Kavin Fatehchand
PhD Candidate

Enhancing monocyte effector functions in antibody therapy against cancer

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Davis Heart and Lung Research Institute 165
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VITA

May 24, 1992..................Born – Chennai, India

2009-2013.....................B.S. Biology, Emory University

2013-present..................Medical Scientist Training Program,
                           The Ohio State University

COMMITTEE MEMBERS

Susheela Tridandapani, Ph.D., Advisor

       John C. Byrd, M.D.

       Larry Schlesinger, M.D.

       Tatiana Oberyszyn, Ph.D
ABSTRACT

The immune system plays an important role in the clearance of pathogens and tumor cells. However, tumor cells can develop the ability to evade immune destruction, making the interaction between the immune system and the tumor an important area of research. The overall goal in my graduate studies, therefore, was to find different ways to enhance the innate immune response against cancer cells. I will describe below my findings to this end.

First, I focused on monoclonal antibody therapy with reference to the role of monocytes/macrophages as immune effectors. Tumor-specific antibodies bind to cancer cells and create immune-complexes that are recognized by IgG receptors (FcγR) on these immune effector cells. FcγRIIb is the sole inhibitory FcγR that negatively regulates monocyte/macrophage effector responses. In the first part of this study, I examined the ability of the TLR4 agonist, LPS, to enhance macrophage FcγR function. I found that TLR4 activation led to the down-regulation of FcγRIIb through the activation of the March3 ubiquitin ligase.

Although monocytes play an important role in tumor clearance, tumor cells take on a crucial role in immune cell evasion. Acute Myeloid Leukemia is a hematologic malignancy caused by the proliferation of immature myeloid cells, which accumulate in the bone marrow, peripheral blood, and other tissues. The progression of AML is largely dependent on immune cell evasion by AML blasts. Since AML cells are of myeloid origin, I next focused on shifting this blast phenotype from an immunosuppressive to effector-like phenotype. In these studies I found that AML blasts can be shifted into a more anti-tumor/M1 by IFNγ. Importantly, IFNγ was also able to up-regulate FcγRI and the antibody target CD38. When AML blasts were treated with the combination of IFNγ and the anti-CD38 antibody, daratumumab, we saw significant increases in cytotoxicity, suggesting that these cells were killing each other, which we call daratumumab-mediated fratricide.
Extending these observations, I examined whether Type 1 IFNs, much like IFNγ, could initiate daratumumab-mediated fratricide in AML. Type 1 IFNs have been used in AML clinical trials before, however, they lose their effect in patients due to their short serum half-life. In order to overcome this problem, I explored the possibility of increasing endogenous Type 1 IFNs by targeting plasmacytoid Dendritic Cells (pDCs) through TLR 7/8 stimulation. Consistent with this notion, R848-treated pDCs had increased markers of pDC activation and an enhanced Type 1 IFN response. IFNβ was also able to shift AML cells to more of an M1 phenotype, increase the antibody target CD38, and enhance daratumumab-mediated toxicity. These findings suggest that it is possible to overturn the tolerogenic phenotype of pDCs in AML, and also demonstrate a possible means of enhancing endogenous Type 1 IFN production for the purpose of inducing daratumumab-mediated fratricide of AML blasts.

In the final part of my graduate research I explored the utility of natural products in AML therapy. To this end, I examined the effect of the natural product, Active Hexose Correlated Compound (AHCC) on AML. I found that AHCC induced extrinsically-mediated apoptosis in AML cells. When tested in a murine engraftment model of AML, AHCC led to significantly increased survival time and decreased blast counts. These results lend support for the further investigation of AHCC as a potential adjuvant for the treatment of AML.

Taken together, these studies have uncovered different ways to target the innate immune system, the immunosuppressive tumor cell, or both in order to fight cancer.
RECENT ABSTRACTS AND PRESENTATION

OSUWMC Trainee Research Day – Columbus, OH - 04/09/2014-04/10/14: Mechanisms of FcγRIIb downregulation- Implications for Monoclonal Antibody-therapy for Cancer


DHLRI Research Day – Columbus, OH - 09/23/2015: Mechanisms of FcγRIIb downregulation- Implications for Monoclonal Antibody-therapy for Cancer

OSUCCC James 15th Annual Scientific Meeting – Columbus, OH – 04/22/2016: Interferon-γ Promotes Antibody-mediated Fratricide of Acute Myeloid Leukemia Cells

Gordon Research Conference – Waterville Valley, NH – 6/11/17-6/16/17: Shifting the plasmacytoid dendritic cell phenotype in Acute Myeloid Leukemia to enhance daratumumab-mediated fratricide

Autumn Immunology Conference – Chicago, IL – 11/17/17-11/20/17: Plasmacytoid Dendritic Cells Enhance AML Fratricide
RECENT PUBLICATIONS


Ren, L., Campbell, A., Fang, H., Gautam, S., Elavazhagan, S., Fatehchand, K., Mehta, P., Stiff, A., Reader, B. F., Mo, X., Byrd,


**Fatehchand, K** et al. Reprogramming the plasmacytoid dendritic cell phenotype in Acute Myeloid Leukemia to enhance daratumumab-mediated fratricide (*in preparation*).
AWARDS AND HONORS

NIH F30 Fellowship

FUTURE PLANS

I plan on entering my last two years of medical school this upcoming Spring. As far as residency, I will most likely pursue a career in Internal Medicine. The fields of Gastroenterology, Allergy Medicine, and Hematology-Oncology all spark my interest. My PhD training will help me pursue my goals as a physician-scientist, focusing on both clinical medicine and translational research.
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