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Research on Targeted FAP Boron Drugs for the Treatment of Pancreatic Cancer

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Abstract: Pancreatic cancer has a low five-year survival rate and poses a significant threat, with high resistance to traditional chemotherapy drugs and clinical treatment difficulties. This article mainly analyzes the impact of miR-30a-5p and 10B-FAPI on inhibiting pancreatic cancer.

Keywords: miR-30a-5p; 10B-FAPI; pancreatic ductal adenocarcinoma; targeted therapy; boron neutron capture imaging.

Pancreatic cancer is often diagnosed at an advanced stage, lacking effective treatment methods. In recent years, molecular biology has made continuous progress, and targeted diagnosis and treatment of tumors have shown high precision and specificity, with outstanding efficacy. Pancreatic cancer patients have a high stromal content, accounting for up to 90% of tumor volume[1]. The tumor microenvironment (TME) is in a highly immunosuppressive state, with dense stroma, which affects blood flow and impedes drug delivery. Fibroblast activation protein (FAP) is one of the marker proteins in tumor-associated fibroblasts (CAFs) and can regulate various proteins and cytokines. MiR-30a-5p is a tumor-suppressive gene that can inhibit the production of FAP.

1. Targeting Fibroblast Activation Protein

1.1 FAP Accelerates Cancer Progression

FAP belongs to the type II transmembrane serine protease family and can accelerate the progression of tumors. In many human epithelial tumors, FAP is often overexpressed in cancer-associated fibroblasts (CAFs). FAP is crucial for tissue remodeling and embryonic development [2]. In normal adult tissues, FAP is either not expressed or expressed insignificantly; however, FAP is highly expressed in wound healing, atherosclerotic plaques, and over 90% of epithelial cancers.

CAFs are essential components of the tumor stroma in cancers such as breast and pancreatic cancer. Existing studies have shown that CAFs can stimulate the production of growth factors, increase the content of inflammatory cytokines, and promote the appearance of chemotactic factors, directly affecting tumor progression [3]. After FAP expression appears in CAFs, they can escape the immune response through various channels, such as recruiting tumor-infiltrating inflammatory cells and excluding CD8+ T cells. CAFs act on the extracellular matrix (ECM), promoting its remodeling and the formation of various structural matrix components, including proteoglycans, collagen, etc., nurturing the tumor microenvironment (TME), promoting tumor proliferation, angiogenesis, and

resistance to treatment [4].

