Identification and preclinical validation of metabolic bottlenecks for radiosensitization in the context of SLC25A1 inhibition.

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Abstract

Introduction: We demonstrated that metabolic reprogramming induced by the inhibition of the mitochondrial citrate transport protein (SLC25A1) enhanced radiosensitivity of cancer cells and delayed repair of radiation-induced DNA damage [1]. Here, we hypothesized that inhibition of SLC25A1 (SLC25A1i) might enhance sensitivity to ionizing radiation (IR) and targeted DNA repair inhibitors by inducing accumulation of D-2-hydroxyglutarate (D2HG), presumably by inducing associated DNA repair defects [1].

Methods: We used pharmacologic SLC25A1i (small molecule SLC25A1 inhibitor CTPi2) to determine effects of SLC25A1i alone or in combination with IR on 2HG-accumulation, and of octyl-D2HG treatment alone or in combination with IR on cellular function, DNA double strand break (DSB) induction, and radiosensitivity in lung cancer (NCI-H460) cell lines in vitro. Finally, we analysed the potential of SLC25A1i to enhance lethality of IR with clinically relevant inhibitor of poly (ADP-ribose)-polymerase (PARPi) in vivo in a chicken chorioallantoic membrane (CAM) model.

Results: SLC25A1i stably induced significant D-2HG accumulation up to 48h in NCI-H460 cells. CTPI2, as well as octyl-D2HG, significantly increased DNA damage when combined with IR. Both CTPI2 and octyl-D2HG provoked ROS, apoptosis, cell death induction, mitochondrial dysfunction, and cell proliferation inhibition, as well as increased radiosensitivity. Inhibition of Histone-lysine-demethylases (KDMs) by JIB-04 reproduced the effects on cell function and DNA damage observed upon CTPI2-treatement. CTPI2 inhibited tumor growth, which was enhanced by PARPi under the condition of IR, in vivo.

Conclusion: D-2HG induction by SLC25A1i or direct treatment with octyl-D2HG impact cellular processes important for survival of irradiated cancer cells. Mechanistically, the effects observed upon CTPI2-induced D-2HG accumulation correlated to the dysfunction of KDMs. SLC25A1i affects the repair of IR-induced lethal DNA lesions by inducing 2HG accumulation and thereby promoting lethality in combination with clinically relevant DSB repair inhibitors.

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References

1. Xiang K, et al., Cell Death Dis. 2022 Jul 22;13(7):641. doi: 10.1038/s41419-022-05098-9.