Aaron Robert Victor, B.S.
PhD Candidate

“Regulation of IL-22 production by immature NK cells and CD16 expression during their maturation”

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VITA

June 30, 1986 . . . . . . . . Born – Wheeling, West Virginia

May 2009 . . . . . . . . . . . . . . . . . . . . . . . . . . . . B.S. in Biochemistry, Case Western Reserve University

COMMITTEE MEMBERS

Michael A. Caligiuri, MD

Mark D. Wewers, MD

Natarajan Muthusamy, DVM, PhD

Jianhua Yu, PhD
ABSTRACT

Natural killer (NK) cells are innate immune cells that play different roles depending on their stage of development. NK cells develop through five stages that can be identified in secondary lymphoid tissue. Stage 3 immature NK (iNK) cells play important roles in homeostasis and defense against infection. They produce the cytokines interleukin (IL)-17 and IL-22 and express the transcription factor RORγt. Because IL-22 is critical to the antibacterial immune response, we sought to identify factors that can promote proliferation and induce or maintain IL-22 production by iNK cells and determine a molecular mechanism for this process. We identified IL-18 as a cytokine that cooperates with an iNK cell survival factor, IL-15, to induce proliferation of iNK cells, as well as induce and maintain IL-22 production. We found that this effect was mediated through the NFκB pathway. Furthermore, we observed that IL-18-producing CD11c+ dendritic cells are found proximal to iNK cells in human tonsil. Stage 4 and 5 mature NK cells are distinguished from iNK cells in several ways. Mature NK
cells play roles in antiviral and antitumor responses. They express CD94, produce the cytokine IFN-γ, and display cytotoxic activity. Stage 5 NK cells are distinguished from stage 4 NK cells by expression of CD16. Because very little is known about how CD16 is regulated, we also sought to identify pre-translational mechanisms governing this process. First, we used chromatin immunoprecipitation (ChIP) to test for the association of STAT1, GATA3, SRF, and SP1 with the CD16 promoter. While each of these transcription factors has a consensus binding sequence in the CD16 promoter, we did not find enrichment of any of these factors. We also investigated DNA methylation in the CD16 promoter and found that it was hypermethylated in stage 4 NK cells and hypomethylated in stage 5 NK cells. These data identify DNA methylation as a possible regulatory mechanism for CD16 expression in NK cells. Finally, we identified a microRNA, mir-218, that seems to negatively regulate CD16. Mir-218 reduces translation of mRNA when it recognizes the CD16 3’ untranslated region in the human embryonic kidney 293t cell line. Furthermore, we found evidence that mir-218 overexpression can reduce CD16 surface expression in mature NK cells; these data were confirmed
in monocytes. These data are the first to show evidence of direct regulation of CD16 at a pre-translational level. Taken together, these discoveries from different stages of NK cell development contribute important elements that may be applied in the future to improve therapeutic targets in a variety of disease settings.
RECENT ABSTRACTS AND PRESENTATION


RECENT PUBLICATIONS


FUTURE PLANS

After completing my PhD, I will return to finish medical school as a third year medical student as part of the Medical Scientist Training Program. Upon completing medical school I plan to go to residency. I have not decided on a specialty yet. I hope to pursue a career that combines clinical medicine and biomedical research. I am particularly interested in immunology and regenerative medicine.
Biomedical Sciences Graduate Program
1170 Graves Hall
333 W. 10th Avenue
Columbus, Ohio 43210