中文題目：針對 FGFR1/Src/NF-κB 訊息傳導治療胰臟癌的新策略

英文題目：The therapeutic targeting of the FGFR1/Src/NF-κB signaling axis inhibits pancreatic ductal adenocarcinoma stemness and oncogenicity

作　　者：賴學緯[1,2]、Oluwaseun Adebayo Bamodu[3,4]、蔡文銓[5,6]、張益銘[5,6]、趙祖怡[1,3,4]

服務單位：[1]臺北醫學大學臨床醫學研究所、[2]國防醫學院三軍總醫院內科部血液腫瘤科、[3]臺北醫學大學雙和醫院血液腫瘤科癌症中心、[4]臺北醫學大學雙和醫院教學研究部、[5]國防醫學院三軍總醫院病理部、[6]國防醫學院醫學科學研究所

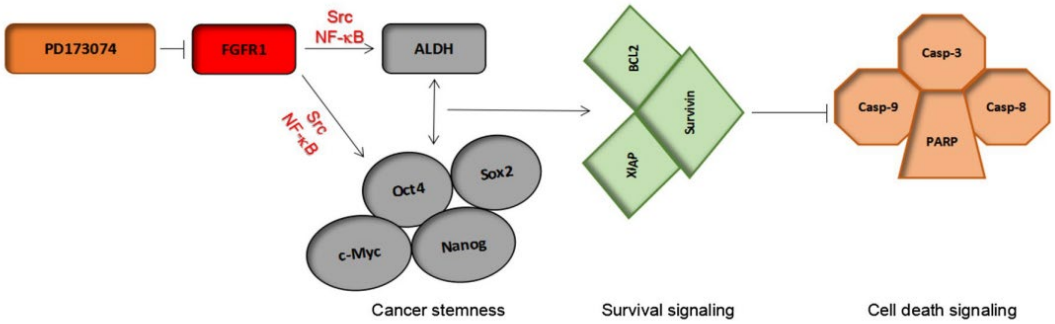
Abstract

Background: The aberrant activation of the FGFR signaling is detected in many solid tumors, including pancreatic ductal adenocarcinoma (PDAC), suggesting it as a potential therapeutic target. In this study, we investigated the antitumor and anti-metastasis efficacy of the selective FGFR1 inhibitor, PD173074 in PDAC.

Methods and Results: We used immunohistochemical and in situ hybridization analyses to demonstrate a strong correlation between FGFR1 amplification and/or expression and disease progression in PDAC patients. We showed that ALDH high ($ALDH^+$) pancreatic cancer cells exhibited stem cell-like phenotype and expressed higher levels of FGFR1, Src, NF-κB, alongside stemness markers like Oct4 and Sox2, compared to their ALDH low/null ($ALDH^-$) counterparts, suggesting the preferential activation of the FGFR1/Src/NF-κB signaling axis in pancreatic cancer stem cells (panCSCs). Furthermore, treatment of the $ALDH^+$/ FGFR1-rich pancreatic cancer cell lines with PD173074, a selective FGFR1 inhibitor, revealed that PD173074 inhibited the proliferation and self-renewal of the panCSCs, and induced their apoptosis by activating caspase-3 and cleaving Poly-ADP ribose Polymerase. The anti-CSCs effect of PD173074 was associated with decreased expression of Oct4, Sox-2, Nanog, and c-Myc, as well as suppression of XIAP, Bcl2, and survivin expression, dose dependently. Additionally, activation of cMet, Src, ERK 1/2 and NFκB (p65) was also inhibited by PD173074. Also, of clinical relevance, the disruption of the FGFR1/Src/NF-κB signaling axis positively correlated with poor clinical prognosis among the PDAC patients. We concluded that PD173074 suppresses the tumorigenesis and CSCs-like phenotype of PDAC cells, highlighting its therapeutic efficacy and providing support for its potential use as a therapeutic option for the 'difficult-to-treat', 'quick-to-relapse' PDAC patients.

Graphical Abstract

Schematic abstract showing how PD173074 inhibits PDAC growth through selective targeting of FGFR1, suppression of cancer stemness, disruption of the FGFR1/Src/NF-κB signaling axis and activation of the cell death signaling pathway.


PD173074
FGFR1
Src
NF-κB
ALDH
Src
NF-κB
Oct4
Sox2
c-Myc
Nanog
BCL2
Survivin
XIAP
Casp-3
Casp-9
Casp-8
PARP
Cancer stemness
Survival signaling
Cell death signaling