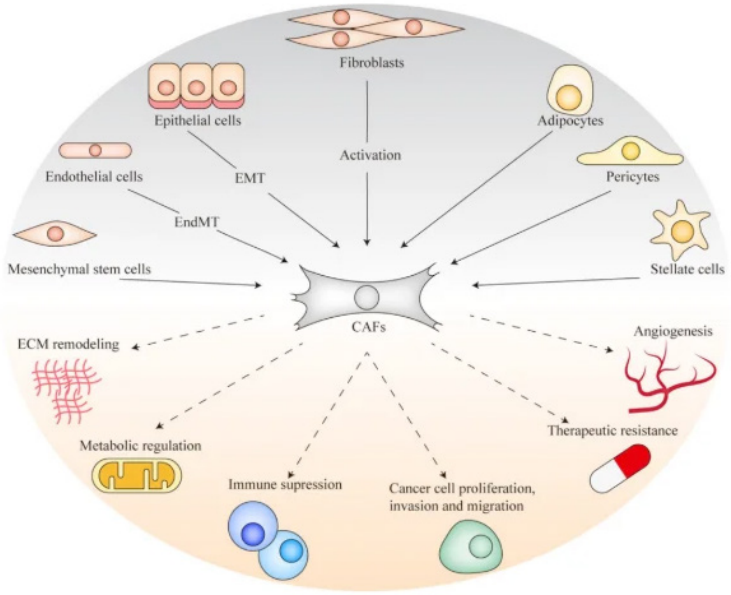

Fig 1. CAFs and FAP

Tumors with a high proportion of tumor stroma are considered viable targets in clinical diagnosis and treatment. Following tumor development, fibroblasts within the tumor harbor FAP, and individuals with its overexpression often exhibit poorer prognoses [5]. Targeted chemotherapy or radiotherapy against FAP typically involves the use of 68Ga-FAPI or 18F-FAPI for PET-CT imaging [6]. In recent years, 10B-FAPI has been employed in boron neutron capture therapy (BNCT), which utilizes the gamma rays obtained from boron neutron capture reactions for instantaneous imaging [7]. This approach, known as boron neutron emission tomography (BNET), achieves integration of diagnosis and treatment, presenting a novel therapeutic strategy for malignant tumors.

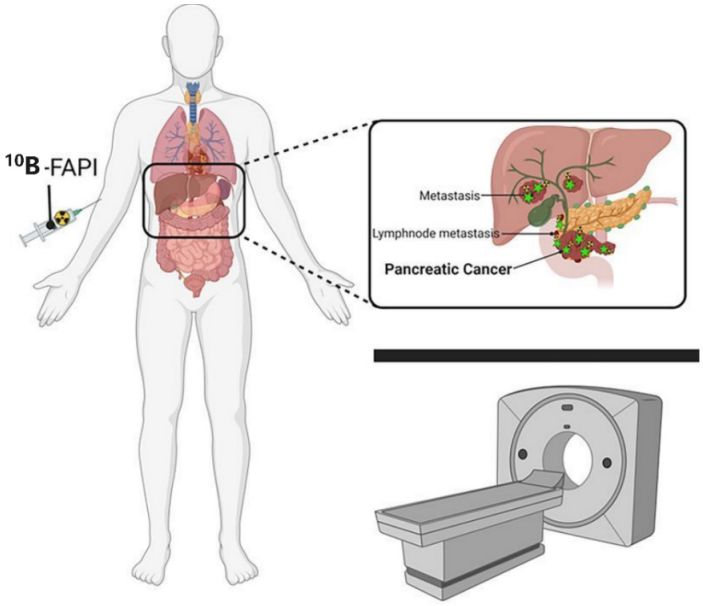

Fig 2. ^{10}B-FAPI used on pancreatic cancer

1.2 FAP Influences TME and Chemotherapy

Overexpression of FAP leads to the formation of numerous stromal fibroblasts, which, in turn, contribute to tumor growth by inducing high fibrinolysis in

stromal cells. Pancreatic cancer tumors exhibit lower perfusion compared to other tumors, making clinical treatment more challenging. The presence of stromal components, including fibrotic stroma and fibroblasts, in pancreatic cancer leads to increased interstitial fluid pressure, inhibiting drug delivery via the bloodstream and resulting in diminished chemotherapy efficacy. Therefore, pharmacological inhibition of FAP enzyme activity or FAP gene knockout can reduce the tumor burden through various pathways.

1.3 FAP-Based Boron Drugs

Several targeting therapies based on FAP include:1) FAP inhibitors (FAPI), which reduce the activity of proteolytic enzymes.2) FAP-specific prodrugs, which target FAP and release toxicity upon contact, effectively targeting tumor cells as well as CAFs and FAP. 3) Chimeric antigen receptor T cells targeting FAP, which can recognize and kill both CAFs and FAP with high specificity. 4) FAP vaccines, which intervene in the TME, alleviate immunosuppression, and activate T cells.

5)FAP bispecific antibodies.

