Targeting Survival Kinase DYRK1B: A novel approach to overcome radiotherapy-related treatment resistance

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Abstract

Dual-specificity tyrosine-regulated kinases (DYRKs) belong to the DYRK subfamily of proteins, which is composed of five members in humans. DYRKs are involved in cancer-associated processes by phosphorylating a wide range of proteins. DYRK1A and DYRK1B are phylogenetically closer and share substrates, although they are not functionally redundant. While DYRK1A has been primarily investigated for its involvement in neurological disorders, such as Alzheimer's disease and Down Syndrome, its involvement in tumor initiation and progression is controversial. On the other hand, accumulating evidence support that DYRK1B is a pro-oncogenic kinase, which is upregulated or activated under stress conditions (e.g. hypoxia, serum deprivation) in cancer cells enhancing survival and mediating treatment resistance. Previous publications have shown a synergistic effect of inhibiting DYRK1B with a kinase inhibitor together with chemotherapy. However, a combined treatment modality with radiotherapy has not been investigated so far. DYRK1B is known as a negative regulator of the cell cycle by counteracting the G0/G1-S transition (e.g. by the phosphorylation of p27Kip1 and cyclin D1) and enhances cell survival due to the upregulation of certain anti-oxidant genes (e.g. ferroxidase and superoxide dismutase 2 and 3 (SOD2, SOD3)) controlling ROS levels in quiescent tumor cells. Furthermore, DYRK1B has also been identified as a mediator of transcription repression on damaged chromatin, orchestrating double-strand break (DSB) repair and chromosomal stability. Therefore, we hypothesize that the inhibition of DYRK1B combined with ionizing radiation (IR) could enhance tumor killing in radioresistant tumor areas.

In my colon and osteosarcoma-oriented project, we investigate the combined treatment modality of ionizing radiation with a highly specific DYRK1B-kinase inhibitor using both 2D and 3D-tumor cell culture systems, including spheroids and patient-derived organoids. Of note, the DYRK1-kinase inhibitor only minimally affects the proliferation of primary fibroblast and endothelial cells. We are currently investigating the (supra-) additive effect of combining both treatment modalities, the role of starvation, the influence on the cell cycle, and the affected downstream signaling on inhibition and downregulation of DYRK1B-kinases alone and in combination with irradiation.