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The impact of DNA repair pathways throughout the Carbon-ion Spread-out Bragg peak

The cellular carbon-ion radiation-induced DNA double-strand break (DSB) repair pathway choice is an essential component behind the fate of the cell's survival. The two main DSB repair pathways in mammalian cells are non-homologous end joining (NHEJ) and homologous recombination (HR). It has been suggested that the balance between which of the two repair pathways is preferentially utilized depends on the DSB complexity. In the case of the carbon-ion beam, the DSB complexity increases within the carbon-ion spread-out Bragg peak (SOBP) as the linear energy transfer (LET) increases. Taking advantage of this increase in DSB complexity with an increase in the LET, we investigated the importance of each DSB repair pathway at each depth within the carbon-ion SOBP range in a single biological system using cell survival as an endpoint and gamma-H2AX as a surrogate marker for DSBs. We addressed the radiosensitivity of CHO mutant cell lines either deficient in NHEJ (V3) or HR (51D1) in comparison to the wild-type CHO cell line (10B2) and the human pancreatic cancer cell line (PANC-1). Our results demonstrated that both NHEJ- and HR-deficient cells portrayed an increase in radiosensitivity throughout the full carbon-beam range. NHEJ-deficient cells had the greatest increase in radiosensitivity in the depths from beam entrance up to the proximal depth of the SOBP and interestingly demonstrated a dosedependent increase in survival throughout the SOBP. HR-deficient cells had the greatest ratio of survival fraction at entrance depth to lowest survival fraction within the SOBP. Collectively, our results suggest that HR may be the most beneficial pathway to inhibit in order to enhance the cell killing effect of CIRT in the targeted cells within the SOBP while limiting unwanted damage to the surrounding cells. As demonstrated here, studies on DSB repair pathway choice at varying depths within the full carbon-ion beam range provide important insight on potential targets to inhibit to enhance the efficiency of CIRT.