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Targeting Ras-MAPK Pathway to Enhance Radiosensitivity in Colorectal Cancer Cell Lines

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Radiotherapy plays a central role in neoadjuvant treatment of locally advanced rectal cancers. However, intrinsic radioresistance of cancers is a major clinical challenge which limits the therapeutic efficacy. Therefore, there is a high demand for radiosensitizers that can be used to improve the treatment of rectal cancers. Aberrant Ras-MAPK signaling is a hallmark of colorectal cancer (CRC). The impact of Ras-MAPK signaling on cellular response to radiation in CRC and the therapeutic value of targeting the pathway to increase radiosensitivity is unclear. The aim of my thesis is to investigate if pharmacological inhibition of the Ras-MAPK pathway at different levels can sensitize CRC cells to ionizing radiation (IR) and to determine potential underlying mechanisms.

Using short-term viability and long-term colony formation assays with different inhibitors of the Ras-MAPK pathway, I showed that the clinically approved MEK1/2 inhibitor (MEKi) trametinib exhibits strong radiosensitizing effects in three colorectal cancer cell lines. The phenotypical effect of MEKi was comparable to the known radiosensitizer nutlin-3A, an inhibitor of MDM2/p53 interaction, but was achieved at much lower drug concentrations. Mechanistically, two distinct mode-of-actions were identified that underlie the radiosensitizing effect. First, immunoblotting revealed that IR induced a transient activation of Ras-MAPK signaling in all CRC cell lines, with increased levels of ERK1/2 phosphorylation. Treatment with MEKi at low nanomolar concentrations efficiently suppressed this IR-induced activation. Secondly, γH2AX foci assay and immunoblotting demonstrated that MEK inhibition did not affect the number of IR-induced DNA double strand breaks. Instead, MEKi selectively downregulated protein levels of two central components of the cellular DNA damage repair machinery, RAD51 and DDB2. This downregulation was not mediated by transcriptional repression and could not be rescued by inhibition of proteasomal degradation. In summary, MEK inhibition was discovered as a novel approach to enhance radiosensitivity in CRC via interference with IR-induced DNA damage repair. These findings may contribute to improving clinical response in patients receiving radiotherapy for rectal cancer.