中文題目：協同 FGFR1 及 PARP 抑制劑以治療胰臟癌的新策略

英文題目：Targeted PARP inhibition in combination with FGFR1 blockade is synthetically lethal to malignant cells in patients with pancreatic cancer

作　　者：賴學緯[1,2]、Oluwaseun Adebayo Bamodu[3,4]、陳佳宏[1,2]、吳駿翊[5]、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]臺北醫學大學醫學科技學院

Abstract

Background: The role and therapeutic promise of PARP inhibitors in anticancer chemotherapy is increasingly being explored, especially in the context of adjuvant/maintenance therapy. Due to increasing incidence of acquired resistance to FGFR1 inhibitor and sequel to our previous work demonstrating in part the caspase-3/PARP-mediated antitumor and anti-metastasis efficacy of PD173074, a selective FGFR1 inhibitor, on ALDHhigh/FGFR1-rich pancreatic ductal adenocarcinoma (PDAC) cells, we investigated the probable synthetic lethality and therapeutic efficacy of targeted PARP inhibition combined with FGFR1 blockade in patients with PDAC.

Methods and Results: Using bioinformatics-based analyses of gene expression profile, co-occurrence and mutual exclusivity, molecular docking, immunofluorescence staining, clonogenicity, western-blot, cell viability/cytotoxicity screening, and tumorsphere formation assays, we demonstrated that FGFR1 and PARP1 are co-occurring, complex-forming, confer survival disadvantage in patients with PDAC, and more expressed in FGFR1 inhibitor (dasatinib)-resistant PDAC cell lines, compared to the sensitive cell lines. Compared to the limited effect of single-agent Olaparib (PARP1 inhibitor) or PD173074 on PANC-1 and SUIT-2 cells, low-dose Olaparib+PD173074 combination treatment inhibited viability of the cells, significantly, dose-dependently and synergistically, with concomitantly up-regulated cleaved-PARP, pro-caspase (CASP)9, cleaved-CASP9, cleaved-CASP3, and down-regulated Bcl-xL protein expression. Furthermore, Olaparib+PD173074 treatment elicited marked suppression of clonogenicity and tumorsphere formation efficiency of the PDAC cells regardless of FGFR1 inhibitor-resistance status, with enhanced Rad51 and γ -H2AX immunoreactivity. Of clinical relevance, in vivo studies showed that both early and late initiation of Olaparib+PD173074 therapy markedly suppressed tumor xenograft growth and weight, howbeit more pronounced in the early initiation group. In conclusion, we show that FGFR1 inhibitor-resistant PDAC cells become sensitive to PD173074 in the presence of Olaparib-mediated loss of PARP1 signaling. This FGFR1/PARP-mediated synthetic lethality

proof-of-concept study provides preclinical evidence for the feasibility and therapeutic efficacy of combinatorial FGFR1/PARP1 inhibition in patients with ‘difficult-to-treat’, ‘quick-to-relapse’ PDAC patients.

Graphical Abstract

Schematic abstract showing how targeted inhibition of PARP1 combined with FGFR1 blockade is concomitantly suppress DNA repair, inhibit viability, colony formation, and tumorsphere formation of erstwhile resistant pancreatic cells as well as suppress tumor growth in vivo, thus indicating the synthetic lethality of the dual PARP1/FGFR1 inhibition to malignant cells in patients with pancreatic cancer.