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Fractionated radiation therapy increases Siglec-7 and -9 ligands expression in cancer cells

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Purpose: Radiation therapy is a standard therapy option in many cancer types. Recently, improved effects were observed when radiation therapy was combined with immunotherapy such as immune checkpoint inhibitors. Indeed, radiation therapy has a systemic immunomodulatory effect by stimulating cancer immunity cycle through the release of cancer antigens and improving immune infiltration. Besides, radiation can also inhibit immune response by an increase in expression of immune suppressor ligands including PD-L1. Siglec ligands are molecules expressed on cancer cells that inhibit immune response by binding to the receptors on immune cells. The purpose of this project is to study the role of Siglec ligands in the context of radiation therapy and immune response.
Methods: We used a panel of human and mouse cancer cell lines (LN18, LN229, SKOV-3, K562, P815) to study Siglec ligands expression after single dose (2, 5, 10 Gy) and fractionated (5x2Gy) radiation. Cells were irradiated and Siglec ligands expression was measured via flow cytometry. Mean fluorescence intensity was quantified. To assess the impact of irradiation on immune response, cells were irradiated and tested in co-culture with NK and CAR T cells. Cells lacking Siglec ligands due to neuraminidase treatment or Cytidine Monophosphate N-Acetylneuraminic Acid Synthetase (CMAS) knockout (KO) were used as negative controls.
Results: Our results indicate an increase of Siglec-7 and -9 ligands expression in the studied cancer cell lines upon radiation therapy, especially after fractionated regimen. Due to this increase in Siglec ligands, fractionated radiation therapy of LN18 and K562 decreased NK cell-mediated anti-tumor responses, whereas neuraminidase treatment of cancer cells improved NK-cell killing. In addition, CAR T-mediated killing was more effective in CMAS KO cells and radiation sensitivity was increased in CMAS KO cell lines.
Conclusion: This study is the first to show that radiation can activate immune suppressor Siglec ligands expression on the surface of cancer cells. This effect may impair concurrent immune activation, hence should be addressed by combining radiation with therapeutics that block Siglec-Siglec ligands axis.

Primary authors: HOVHANNISYAN, Lusine (University of Bern, University Hospital Bern); Mrs HUGONNET, Marjolaine; Dr MEDOVÁ, Michaela; VON GUNTEN, Stephan; ZIMMER, Yitzhak

Presenter: HOVHANNISYAN, Lusine (University of Bern, University Hospital Bern)

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