1101 ACTIVATION OF MYELOID CELLS SUPPRESSES METASTATIC OVARIAN CANCER VIA TUMORICIDAL NEUTROPHILS AND IL-27-SECRETING MACROPHAGES

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Background Eradication of intraperitoneal metastasis of ovarian cancer (OC) remains an unmet challenge. Current T cell-mediating immunotherapies have not been applied to OC due to lack of efficacy in most patients. Immunosuppressive myeloid cells associate with tumor progression and treatment resistance in the metastatic sites of OC. The purpose of this study is to develop a novel immunotherapy that activates myeloid cells with the goal of eradicating metastatic OC.

Methods Recently established, clinically relevant murine OC cells, that are homologous recombination proficient, KPCA (*KRAS^{G12V}Trp53^{R172H}Ccne1^{OE}Akt2^{OE}*), were intraperitoneally injected to build the murine metastatic OC model. β-glucan and interferon (IFN) γ were used to activate myeloid cells. β-glucan is a yeast cell wall polysaccharide that is currently in clinical trials to treat multiple cancers. It canonically activates myeloid cells through the Dectin-1 pathway and induces infiltration of monocytes and neutrophils. IFNγ activates macrophages to an anti-tumor status. Tumor burden and tumor microenvironment in the ascites and omentum were evaluated using bioluminescence imaging, confocal imaging, flow cytometry, and single-cell RNA sequencing (scRNA seq) to investigate whether and how β-glucan modulates metastatic OC with or without IFNγ. Furthermore, OC patient survival was analyzed based on gene expression using public dataset. Finally, combination of myeloid cell activation with carboplatin was tested.

Results β-glucan alone was efficient in clearing ascites, although it did not affect total metastases. On the other hand, combining β-glucan with IFNγ (β-glucan/IFNγ) not only cleared ascites but also reduced total metastases compared to PBS-, β-glucan-, or IFNγ-treated mice. This anti-tumor immunity required T cells and non-tumor IFNγ signaling in the host. scRNA seq of omental tumors revealed β-glucan/IFNγ induced the enrichment of a unique subset of neutrophils and macrophages compared to other groups. The neutrophil subset upregulated *Camp* and *Ltf*, which are granule proteins known to have tumoricidal function. Eukaryotic initiation factor-2 signaling, which is associated with reactive oxygen species (ROS) production, is the most upregulated pathway in the neutrophil subset. The macrophage subset selectively expressed interleukin (IL)-27, which has anti-tumor potential mainly through T cells. Blocking IL-27 significantly impaired the anti-tumor response of β-glucan/IFNγ. OC patients with high expression of these genes identified in the novel myeloid cell subsets correlate with better overall survival. Finally, combining β-glucan/IFNγ with carboplatin nearly eradicated chemoresistant KPCA tumors.

Conclusions β-glucan/IFNγ suppressed metastatic OC enriching anti-tumor myeloid cell populations. Combination therapy of this myeloid cell activation and standard-of-care chemotherapy could potentially transform treatments against metastatic OC.

Ethics Approval This study is approved by IACUC (#201536).

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