创新研究论坛

基础临床

CXCR2 介导胰腺癌细胞对不可逆电穿孔治疗响应的研究

摘要： 胰腺导管癌（PDAC）是胰腺部位出现的的恶性肿瘤，一般病人确诊后，五年生存率不到 10%，中位生存期<11 个月。不可逆电穿孔（irreversible electroporation, IRE）消融技术是一种非热消融治疗技术，不会影响周围组织的结构完整性，因此能够治疗重要结构附近的肿瘤。在临床实践中发现单独应用 IRE 治疗效果有限，仍有肿瘤复发的情况，因此迫切需要寻找一种疗法，联用 IRE 后提升肿瘤的治疗效果。CXCR2 是一种趋化因子受体，广泛表达于胰腺癌细胞与部分免疫细胞中，并与胰腺癌的肿瘤生成、增殖、转移等过程密切相关，通过靶向 CXCR2 增强 IRE 治疗胰腺癌的疗效拥有巨大潜力。**目的：** 1、探究 IRE 术后胰腺肿瘤微环境中免疫细胞的浸润情况以及 CXCR2 抑制剂对其的影响。2、现有研究发现 CXCR2 在胰腺癌细胞中广泛表达。探究 CXCR2 抑制剂能否抑制胰腺癌细胞在 IRE 术后的侵袭与转移能力。**方法：** 1、动物实验测定小鼠胰腺癌原位癌模型在对照、IRE、IRE+SB 三种处理条件下中性粒细胞与 CD8 阳性的 T 细胞在肿瘤微环境中的聚集情况，通过 CD8 和 LY6G 免疫组化染色实现。2、Transwell 实验测定胰腺癌细胞在 IRE 与 CXCR2 抑制剂 SB225002 联合处理之后侵袭能力的改变。3、趋化实验测定加入了 CXCR2 抑制剂 SB225002 的 IRE 处理的胰腺癌细胞裂解液对于中性粒细胞的趋化作用（有文献表明胰腺癌肿瘤微环境中 N2 型的中性粒细胞有促肿瘤效应）。4、制备 SB225002 给药剂型 BSA 物理混合 mPEG5000-PLA。**结果：** 1、小鼠原位癌模型当中 IRE 与 SB225002 的联合使用可以减少术后肿瘤微环境中的中性粒细胞浸润，而对 T 细胞的影响未发现明显趋势。2、Transwell 实验表明 IRE 与 SB225002 联合使用可以降低电脉冲处理后胰腺癌细胞的侵袭能力。3、BSA 物理混合 mPEG5000-PLA 的 SB225002 给药剂型在小鼠体内有较好的血药浓度特性。4、中性粒细胞的趋化实验表明 SB225002 可以降低胰腺癌细胞 IRE 处理后的裂解液对中性粒细胞的趋化作用。**结论：** CXCR2 抑制剂 SB225002 可以降低 IRE 处理后小鼠胰腺癌原位癌肿瘤微环境中的中性粒细胞浸润程度，而在肿瘤细胞微环境中的中性粒细胞多为 N2 型的促肿瘤亚型，同时 CXCR2 抑制剂也可以直接减弱 IRE 处理之后的肿瘤细胞的侵袭能力，以上实验表明 CXCR2 抑制剂与 IRE 联合使用在胰腺癌治疗中有巨大的应用潜力。

关键词： 胰腺癌；CXCR2；不可逆电穿孔

Innovative Research Forum

Basic Clinical Research

Study on CXCR2-Mediated Response of Pancreatic Cancer Cells to Irreversible Electroporation Treatment

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is a malignant tumor that occurs in the pancreas. Generally, after diagnosis, the five-year survival rate is less than 10%, with a median survival of less than 11 months. Irreversible electroporation (IRE) is a non-thermal ablation technique that does not affect the structural integrity of surrounding tissues, thus enabling the treatment of tumors near vital structures. Clinical practice has shown limited efficacy when IRE is used alone, leading to tumor recurrence. Therefore, there is an urgent need to find a treatment that, when combined with IRE, enhances the therapeutic effect on tumors.CXCR2 is a chemokine receptor widely expressed in pancreatic cancer cells and some immune cells, closely related to tumor formation, proliferation, and metastasis in pancreatic cancer. Targeting CXCR2 to enhance the therapeutic efficacy of IRE in treating pancreatic cancer holds great potential.**Objectives:**1.Investigate the infiltration of immune cells in the tumor microenvironment after IRE and the impact of CXCR2 inhibitors on them.2.Existing studies have found widespread expression of CXCR2 in pancreatic cancer cells. Explore whether CXCR2 inhibitors can suppress the invasive and metastatic abilities of pancreatic cancer cells after IRE.**Methods:**Animal experiments were conducted to determine the aggregation of neutrophils and CD8-positive T cells in the tumor microenvironment of mouse pancreatic cancer in three treatment conditions: control, IRE, and IRE+SB, using immunohistochemical staining with CD8 and LY6G.Transwell experiments were performed to assess changes in the invasive ability of pancreatic cancer cells after combined treatment with IRE and the CXCR2 inhibitor SB225002.Chemotaxis assays were conducted to evaluate the chemotactic effect of pancreatic cancer cell lysates treated with IRE and SB225002 on neutrophils (literature suggests N2-type neutrophils in the pancreatic cancer tumor microenvironment have a pro-tumor effect).Preparation of SB225002 dosage form BSA physical mixture mPEG5000-PLA.**Results:** The combined use of IRE and SB225002 in the mouse pancreatic cancer in situ model reduced neutrophil infiltration in the postoperative tumor microenvironment, with no significant trend observed for T cells.Transwell experiments indicated that the combined use of IRE and SB225002 reduced the invasive ability of pancreatic cancer cells after electroporation.The SB225002 dosage form BSA physical mixture mPEG5000-PLA showed good pharmacokinetic properties in mice.Chemotaxis assays of neutrophils demonstrated that SB225002 reduced the chemotactic effect of pancreatic cancer cell lysates treated with IRE on neutrophils.**Conclusion:** The CXCR2 inhibitor SB225002 can reduce neutrophil infiltration in the tumor microenvironment of mouse pancreatic cancer

after IRE treatment. Neutrophils in the tumor cell microenvironment are mostly of the pro-tumor N2 subtype. Additionally, CXCR2 inhibitors can directly weaken the invasive ability of tumor cells after IRE treatment. The above experiments indicate that the combined use of CXCR2 inhibitors and IRE has significant potential in the treatment of pancreatic cancer.
Keywords: Pancreatic cancer; CXCR2; Irreversible electroporation