In the various methods mentioned above, the combination of highly electronegative boron atoms with various drugs that inhibit FAP activity forms 10B-FAPI drugs. This achieves selective inhibition of FAP and allows for real-time PET-CT imaging assessment of in vitro and in vivo anti-tumor activity. Specifically:1) 10B-FAPI drugs inhibit the activity of tumor cell cycle proteins, disrupting the tumor cell cycle progression and causing cell cycle arrest at specific stages, preventing normal cell division and proliferation.2) 10B-FAPI induces tumor cell apoptosis through multiple pathways, including activating apoptosis signaling pathways and regulating the expression of apoptosis-related proteins.3) 10B-FAPI inhibits tumor angiogenesis, weakening tumor nutrient supply and oxygen delivery, further suppressing tumor proliferation.4) 10B-FAPI promotes the activation and infiltration of immune cells, increases the production of anti-tumor cytokines, and enhances the body's immune response to tumors.5) 10B-FAPI interferes with cell cytoskeleton, particularly microfilament and microtubule protein aggregation and depolymerization, inhibiting the formation and contraction of cell pseudopods and reducing cell mobility.6) Matrix metalloproteinases (MMPs) are a class of proteases that degrade the basement membrane of tumor cells and invade surrounding tissues by degrading ECM. 10B-FAPI directly inhibits the expression or activity of MMPs or increases the expression of their inhibitors such as TIMPs (tissue inhibitors of metalloproteinases) to reduce ECM degradation, thereby inhibiting migration and invasion.7) Many signaling pathways such as PI3K/Akt, MAPK/ERK, and Wnt/β-catenin are closely related to tumor cell migration and invasion. 10B-FAPI intervenes in these signaling pathways by targeting key molecules such as receptor tyrosine kinases and small GTPases (such as Ras and Rho families), affecting downstream signal transduction, thereby inhibiting migration and invasion.8) 10B-FAPI changes the expression or function of cell surface adhesion molecules such as integrins and cadherins, affecting cell-cell interactions and cell-ECM connections, thereby inhibiting migration and invasion.9) 10B-FAPI regulates various aspects of the TME, including ECM remodeling and immune cell function regulation. Studies have shown that 10B-FAPI can degrade ECM components, thereby altering its structure and function. 10B-FAPI can also regulate immune cell functions, such as inhibiting NK cell activity and promoting Treg cell differentiation. It can affect the activity of multiple signaling pathways such as the Wnt/β-catenin pathway, PI3K/AKT pathway, etc. Other cell types in the TME (such as fibroblasts, immune cells, etc.) and their secreted growth factors, cytokines, and chemokines are also involved in regulating tumor cell migration and invasion. 10B-FAPI indirectly inhibits tumor cell migration and invasion by affecting these factors and altering the TME.10) 10B-FAPI is very convenient for studying pharmacokinetic properties, which helps understand the behavior and duration of drug efficacy of various 10B-FAPI drugs in organisms.11) Research on the effects of 10B-FAPI drugs on the animal immune system, including changes in the activity and quantity of immune cells (such as T cells, NK cells, etc.) and the regulation of immune-related factors (such as cytokines, antibodies, etc.), helps understand whether various 10B-FAPI drugs have immune-enhancing or immune-regulating properties during the anti-tumor process.

2.miR-30a-5p

miR-30a-5p is a type of microRNA (miRNA),

which belongs to small non-coding RNA molecules containing approximately 20-24 nucleotides. It exhibits endogenous properties and is found to be dysregulated in numerous tumor cells. In the progression of tumors, miRNA plays a crucial regulatory role by inhibiting the translation of mRNA into proteins via binding to the 3' untranslated regions (UTRs) of mRNA.

Within the miR-30a family, miR-30a-5p is implicated in both pathological processes and various biological functions. For example, in colorectal cancer, gastric cancer, liver cancer, and other cancers, miR-30a-5p acts as a tumor suppressor and impedes cancer growth. Studies have revealed that miR-30a-5p is downregulated in pancreatic cancer cells, and lower expression of miR-30a-5p correlates with poorer survival rates among cancer patients. Therefore, clinically, miR-30a-5p can be considered as a target for intervention.

Related research suggests that treatment with miR-30a-5p mimics for pancreatic cancer leads to a significant increase in miR-30a-5p expression, both in Panc-1 and BxPC-3 cells. Flow cytometry assays have shown that overexpression of miR-30a-5p promotes cell apoptosis, inhibits cell cycle progression, and reduces the expression of CD73 and TNFR2 in nude mouse cancer cells.

