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Radiation quality effects on transcriptome profiles in 3-d cultures after charged particle irradiation

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In this work, we evaluate the differential effects of low- and high-LET radiation on 3-D organotypic cultures in order to investigate radiation quality impacts on gene expression and cellular responses. Reducing uncertainties in current risk models requires new knowledge on the fundamental differences in biological responses (the so-called radiation quality effects) triggered by heavy ion particle radiation versus low-LET radiation associated with Earth-based exposures. We are utilizing novel 3-D organotypic human tissue models that provide a format for study of human cells within a realistic tissue framework, thereby bridging the gap between 2-D monolayer culture and animal models for risk extrapolation to humans. To identify biological pathway signatures unique to heavy ion particle exposure, functional gene set enrichment analysis (GSEA) was used with whole transcriptome profiling. GSEA has been used extensively as a method to garner biological information in a variety of model systems but has not been commonly used to analyze radiation effects. It is a powerful approach for assessing the functional significance of radiation quality-dependent changes from datasets where the changes are subtle but broad, and where single gene based analysis using rankings of fold-change may not reveal important biological information. We identified 45 statistically significant gene sets at 0.05 q-value cutoff, including 14 gene sets common to gamma and titanium irradiation, 19 gene sets specific to gamma irradiation, and 12 titanium-specific gene sets. Common gene sets largely align with DNA damage, cell cycle, early immune response, and inflammatory cytokine pathway activation. The top gene set enriched for the gamma- and titanium-irradiated samples involved KRAS pathway activation and genes activated in TNF-treated cells, respectively. Another difference noted for the high-LET samples was an apparent enrichment in gene sets involved in cycle cycle/mitotic control. It is plausible that the enrichment in these particular pathways results from the complex DNA damage resulting from high-LET exposure where repair processes are not completed during the same time scale as the less complex damage resulting from low-LET radiation.