Stephen M Bergin
PhD Candidate

Activation of Hypothalamic BDNF Modulates Lymphocyte Immunity

February 17th, 2017
Room 105, Biomedical Research Tower
1:00pm
VITA

12/24/1988 ........................................... Born, Dayton, OH

05/21/2011 .......................... Bachelor of Science, Chemistry,
Duke University

2011-present ............................... M.D., Ph.D. Candidate
The Ohio State University

COMMITTEE MEMBERS

Michael A. Caligiuri, M.D., Advisor

Lei Cao, Ph.D.

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ABSTRACT

Macro-environmental factors, including a patient's physical and social environment, play a role in obesity, cancer risk, and tumor progression. Living in an enriched environment (EE) providing complex stimuli leads to improved cognitive and metabolic health, and our previous studies show that EE confers anti-obesity and anticancer phenotypes in mice. These phenotypes are mediated in part by a specific brain-fat, neuroendocrine axis, with brain-derived neurotrophic factor (BDNF) as the key brain mediator, whose upregulation elevated sympathetic tone preferentially to the white adipose tissue leading to the induction of beige cells and the robust reduction of leptin production and secretion.

We investigated how an EE modulated T-cell immunity and its role in the EE-induced anticancer effects. Our data demonstrated that CD8 T cells were required to mediate the anticancer effects of an EE in an orthotopic model of melanoma. In secondary lymphoid tissue (SLT), an EE induced early changes in the phenotype of T-cell populations, characterized by a decrease in the ratio of CD4 T helper to CD8 cytotoxic T lymphocytes (CTLs). Overexpression of hypothalamic BDNF reproduced EE-induced T-cell phenotypes in SLT whereas knockdown of hypothalamic BDNF inhibited EE-induced immune modulation in SLT. Both propranolol and mifepristone blocked the EE-associated modulation of CTLs in SLT suggesting both the sympathetic nervous system and hypothalamic-pituitary-adrenal axis were involved. Our results demonstrated that enhanced anticancer effect of an EE was mediated at least in part through modulation of T-cell immunity and provided support to the emerging concept of manipulating a single gene in the brain to improve cancer immunotherapy.

Diet-induced obesity (DIO) promotes a pro-inflammatory microenvironment within visceral adipose tissue (VAT), but the molecular interactions regulating VAT and immune cells are
mostly unknown. Innate lymphoid cells (ILC) are a newly characterized immune cell present within the VAT microenvironment, which regulates adipocyte insulin sensitivity and energy expenditure and represents a cellular target for treating obesity. We investigated how the EE modulated the homeostasis of ILC frequency within the VAT microenvironment. EE increased ILC numbers and frequency within VAT compared to SE mice. Overexpression of hypothalamic BDNF in SE mice increased the frequency and number of ILCs in VAT, demonstrating the sufficiency of hypothalamic BDNF to reproduce the EE-ILC phenotype. In DIO mice, the increase of ILC frequency within VAT-associated with EE was maintained and associated with an improved metabolic phenotype. This ILC increase was induced independently of activation of the hypothalamic-pituitary-adrenal stress axis. Overall, our results suggest that EE regulates ILC function and homeostasis within VAT and can be therapeutically targeted to treat obesity.
RECENT ABSTRACTS AND PRESENTATION


**Bergin SM** Run Xiao, Ryan Judd, Huang Wei, Lei Cao, Michael Caligiuri. “Genetic and environmental activation of hypothalamic BDNF alters the adipose tissue immune microenvironment”. Poster presentation, Annual OSUMC Trainee Research Day, Columbus, OH. April 2016.

**Bergin SM** Run Xiao, Ryan Judd, Huang Wei, Lei Cao, Michael Caligiuri. “Genetic and environmental activation of hypothalamic BDNF modulate Tcell immunity to inhibit tumor growth”. Poster presentation, Annual OSUMC Trainee Research Day, Columbus, OH. April 2015.
*Indicates co-first authorship

Bergin SM*, Xiao R*, Huang W, Slater A, Judd R, Chen L, Caligiuri MA, Cao L. “Environmental and genetic activation of hypothalamic BDNF modulates the adipose immune microenvironment to improve metabolic health.” *In preparation*


AWARDS AND HONORS

2016  Research Day Travel Award, OSU

2013  P4 Summer Scholars Programs

2013  Medical Scientist Training Program Leadership and
      Academic Achievement Award, OSU

2012  Medical Scientist Training Program Leadership and
      Academic Achievement Award, OSU

2012  Patient Ethics Essay Award, Office of Research Education,
      OSU

FUTURE PLANS

Stephen Bergin will return to medical school to complete his
medical training, after which he will pursue a research residency.