Elizabeth L. McMichael, B.S.
PhD Candidate

“Role of Interleukin-21 and the Interleukin-21 Receptor in Natural Killer Cell Activation”

April 13, 2016
The James L035
2:00 pm
VITA

December 19, 1989 ........................................ Born – Rochester, Pennsylvania

2012 ................................................................ B.S., Biochemistry,
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2012 to present ............................................... Graduate Research
Associate, The Ohio State University

COMMITTEE MEMBERS

Dr. William E. Carson, III, M.D., Advisor

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ABSTRACT

Natural killer (NK) cells are innate immune effector cells that play a crucial role in cancer rejection and immunosurveillance. Importantly, NK cells express the Fcγ receptor IIIa (FcγRIIIa) and various cytokine receptors, which can be activated upon encountering antibody-coated targets and cytokines in the tumor microenvironment.

Previous work from our group reported that CD56dimCD16+ NK cells co-stimulated via the Fc receptor (FcR) and the interleukin (IL)-12 receptor leads to the expression of genes encoding cytotoxicity receptors, apoptotic proteins, intracellular signaling molecules, and cytokines that could mediate enhanced cytotoxicity and interactions with other immune cells within inflammatory tissues. Microarray gene expression analysis revealed that the IL-21 receptor (IL-21R) was upregulated following FcR stimulation alone. We hypothesized that the upregulation of IL-21R occurs in a time-dependent fashion and that the upregulation of IL-21R on the surface of NK cells would lead to enhanced NK cell-mediated effector functions. The IL-21R was found to be upregulated on NK cells following immobilized-IgG treatment by RT-PCR, immunoblot, and flow cytometry, with expression peaking at 8 hours post-stimulation. The upregulation of the IL-21R on the surface of NK cells was found to be mediated through the MAPK pathway, as an inhibitor of a downstream member of the pathway, ERK, resulted in the inhibition of IL-21R expression. The upregulation of the IL-21R on the surface of NK cells sensitized them to IL-21, as the addition of IL-21 to FcR-stimulated NK cells increased the phosphorylation of STAT1 and STAT3, as determined by flow cytometry and immunoblot analysis. The addition of IL-21 to FcR-stimulated NK cells also increased NK cell-mediated tumor cell apoptosis of trastuzumab-coated SkBr3 tumor cells, and increased the production of IFN-γ by NK cells co-cultured with trastuzumab-coated SkBr3 tumor cells.

In an effort to extrapolate our findings to the context of antibody-therapy, we utilized a combination therapy approach with IL-21 and cetuximab in pancreatic cancer. We hypothesized that IL21 would enhance the NK cell response to cetuximab-coated, EGFR-positive pancreatic tumor cells, irrespective of KRAS mutational status. NK cells from healthy donors and pancreatic cancer patients were able to lyse cetuximab-coated wild-type and
mutant KRAS cell lines to a significantly higher degree following IL-21 treatment, as compared to controls. In response to cetuximab-coated pancreatic tumor cells, IL-21 treated NK cells secreted significantly higher levels of IFN-γ, released higher levels of chemokines, induced greater chemotaxis of T cells and exhibited enhanced signal transduction via the MAPK and Jak/STAT pathways. Treatment of mice bearing subcutaneous or intraperitoneal EGFR-positive/KRAS mutant pancreatic tumor xenographs with mIL-21 and cetuximab led to significant inhibition of tumor growth as compared to control conditions. Results suggest that cetuximab treatment in combination with IL-21 can greatly enhance NK cell FcR-mediated effector functions and stimulate a significant anti-tumor response against EGFR-positive pancreatic cancers that bear a mutated KRAS gene.

Taken together, these data suggest that a combinatorial approach to the treatment of cancer could be advantageous. These studies indicate that the anti-tumor effects observed with cetuximab on EGFR-positive tumor cells can be enhanced by the addition of IL-21 and provide a rationale for the co-administration of NK cell-activating cytokines with therapeutic antibodies. Further understanding of the exact mechanisms of action for these combinatorial approaches may allow for more targeted treatments and decreased detrimental effects of unnecessary therapies.
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