SELECTIVE INTERNALIZATION OF MICROBIAL MIMETIC MESOPOROUS SILICA NANOPARTICLES BY MYELOID-DERIVED SUPPRESSOR CELLS WITH TRAFFICKING TO TUMOR-BURDENED TISSUES IN A MOUSE MODEL OF OVARIAN CANCER

Benjamin R Marwedel, Erica Flores, John O-Rourke, Eric Bartee, Achraf Noureddine, Rita E Serda.

University of New Mexico Comprehensive Cancer Center, Albuquerque, NM, USA; Bennubio, Albuquerque, NM, USA

Background For the majority of women with ovarian cancer, the disease remains undetectable until later stages, where it is largely incurable. Fortunately, some patients have experienced remarkable responses to immune therapy. We have fabricated mesoporous silica nanoparticles (MSN) that present the Toll-like receptor (TLR) agonists polyethyleneimine (PEI), CpG oligonucleotide, and monophosphoryl lipid A (MPL-A), creating microbial mimetic MSN. The efficacy and fate of these MSN following intraperitoneal (IP) administration into the tumor microenvironment was studied in a mouse model of serous epithelial ovarian cancer.

Methods Fluorescent MSN or MSN-PEI-CpG-MPL-A (100 or 600 nm) were IP injected into mice 19 days post IP BR5-Akt-Luc cancer challenge. Cell association in ascites fluid and tissues were studied from 10 minutes to 24 hours post injection using fluorescent animal and tissue imaging (IVIS Spectrum), high throughput flow cytometry (Cytek), Velocyt acoustic cytometry (Bennubio), and confocal microscopy (Leica SP8). In addition, the therapeutic efficacy of MSN-PEI-CpG-MPL-A was assessed following 2 weekly injections beginning 4 days post tumor challenge by measuring weight, tumor bioluminescence (IVIS Spectrum), and survival.

Results MSN were rapidly (within 10 minutes) associated with ascites spheroids, followed by steady declines within the first hour (figure 1). In mice, two major subsets of myeloid-derived suppressor cells (MDSCs) exist, monocytic (M-MDSC) and polymorphonuclear (PMN-MDSC) with surface expression of CD11b+Ly6C++Ly6G- and CD11b +Ly6CloLy6G+, respectively. Within one-hour post IP injection in mice, MSN colocalized with CD11b +Ly6C+Ly6G- and CD11b +Ly6Clo-Ly6G+ cells. Within 24 hours of injection, approximately 85% of MSN were located in peritoneal tumor-burdened tissues. Tumor-specific accumulation was independent of particle size (100 vs 600 nm) and the presence of surface TLR agonists. Studies also examined the therapeutic impact of adjuvanted MSN in mice with ovarian cancer. IP delivery of MSN-PEI-CpG-MPL-A or MSN-PEI-CpG (2 weekly doses) reduced tumor burden, resulting in tumor-free survival.

Conclusions The tumor immune microenvironment is a key contributing factor to tumor progression. Immature myeloid cells become MDSC, supporting tumor progression by suppressing T cells. Specific localization of MSN-PEI-CpG-MPL-A in MDSCs and functional plasticity within this population provides opportunities to covert tumor-promoting myeloid cells into tumor-fighting immune cells.

Acknowledgements We are grateful for assistance from the University of New Mexico Comprehensive Cancer Center Animal Models (Irina Lagutina and Lillian Fitzpatrick), Fluorescence Microscopy (Michael Paffett), Flow Cytometry (Wade Johnson) and Histology Shared Resources, supported by NIH grant NCI 2P30 CA118100.

REFERENCES


Ethics Approval The study was approved by the University of New Mexico IACUC, approval number 20–201067-HSC.

Myeloid (control)  
MSN (10 min)  
Time course

Abstract 1218 Figure 1 MSN temporally accumulate in ascites spheroids in mice with ovarian cancer. Velocity imaging of CD11b+ myeloid cells (left, yellow) and MSN (middle, green) in ascites spheroids 10 minutes post control PBS or MSN intraperitoneal (IP) injection, respectively. MSN content in small spheroids across time post IP injection is shown to the right.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1218