Cureus

DDR1 Inhibition Combined with Radiation Therapy as a Novel Strategy for Pancreatic Cancer

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Abstract
Published 01/26/2026

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Categories: Radiation Oncology
Keywords: pancreatic cancer, radiation biology, radiation oncology

How to cite this abstract
Samala S (January 26, 2026) DDR1 Inhibition Combined with Radiation Therapy as a Novel Strategy for Pancreatic Cancer. Cureus 18(1): a1597

Abstract

Purpose: Pancreatic ductal adenocarcinoma (PDAC) treatment involves various combination treatments involving surgery, systemic therapy, and radiation therapy (RT). Despite multimodal treatment, the overall survival remains poor. Discoidin domain receptor 1 (DDR1) is a collagen-activated receptor tyrosine kinase (RTK) that is commonly overexpressed in cancer cells and promotes cancer cell growth, proliferation, invasion, immune exclusion, and an increase in neutrophil extracellular traps (NETs)1. Prior studies have evaluated a combination of DDR1 inhibitors with other targeted agents in Kras-driven tumors2. In this study, we investigated the effects of pharmacological inhibition of DDR1 in combination with RT in various pancreatic cell lines.

Methods: DDR1 proteogenomic expression among various tumor types, including PDAC, was evaluated using the web-based Cancer Proteogenomic Data Analysis Site (cProSite). In vitro studies were performed on murine (Panc02 and KPC) and human (Panc1) pancreatic cancer cell lines. DDR1 inhibition was achieved using the small molecule inhibitor 7rh. The effect of combining DDR1 inhibition with RT was assessed using clonogenic assays, cell viability assays, and apoptosis assessments using Annexin V/propidium iodide (PI) flow cytometry. Western blot assay was used to analyze DDR1 inhibition and its effect on downstream signaling.

Results: Database analyses revealed increased expression of DDR1 in several cancers, including PDAC, and increased protein abundance in PDAC compared to normal tissue. Western blot assays demonstrated that 7rh inhibits DDR1 and downstream signaling. Combination therapy with 7rh and RT significantly decreased cell viability compared to RT alone. Flow cytometry analysis using Annexin V/PI staining showed increased apoptosis with combination therapy across 12 to 48 hours. Clonogenic assays showed decreased survival with 7rh, and RT compared to RT alone, with a Sensitizer Enhancement Ratio (SER) > 1.2.

Conclusion: DDR1 expression levels are higher in PDAC cells than in normal tissue, making it a rational target for anti-cancer therapy. DDR1 inhibition with 7rh combined with RT results in inhibition of downstream pathways of DDR1, decreased cell viability, increased apoptosis, and impaired clonogenic survival. The DDR1–collagen axis is essential to immune exclusion and NET formation. Given the desmoplastic and immune-excluded microenvironment of PDAC, DDR1 inhibition with RT may not only enhance the direct effects of RT but also reprogram the tumor immune microenvironment (TIME). Ongoing work will explore changes in TIME in vivo and evaluate combinations with RT and immunotherapy.