Glutaminase Inhibition Radiosensitizes Non-Small Cell Lung Cancer Cells to X-rays and Protons

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Objective:
The purpose of this study is to investigate the effect of glutaminase inhibition on the radiosensitivity of lung carcinoma cells to x-rays and protons. We hypothesize that IACS-6274, a GLS1 inhibitor, is an effective radiosensitizer of non-small cell lung cancer cells to x-rays and even more so to protons, likely due to more complex DNA damage and increased ROS production induced by protons.

Background:
Glutamine is an essential amino acid required for cell proliferation. Cancer cells demonstrate increased glutamine metabolism, controlled in part by oncoprotein-induced expression of Glutaminase-1 (GLS1).\(^1\) GLS1 converts glutamine to glutamate. Glutamate can synthesized via \(\gamma\)-glutamylcysteine (GGC) to form glutathione (GSH), an important cellular antioxidant, or nucleotides needed for DNA replication. Low GSH levels impair a cell's ability to prevent damage caused by reactive oxygen species (ROS).\(^1\) and failure to produce nucleotides can induce replication fork stalling, both of which may intensify the effects of radiotherapy (RT). Here we examine the impact of a GLS1 inhibitor (GLS1i) that is being used in a clinical trial (NCT03894540), on the radiosensitization of non-small cell lung cancer cells to two forms of radiation, X-rays, and protons, which vary in their ability to produce clustered DNA damage.

Materials and Methods:
We performed clonogenic assays with H460 lung carcinoma cells exposed to 6 MV X-rays or 9.9 keV/\(\mu\)m protons with and without a GLS1i (IACS-6274; 0.1 and 1 \(\mu\)M). The cells were fixed 7-10 days post-irradiation, and ImageJ macros were used to count the colonies. Radiosensitivity was represented using SF2Gy (surviving fraction at 2 Gy). We also quantified the efficacy of GLS1i-protons by comparing the relative biological effectiveness (RBE, the ratio of SF2Gy for X-rays divided by SF2Gy for protons) of vehicle vs GLS1i.

Results:
H460 cells exposed to X-rays demonstrated a SF2Gy of 0.51±0.03 with vehicle. GLS1i minimally sensitized cells with 0.1 \(\mu\)M (0.50±0.06) but strongly sensitized with 1 \(\mu\)M (0.41±0.07) concentration. H460 cells exposed to protons exhibited a SF2Gy of 0.42±0.03 with vehicle. GLS1i showed strong sensitization at both 0.1 \(\mu\)M (0.16±0.016) and 1 \(\mu\)M (0.10±0.02) concentrations. Protons combined with vehicle had an RBE of 1.21±0.11, whereas the RBE for protons combined with GLS1i had RBE values of 3.0±0.5 for 0.1 \(\mu\)M, and 4.0±1.0 for 1 \(\mu\)M GLS1i.

Conclusions:
- GLS1 inhibition via IACS-6274 effectively radiosensitized H460 cells to X-ray and proton RT.
- GLS1i appeared to be a more effective radiosensitizer for protons than X-rays, possibly due to increased ROS production by protons combined with oxidative stress induced by GLS1i.
- Future analysis will investigate the mechanism of radiosensitization and increased RBE, focusing on DNA damage response and cell cycle progression.

References: