Characterization of A Novel Groundbreaking Radioresistance Pathway in the Endometrial Cancer Stem Cell Niche: The Interplay of WNT, Cyclooxygenase-2 (COX-2), and Hypoxia Inducible Factor-1a (HIF-1a)

Lin, Nelly

Chen, Ker-Cheng

Recent changes in the field of oncology have placed an emphasis on targeting cancer stem cells (CSCs) in order to effectively treat cancer. Despite the increased attention, an effective mechanism for targeting CSCs has yet to be discovered. The purpose of this study is to use endometrioid adenocarcinoma as a model to understand CSCs' abilities to survive radiation treatment and to unravel the mysteries of radioresistance. For the first time, we report a groundbreaking, novel signaling pathway for radioresistance in EnCSCs involving a delicate interplay among Wnt, cyclooxygenase-2 (COX-2), and hypoxia inducible factor-1a (HIF-1a) in the context of the EnCSC niche. Using the Hybrid Spheroid Assay, a 3D bio-matrix which replicates the in vivo CSC niche ex vivo, we have shown that CSCs exist within a niche of intracellular hypoxia, facilitated by basal expression of HIF-1a as a protective barrier against indirect radiation-induced DNA damage. Upon exposure to radiation, EnCSCs up-regulate HIF-1a expression, which acts as a free radical scavenger to minimize DNA breakage. Furthermore, up-regulated COX-2 production by the EnCSCs arrests the CSC and surrounding cells in the cell cycle, preventing subsequent direct damage to DNA. Following the heightened state of radioresistance, EnCSCs return to its initial proliferative conditions through the canonical Wnt pathway, which specializes in survival. We also show the existence of two unique CSC populations cohabiting a single niche; epithelial EnCSCs and mesenchymal EnCSCs. Discovery of this pathway enables future designs to eliminate radioresistance through the pathway's manipulation, thus altering the efficacy of radiation therapy to potentially save countless lives of patients with resistant metastasis and reoccurrences.

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