Alena Cristina Jaime-Ramirez
PhD Candidate

“The NK Cell-mediated Anti-tumor Effects of a Folate-conjugated Immunoglobulin are Enhanced by Cytokines”

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Meiling 234
9:00 am
VITA

September 1978 ............................................Born, El Paso, Texas
2001 ...............................................................Certificate in
Japanese Studies, University of Maryland University College-Asian Division, Okinawa, Japan
2004 ...............................................................A.A. Chemistry, MiraCosta College, Oceanside, California
2007 ...............................................................B.S. Biology, California State University San Marcos, San Marcos, California
2007- present .................................................Graduate Research Associate, Biomedical Sciences Graduate Program, The Ohio State University

COMMITTEE MEMBERS

William E. Carson III, M.D.
Pravin T. Kaumaya, Ph.D.
Balveen Kaur, Ph.D.
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AWARDS AND HONORS

2007 ...............................................................OSU Graduate Enrichment Fellowship, The Ohio State University
2008-2010 .....................................................NIH Fellow, Systems of Integrated Biology T32 Fellowship, The Ohio State University (T32 GM068412)

FUTURE PLANS

I plan to conduct post-doctoral research in the laboratory of Dr. Balveen Kaur.
In the future, I plan to continue research in the field of cancer immunotherapy and immunology.
Folate-conjugated Immunoglobulin are Enhanced by Cytokines. In preparation.


ABSTRACT

The anti-tumor effects of therapeutic monoclonal antibodies (mAb) may depend on immune effector cells that express Fc receptors (FcR) for immunoglobulin G. 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 a significant association between elevated IFN-γ levels in patients receiving Trastuzumab plus the cytokine interleukin-12 (IL-12) and more favorable outcomes in phase I clinical trials. We hypothesized that co-administration of IL-12 with an anti-HER2 mAb (4D5) would enhance the FcR-dependent immune mechanisms and IFN-γ production and contribute to its anti-tumor activity. We aimed to elucidate the cell type responsible for this elevated IFN-γ production and further determine how this subset affected combination therapy. Treatment with IL-12 and 4D5 significantly inhibited the growth of CT-26HER2, a murine cancer cell line that expresses human HER2. Combination therapy was associated with increased circulating levels of IFN-γ, MIG and RANTES. IFN-γ-deficient mice demonstrated that this cytokine was necessary for the observed anti-tumor effects of therapy with IL-12 plus 4D5. Dual therapy induced tumor necrosis and depletion studies confirmed that NK cells mediated the anti-tumor effects of this treatment combination.

In an effort to extrapolate our findings with other antibody and cytokine therapies, a novel folate immunoglobulin (F-IgG) construct was created to direct innate immune cells to folate receptor-expressing cancer cells. We hypothesized that F-IgG could bind to tumor cell folate receptors (FR) and mediate NK cell antibody dependent cell-mediated cytotoxicity (ADCC) and cytokine production, an effect that would be enhanced by cytokine therapy. F-IgG bound to both human KB and HeLa and murine
L1210JF FR over-expressing cancer cells. Recognition of F-IgG by NK cell FcyRIIIa receptors led to phosphorylation of the ERK transcription factor and increased NK cell CD69 expression. NK cell lysis of KB tumor cells was synergistically enhanced following treatment with IL-2, IL-12, IL-15 or IL-21. Moreover, NK cell production of IFN-γ, MIP-1α and RANTES was significantly increased in response to F-IgG-coated KB target cells in the presence of IL-12. Studies in a murine leukemia model confirmed the anti-tumor activity and intra-tumoral localization of F-IgG, an effect that was enhanced by the NK cell-activating cytokine IL-12. As was observed with IL-12 and 4D5 dual therapy, the anti-tumor effect of F-IgG and IL-12 was dependent on NK cells, and led to decreased tumor cell proliferation in these studies.

Taken together, these data suggest that tumor regression in response to 4D5 or F-IgG plus IL-12 is mediated through the NK cell compartment. These studies indicate that the anti-tumor effects observed with these antibodies can be augmented with various cytokines 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.

RECENT PUBLICATIONS


