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Targeting Metabolic Vulnerabilities with L-Asparaginase as a Radiosensitizer in Solid Tumors: Synergy Assessment and Cell Cycle Modeling

L-Asparaginase (L-ASNase) is a chemotherapy agent depriving cancer cells of asparagine/glutamine as essential amino acids, commonly used in acute lymphoblastic leukemia, but underexplored in solid tumors.
This study investigates combined L-ASNase and ionizing radiation (IR) effects across *in vitro* solid tumor models, quantifying synergy through proliferation and colony formation assays. Monotherapies dose-response curves inform Bliss Independence modeling, generating Combination Indexes (CI, where CI<1 indicates synergy).
Colorectal cancer cells exhibited significant synergy (CI<0.68) at low L-ASNase concentrations (0.05–0.1 U/mL) and moderate IR doses (3–5 Gy). Renal and lung models showed additive effects (CI≈1), while triple-negative breast cancer models displayed cytostatic responses with G1-S arrest and variable combination effects.
Experimental data were integrated with parametrized compartmental models to predict phase-delay cell cycle perturbations induced by treatments, enhancing mechanistic understanding.
These findings establish a quantitative framework for metabolic radiosensitization strategies, identifying colorectal cancer as a promising candidate for L-ASNase–IR combination therapy.

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