Andrew Stiff
PhD Candidate

Enhancing Immune Therapy for Cancer by Targeting Myeloid Derived Suppressor Cells

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James L045
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VITA

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2009 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Bachelor of Science, The University of Pittsburgh

2011-2013 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Medical Student, The Ohio State University

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ABSTRACT

The last two decades have yielded unprecedented successes in the treatment of numerous types of cancer. Monoclonal antibodies (mAb) are one the key molecules underlying this success. mAbs work in part by activating the immune system to target tumor cells, and they can be broadly divided into two groups based on how they do this. The first group consists of antibodies such as trastuzumab that contain Fc domains that are recognized by the FcγRIIIa receptor (FcR) expressed by innate immune cells including natural killer (NK) cells. FcR stimulation activates the ability of NK cells to directly kill antibody coated tumor cells through a process termed antibody dependent cellular cytotoxicity (ADCC) and secrete cytokines with anti-tumor properties. Other mAbs are known as immune checkpoint inhibitors such as pembrolizumab. These mAbs target inhibitory immune checkpoint receptors or ligands that inhibit the anti-tumor function of T cells. Blocking these inhibitory signaling pathways results in enhanced anti-tumor T cell function. For mAbs to be clinically effective the anti-tumor effector function of the immune cell population they target must be intact.

Unfortunately, in the setting of cancer there is an expansion of immune suppressive myeloid cells including myeloid derived suppressor cells (MDSC). MDSC inhibit the function of both NK cells and T cells by a number of mechanisms that are independent of checkpoint receptors. As a result MDSC have become an attractive target to enhance the efficacy of immune based mAb cancer therapies. To date most work regarding targeting MDSC has focused on enhancing T cell directed immune checkpoint blockade. Given the significant role NK cells play in the response to FcR stimulating mAbs we sought to investigate what impact MDSC have on NK cell FcR mediated functions and the response to FcR stimulating mAbs. This work showed that co-culture of MDSC with NK cells from patients with multiple types of cancer inhibited NK cell FcR mediated ADCC, cytokine production, and signal transduction. Furthermore, it was found that nitric oxide (NO) production by MDSC was critical to this inhibitory effect. Finally, in an immune competent breast cancer model depletion of
MDSC or treatment with the iNOS inhibitor L-NIL significantly improved the anti-tumor effect of trastuzumab. To our knowledge this work is the first to demonstrate that MDSC are capable of inhibiting FcR mediated NK cell function and antagonizing the efficacy of FcR stimulating mAbs. This work provides rationale for combining FcR stimulating mAbs with agents capable of depleting MDSC or inhibiting their ability to produce NO in clinical trials.

An obvious step in the development of such combination therapies is to identify molecules that can effectively target MDSC. Ibrutinib is an inhibitor of Bruton’s tyrosine kinase (BTK) that is FDA approved for the treatment of B cell malignancies. Given the known role of BTK in the development and function of multiple myeloid cell lineages it was hypothesized that inhibition of BTK might impair MDSC expansion or immune suppressive function. MDSC from multiple murine tumor models and from patients with melanoma were found to express BTK. Treatment of MDSC with ibrutinib impaired their ability to produce cytokines, migrate, and produce NO. Importantly, ibrutinib significantly reduced the ability of MDSC to suppress CD8$^+$ T cell proliferation. Finally, ibrutinib was found to reduce the frequency of MDSC in vivo in multiple murine tumor models and enhance the efficacy of an anti-PDL1 mAb. Taken together this work suggests that ibrutinib could have broader applications in cancer therapy as part of a combination therapy to enhance mAb immune checkpoint blockade.

In sum, this work highlights the ability of MDSC to antagonize the efficacy of mAb therapy. The ability of MDSC to antagonize FcR mediated NK cell functions and the response to FcR stimulating mAbs via the production of NO is characterized, to our knowledge, for the first time. This discovery suggests that therapeutic strategies targeting MDSC could be an effective way to enhance the efficacy of these mAbs. In addition, BTK is identified to be important to regulating MDSC expansion and immune suppressive function suggesting BTK inhibitors can be effective agents to target MDSC. This provides rationale for including these already FDA approved agents into combination therapies with mAbs for rapid clinical testing.
RECENT ABSTRACTS AND PRESENTATION


RECENT PUBLICATIONS


AWARDS AND HONORS

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FUTURE PLANS

Clinically I would like to specialize in the surgical treatment of patients with head and neck cancer. As a result after completing medical school I plan to do a residency in otolaryngology followed by a fellowship in microvascular reconstruction and head and neck surgery. I would also like to have my own translational therapeutics lab focused on the development novel immune based therapies for head and neck cancer patients.