975 ACTIVATION OF MYELOID CELLS BY β-GLUCAN CLEARS DISSEMINATING OVARIAN CANCER CELLS FROM THE PERITONEAL FLUID THROUGH MACROPHAGE-MEDIATED CLOTTING AND OMENTUM NEUTROPHIL EXTRACELLULAR TRAPS

[1]Brennah Murphy*, [1]Taito Miyamoto, [1]Bryan Manning, [2]Rugang Zhang, [1]Yulia Nefedova, [1]Nan Zhang. [1]*The Wistar Institute, Philadelphia, PA, USA*; [2]*MD Anderson Cancer Center, Houston, TX, USA*

Background Ovarian cancer (OvCa) is the most lethal gynecological cancer and the fifth leading cause of cancer-related deaths in women. Despite an initial positive response to therapy, most patients relapse and present with chemotherapy resistance. The prognosis for recurrent disease is poor, with a 5-year survival rate of < 30%. One contributor to disease recurrence and therapy resistance is the presence of disseminated cancer cells that remain in the peritoneal fluid after treatment. A growing body of evidence suggests that these cells exhibit dormancy characteristics that render them resistant to most therapies. Moreover, cancer cells in fluid are unable to be surgically resected. Because 75% of relapsed patients present with therapy-resistant intraperitoneal disease, developing new strategies to effectively target disseminating OvCa cells in the peritoneal fluid is crucial for the effective treatment of OvCa. Two key players in peritoneal immunity, the omentum and peritoneal resident macrophages (PRMΦs), are known to sequester pathogens in the peritoneal fluid and coordinate an inflammatory immune response in the peritoneum. One such activator of peritoneal immunity is β-glucan, a sugar found on the cell walls of yeasts.

Objective To target disseminating OvCa cells in the peritoneal fluid by activating myeloid cells in the peritoneal cavity via intraperitoneal administration of β-glucan.

Methods C57bl/6J mice were injected with GFP-labeled murine OvCa cells (**KPCA**: $Trp53^{-/-R172H}Ccne1^{OE}Akt2^{OE}KRAS^{G12V}$) immediately followed by 500μg β-glucan (i.p.). Five hours later, mice were euthanized and their peritoneal lavage was analyzed for the presence of OvCa cells. To model advanced disease, Luciferase-KPCA cells were seeded in C57bl/6J mice one week prior to biweekly β-glucan treatment and imaged 3 weeks later.

Results First, we found that β-glucan was highly efficient in acutely clearing OvCa cells from the peritoneal fluid. Mechanistically, β-glucan captured free-floating OvCa cells into solid nodules through two non-redundant and equally important pathways: (1) an unexpected Dectin-1/SYK-independent, heparin-sensitive pathway that was mediated by PRMΦ aggregation in the peritoneal fluid; and (2) a Dectin-1/SYK/PAD4-dependent pathway that was mediated by neutrophil extracellular traps in the omentum. Second, we found that β-glucan also completely cleared cancer from the peritoneal fluid and prevented ascites accumulation in advanced disease. Combining β-glucan with IFNγ (β-glucan/IFNγ) not only cleared ascites but also regressed omentum tumors and prevented intraperitoneal metastases as compared to PBS-, β-glucan-, or IFNγ-treated mice.

Conclusions Intraperitoneal injection of β-glucan clears OvCa cells from the peritoneal fluid and has therapeutic potential to control OvCa metastasis.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0975

J Immunother Cancer: first published as 10.1136/jitc-2023-SITC2023.0975 on 2 November 2023. Downloaded from http://jitc.bmj.com/ on March 3, 2024 by guest. Protected by copyright.