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Original Articles

Secretory Trefoil Factor 1 (TFF1) promotes gemcitabine resistance through chemokine receptor CXCR4 in Pancreatic Ductal Adenocarcinoma

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ABSTRACT

Gemcitabine is the first-line treatment option for patients with locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC). However, the frequent adoption of resistance to gemcitabine by cancer cells poses a significant challenge in treating this aggressive disease. In this study, we focused on analyzing the role of trefoil factor 1 (TFF1) in gemcitabine resistance in PDAC. Analysis of PDAC TCGA and cell line datasets indicated an enrichment of TFF1 in the gemcitabine-resistant classical subtype and suggested an inverse correlation between TFF1 expression and sensitivity to gemcitabine treatment. The genetic ablation of TFF1 in PDAC cells enhanced their sensitivity to gemcitabine treatment in both *in vitro* and *in vivo* tumor xenografts. The biochemical studies revealed that TFF1 contributes to gemcitabine resistance through enhanced stemness, increasing migration ability of cancer cells, and induction of anti-apoptotic genes. We further pursued studies to predict possible receptors exerting TFF1-mediated gemcitabine resistance. Protein-protein docking investigations with BioLuminate software revealed that TFF1 binds to the chemokine receptor CXCR4, which was supported by real-time binding analysis of TFF1 and CXCR4 using SPR studies. The exogenous addition of TFF1 increased the proliferation and migration of PDAC cells through the pAkt/pERK axis, which was abrogated by treatment with a CXCR4-specific antagonist AMD3100. Overall, the present study demonstrates the contribution of the TFF1-CXCR4 axis in imparting gemcitabine resistance properties to PDAC cells.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC), having a low 5-year survival of 12 %, is expected to be the second major cause of cancer-related deaths by 2030 [1–3]. Several therapeutic regimens, including gemcitabine, 5-FU, nab-paclitaxel, and FOLFIRINOX, have been developed for PDAC [4]. Although greater overall survivals have been achieved with FOLFIRINOX, severe toxicity issues have limited its utility in the clinical setting, making gemcitabine combined with nab-paclitaxel the standard-of-care chemotherapeutic regimen for PDAC management. However, the adoption of therapeutic resistance to gemcitabine by cancer cells results in poor outcomes in PDAC patients [5,6]. Many studies have attempted to comprehensively understand the molecular mechanisms mediating gemcitabine resistance in patients, cell lines, and animal models [7–9].

The research focused on utilizing gene signatures for predicting therapeutic response to gemcitabine have stratified PDAC patients into basal, classical, and quasi-mesenchymal subtypes, with the subtypes demonstrating varying responses to drug treatment [10–12]. Interestingly, molecular subtyping studies have indicated the presence of a

Abbreviations: PDAC, Pancreatic Ductal Adenocarcinoma; TFF1, Trefoil factor 1; CXCR4, C-X-C chemokine receptor type 4; SPR, Surface plasmon resonance.

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