Salvesen HB,Chen TH,et al.Drug-sensitive FGFR2 mutations in endometrial carcinoma [J] .Proc Natl Acad Sci USA,2008,105(25):8713-8717.
- [24] Pollock PM,Gartside MG,Dejeza LC,et al.Frequent activating FGFR2 mutations in endometrial carcinoma parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes [J] .Oncogene,2007,26(50):7158-7162.
- [25] Liao RG,Jung J,Tchaicha J,et al.Inhibitor-sensitive FGFR2 and FGFR3 mutations in lung squamous cell carcinoma [J] .Cancer Res,2013,73(16):5195-5205.
- [26] Flockenzi FA,Roggia C,Langer F,et al.FGFR1 gene amplification in squamous cell carcinomas of the lung:A potential favorable prognostic marker for women and for patients with advanced cancer [J] .Virchows Arch,2018,472(5):759-769.
- [27] Matakidou A,Ei Galta R,Rudd MF,et al.Further observations on the relationship between the FGFR4 Gly388Arg polymorphism and lung cancer prognosis [J] .Br J Cancer,2007,96(12):1904-1907.
- [28] Villalonga A,Marquez L,Marrugal A,et al.The FGFR4-388arg variant promotes lung cancer progression by N-cadherin induction [J] .Sci Rep,2018,8(1):2394.
- [29] Capelletti M,Dodge ME,Ercan D,et al.Identification of recurrent FGFR-3-TACC3 fusion oncogenes from adenocarcinoma [J] .Clin Cancer Res,2014,20(24):6551-6558.
- [30] Wang R,Wang L,Li Y,et al.FGFR1/3 tyrosine kinase fusion define a unique molecular subtype of non-small cell lung cancer [J] .Clin Cancer Res,2014,20(15):4107-4114.
- [31] Majewski IJ,Mitttempergher L,Davidson NM,et al.Identification of recurrent FGFR3 fusion genes in lung cancer through kinomecentred RNA sequencing [J] .J Pathol,2013,230(3):270-276.
- [32] Wu YM,Su F,Kalyana-Sundaram S,et al.Identification of targetable FGFR gene fusions in diverse cancers [J] .Cancer Discov,2013,3(6):636-647.
- [33] Best SA,Harapas CR,Kersbergen A,et al.FGFR3-TACC3 is an oncogenic fusion protein in respiratory epithelium [J] .Oncogene,2018.doi:10.1038/s41388-018-0399-5.
- [34] Gavine PR,Mooney L,Kilgour E,et al.AZD4547:An orally bioavailable,potent,and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family [J] .Cancer Res,2012,72(8):2045-2056.
- [35] Ji W,Yu Y,Li Z,et al.FGFR1 promotes the stem cell-like phenotype of FGFR1-amplified non-small cell lung cancer cells through the Hedgehog pathway [J] .Oncotarget,2016,7(12):15118-15134.
- [36] Paik PK,Shen R,Ferry D,et al.A phase 1b open-label multicenter study of AZD4547 in patients with advanced squamous cell lung cancer:Preliminary antitumor activity and pharmacodynamics data [J] .J Clin Oncol,2014,32(15):8035.
- [37] Guagnano V,Kauffmann A,Wohrle S,et al.FGFR genetic alterations predict for sensitivity to NVP-BGJ398,a selective panFGFR inhibitor [J] .Cancer Discov,2012,2(12):1118-1133.

- [38] Nogova,Sequist LV,Perez Garcia JM,et al.Evaluation of BGJ398,a fibroblast growth factor receptor 1-3 kinase inhibitor,in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors:Results of a global phase 1,dose-escalation and dose-expansion study [J] .J Clin Oncol,2017,35(2):157-165.
- [39] Michael M,Bang YJ,Park YS,et al.A phase 1 study of LY2874455,anoral selective pan-FGFR inhibitor,in patients with advanced cancer [J] .Target Oncol,2017,12(4):463-474.
- [40] Tabernero J,Bahleda R,Dienstmann R,et al.Phase I dose-escalation study of JNJ-42756493,an oral pan fibroblast growth factor receptor inhibitor,in patients with advanced solid tumors [J] .J Clin Oncol,2015,33(30):3401-3408.
- [41] Harding TC,Long L,Palencia S,et al.Blockade of nonhormonal fibroblast growth factors by FP-1039 inhibits growth of multiple types of cancer [J] .Sci Transl Med,2013,5(178):178ra39.
- [42] Tolcher A,Papadopoulos K,Pantniak A,et al.381 preliminary results of a dose escalation study of the fibroblast growth factor(FGF)"trap"FP-1039(FGF-R1:Fc) in patients with advanced malignancies [J] .Eur J Cancer,2010,8(7):121.
- [43] Reck M,Kaiser R,Mellemgaard A,et al.Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-lung 1):A phase 3,double-blind,randomised controlled trial [J] .Lancet Oncol,2014,15(2):143-155.
- [44] Motzer RJ.Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma:an open-label,randomised phase 3 trial [J] .Lancet Oncol,2014,15(3):286-296.

备注/Memo: -

更新日期/Last Update: 1900-01-01