INVESTIGATING THE ABILITY OF TUMOR CELL-DERIVED TYPE I INTERFERON TO POTENTIATE ANTI-OVARIAN CANCER IMMUNE RESPONSES

Fiona Chatterjee*, Ellen Duong, Arjun Bhutkar, Stefani Spranger. Massachusetts Institute of Technology, Cambridge, MA, United States

Background Ovarian cancer is the fifth leading cause of cancer-related death in women in the United States. The standard of care for ovarian cancer remains surgical debulking and chemotherapy. While this treatment is effective initially, most patients experience relapse within five years of initial diagnosis, and recurrent tumors are often chemotherapy-resistant. Ovarian cancer generally induces extremely poor immune responses (characterized by poor effector immune cell infiltration and a lack of innate immune activation), and thus, efforts to induce robust anti-tumor immunity will require potent activation of the innate immune system. The period between the end of chemotherapy and disease recurrence, often termed first remission, presents a unique opportunity to induce anti-tumor immune responses to delay or even prevent tumor regrowth. Recent work in our lab has demonstrated that inducing tumor cell-derived type I interferon (IFN-I) can rescue dysfunctional anti-tumor immune responses by activating a specific dendritic cell subset that subsequently activates CD8+ T cells. In this project, we aim to investigate how tumor cell-derived IFN-I induction impacts anti-ovarian cancer immunity.

Methods To model first remission and the subsequent tumor regrowth, we inoculated syngeneic ovarian cancer cells into the intraperitoneal spaces of mice, which resulted in the development of solid metastatic tumors and ascites. We utilized two cell lines: BPPNM, driven by Brca1−/− p53−/− R172H Pten−/− N1−/− and MycOE, to model homologous recombination-deficient (HR-deficient) tumors and CPAK, driven by Ccne1OE p53−/− R172H Akt2OE and KrasG12V, to model homologous recombination-proficient (HR-proficient) tumors. Interferon beta and interferon-stimulated gene transcript levels were assessed by qPCR. Dendritic cell and T cell infiltration were assessed by flow cytometric analysis of BPPNM and CPAK tumors 14 days after injection into wildtype mice.

Results BPPNM tumor cells, which are HR-deficient, expressed higher levels of interferon beta and downstream signaling target transcripts compared to CPAK tumor cells, which are HR-proficient. Flow cytometry immunophenotyping of BPPNM and CPAK tumors revealed that BPPNM tumors were more infiltrated by DC1, DC2, ISG+ DC, CD8+ T cells, and CD4+ T cells. Finally, wildtype C57BL/6 mice implanted with BPPNM tumors displayed extended survival compared to mice implanted with CPAK tumors.

Conclusions Our data suggest that ovarian cancer cells with the ability to produce IFN-I induce more potent anti-tumor immune responses. Understanding how to induce IFN-I production in HR-proficient ovarian cancer could not only improve our knowledge of interactions between ovarian cancer cells and immune cells but also lead to novel therapeutic strategies for ovarian cancer.

Acknowledgements We would like to thank MIT’s Department of Comparative Medicine and the Koch Institute’s Swanson Biotechnology Core Facility. This work was supported by Break Through Cancer.

REFERENCES

Ethics Approval All mouse experiments were approved by MIT’s Committee on Animal Care (CAC) – PHS Animal Welfare Assurance # D16-00078 (A3125-01).