The Effects of Radiotherapy on the Presentation of Phosphorylated Antigens by Cancer Cells

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Abstract: Radiotherapy (RT) impacts anti-tumor immunity by several mechanisms. The effects of RT on tumors include the regulation of genes in many signaling pathways that are mutated to give survival advantage, e.g., DNA repair- and antigen presentation-related genes. Recently, it has been discovered that major histocompatibility complex class-I (MHC-I) molecules on the surface of both virally infected cells and cancer cells can present peptides from proteins that have been phosphorylated. This raises the possibility that the immune system can attack virally infected cells or cancerous cells based on their differential activation of these pathways, as the immune system has T-lymphocytes primed to recognize these abnormal cells and kill them.

It has been shown that phosphorylated peptides are an important target of anti-tumor T cell responses. Herein our main hypothesis is that radiation therapy (RT), by changing the cellular phosphoproteomics, will also qualitatively and quantitatively change the number of phosphopeptides presented by MHC-I molecules. As such, the purpose of this grant is to identify phosphorylated peptides presented on MHC-I proteins at the surface of irradiated cancer cells and compare them to non-irradiated cancer cells. Our plan is to characterize the phosphorylated antigens presented on MHC-I in irradiated cancer samples, by using highly sensitive mass-spectrometry and computational analysis. Then, we will use genomics and proteomics data to connect the observed phosphorylated antigens to related signaling events tied to those specific phosphorylated peptides.

The overall goal is to identify phosphopeptides that can induce a robust anti-tumor T cell response via activated and cytotoxic T cells, promote antigen spread, and generate anti-tumor immune responses which will lead to the regression of non-irradiated lesions. Since it is possible to irradiate multiple tumors, this strategy could be employed in combination with vaccination to treat patients with metastatic disease.