

## **Ferroptosis Induction via Glutathione Peroxidase 4 Inhibition Sensitizes Pancreatic Cancer Stem Cells to Radiotherapy**

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### **Abstract**

Pancreatic ductal adenocarcinoma (PDAC) stem cells (CSCs) exhibit intrinsic radioresistance driven by robust antioxidant defenses. We demonstrate that CSCs isolated from patient-derived xenografts exhibit elevated glutathione (GSH) synthesis and GPX4 expression, rendering them resistant to lipid peroxidation. Pharmacological inhibition of GPX4 using RSL3 or genetic knockdown induced ferroptosis selectively in CSCs while sparing differentiated tumor cells. Combination of GPX4 inhibition with stereotactic body radiation therapy (SBRT) eradicated CSC pools, prevented tumor relapse, and prolonged survival in immunocompromised mice. RNA-seq analysis revealed downregulation of SLC7A11 and activation of ACSL4 as molecular determinants of ferroptotic susceptibility.

**Keywords:** ferroptosis, GPX4 inhibition, cancer stem cells, pancreatic cancer, radioresistance, lipid peroxidation



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