In a study involving 88 pancreatic cancer patients receiving gemcitabine chemotherapy, a significant negative correlation was observed between miR-30a-5p expression and drug resistance ($P < 0.001$, $r = -0.318$), indicating that lower expression of miR-30a-5p is associated with increased drug resistance. Subsequent studies have demonstrated that miR-30a-5p targets the SNAI1-AKT pathway, acting on AKT/ERK, enhancing its activity, promoting its phosphorylation, and thereby contributing to the efficacy of gemcitabine against pancreatic cancer.

3. The therapeutic effect of miR-30a-5p targeting FAP in pancreatic cancer.

Research suggests that miR-30a-5p has a direct targeting effect on FAP, which can hinder the migration and proliferation of oral cancer cells, indicating a close relationship between the two. However, there are currently no reports specifically addressing their interaction in pancreatic cancer. Through searches in the TargetScan database, it was found that there are 8mer binding sites between FAP and miR-30a-5p. The latter acts as a tumor suppressor gene and when overexpressed, it can hinder the progression of pancreatic cancer and enhance sensitivity to chemotherapy. On the other hand, FAP is an oncogenic protein that accelerates the progression of pancreatic cancer. Therefore, utilizing miR-30a-5p to regulate FAP could potentially prevent the migration of pancreatic cancer cells and inhibit their proliferation.

4. Conclusion

In summary, FAP promotes the progression of pancreatic cancer and affects the efficacy of chemotherapy. Targeting FAP with miR-30a-5p can reduce FAP levels, inhibit pancreatic cancer tumor growth and proliferation, prevent angiogenesis, and alleviate inflammation reactions, thereby assisting gemcitabine chemotherapy and enhancing its effectiveness. However, current research on this topic is limited, and the expression of FAP when using miR-30a-5p therapy is not yet clear, and the correlation of characteristics has not been verified. Utilizing PET-CT observations with 10B-FAPI can help better understand the molecular mechanisms of miR-30a-5p and, combined with the physical therapy methods of BNCT, achieve effective treatment goals.

References

[1] Looi CK, Chung FF, Leong CO, et al. Therapeutic challenges and current immunomodulatory strategies in targeting the immunosuppressive pancreatic tumor microenvironment. *J Exp Clin Cancer Res*. 2019;38(1):162.

[2] Huang H, Li W, Zhang MK, Sun ZK, Li YB, Guo ZY, Li YM. Mechanism of microRNA-30a-5p activating Wnt/β-catenin signaling pathway on proliferation and invasion of gastric cancer cells. *Chin J Exp Surg*. 2023;40(5):863-866.

[3] He Y, Dong BL, Wang XX, Li Y, Yang XJ. miR-30a-5p targets fibroblast activation protein-1 to inhibit proliferation and migration of pancreatic ductal adenocarcinoma. *J Lanzhou Univ* (Med Sci). 2023;49(3):5-11.

[4] Xia JH, Zhou LQ, Yan Y, Ma TT, Su XY. miR-30a-5p regulates invasion and migration of lung adenocarcinoma cells by inhibiting ECM receptor interaction signaling pathway-related proteins.

Zhejiang Med J. 2023;45(1):21-27.

[5] Zhang DL, Liang SB, Wei W, Zhuang Y, Zhang K. Serum miR-30a-5p affects the development of knee osteoarthritis by targeting FOXD1. *J Guangxi Med Univ*. 2023;40(2):282-287.

[6] Ni MQ, Wu S, Jin CT, Tian M. Clinical application of 68Ga-FAPI PET/CT in malignant tumors. *Int J Radiat Med Nucl Med*. 2021;45(05):305-312.

[7] Wang XW, Tang JT. Tumor particle therapy engineering technology. *China Science and Technology Press*. 2022:69-72.

[8] Zhou L, Jia S, Chen Y, et al. The distinct role of CD73 in the progression of pancreatic cancer. *J Mol Med* (Berl). 2019;97(6):803-815.