Cell fate decisions upon exposure to ionizing radiation in tumor and normal tissue: Implications for the treatment outcome of cancer radiotherapy

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Radiotherapy is a central component of multi-modal cancer therapy. The induction of tumor cell death and the abrogation of clonogenic tumor cell survival are considered to be central determinants of its therapeutic success. At the same time, radiotherapy damages cells of the normal tissue, thus giving rise to acute and chronic radiation injury. On the subcellular level ionizing radiation induces DNA damage leading to the activation of the highly sophisticated and finely tuned signaling cascade of the DNA damage response and – depending on the extent of damage – to transient or permanent cell cycle arrest, and/or other cell fate decisions, respectively. However, these cell fate decisions reveal a wide range of heterogeneity and dynamics depending on physical (radiation quality, dose, etc.), cell biological (origin of the cell, genetic repertoire, cell cycle phase, cell state, etc.), microenvironmental (oxygenation, nutrient supply, pH, etc.), and systemic (overall condition, age, sex, time-of-day, etc.) parameters and have distinct cell autonomous and non-cell autonomous consequences with large impact on the treatment success and adverse side effects. The long-term goal of our work is to understand the mechanistic drivers of this heterogeneity and to develop and evaluate combined modality radiotherapy approaches personalized towards cell fate-related vulnerabilities.