2025 ACG-IRG Pilot Grant

Decoding the RNA Oxidation Landscape in Irradiated Glioblastoma: A New Frontier in Cancer Treatment

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Abstract:

Glioblastoma Multiforme (GBM) remains a highly aggressive and deadly brain cancer with significant therapeutic challenges. While radiotherapy (RT) with ionizing radiation (IR) combined with chemical treatment temozolomide (TMZ) remains a foundation of glioblastoma treatment, its effectiveness is severely limited due to the inherent and developed resistance by the cancer cells. The primary mechanism for IR treatment involves direct and indirect damage to DNA, however it also generates significant reactive oxygen species (ROS) that contribute to cellular damage. Importantly, RNA molecules are highly susceptible to oxidation damage, which can be recognized by RNA binding proteins (RBPs) that regulate cellular pathways. Notably, some GBM therapeutic resistance mechanisms involve upregulating antioxidant signaling pathways to counteract elevated ROS levels. However, the consequence of RNA oxidation damage and its cellular responses in glioblastoma remain poorly understood. This knowledge gap hinders the development of more effective therapeutic interventions. We hypothesize that IR causes significant levels of RNA oxidation damage that play an important role in GBM progression and resistance mechanisms, and that uncovering the RBPs that respond to oxidized RNA will be critical for guiding future treatments. Our research objectives will be pursued through three specific aims: (1) Define the landscape of RNA oxidation damage caused by ionizing radiation using innovative LC-MS and next-generation sequencing methods to quantify and map oxidation sites; (2) Determine how known oxidized-RNA binding proteins HNRNPC, PCBP1, and PCBP2 regulate cellular response to radiation damage through genetic manipulation and advanced imaging approaches; and (3) Identify and characterize new RBPs that sense radiation damage to RNA using unbiased proteomic screening. By conducting this work in GBM cell lines and combining cutting-edge technologies, our findings will provide unprecedented insights into radiation-induced RNA damage and cellular responses. The resulting datasets will serve as a valuable resource for the cancer biology community and may fundamentally change our approach to radiation therapy in GBM, potentially leading to more effective treatments for patients with this devastating disease.