Lifestyle Improvements Enhance Metabolic Function and Mitigate Breast Cancer Progression

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The James L035
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VITA

04.09.1989 . . . . . . . . . . . . . . . . . . . . . . . . . .  Born –
                Cincinnati, OH

2007-2011 . . . . . . . . . . . . . . . . . . . . . . . . . . . Bachelor of Science,
                        Miami University,
                        OH

2013-present . . . . . . . . . . . . . . . . . . . . . . . . . Graduate Research
                       Associate and Fellow
                       Biomedical Sciences
                       Graduate Program,
                       The Ohio State
                       University, OH
                       Pelotonia Graduate
                       Fellowship, The Ohio
                       State University, OH
                       NRSA Individual
                       Predoctoral
                       Fellowship (F31),
                       National Institutes of
                       Health, MD.

COMMITTEE MEMBERS

Dr. Lei Cao, Ph.D., Advisor

Dr. Steven Clinton, MD PhD

Dr. Michael Ostrowski, PhD

Dr. Ouliana Ziouzenkova, PhD
ABSTRACT

About 70% of the adult U.S. population is overweight or obese, which is among the most common etiological factors for chronic diseases, including cancer. Progression to obesity can largely be slowed or reversed with lifestyle changes, thus also having the potential to mitigate cancer. A mouse model of environmental enrichment (EE) to improve motosensory, cognitive, and social stimulation by increasing physical engagement and social interaction triggers vast improvements in overall health, including cognitive abilities, reducing adiposity, prevention of diet-induced obesity (DIO), promoting the white to brown fat transition, enhancing insulin sensitivity, improving immune function, limiting inflammation, and inhibition of cancer growth. The purpose of this dissertation was to further elucidate and mechanistically describe the central-hypothalamic metabolic regulatory pathway involved in the response to EE and expand its cancer mitigating effects to various models of breast cancer while considering the influence of obesity and endocrine signaling in the breast cancer microenvironment.

The central mechanism of EE is the induction of brain-derived neurotrophic factor (BDNF) and the subsequent activation of the hypothalamic-sympathoneural-adipocyte (HSA) axis. The HSA axis is a specific neuroendocrine route in which the brain communicates with adipose tissue via the sympathetic nervous system. Once activated, norepinephrine (NE) is released onto adipose tissue which induces the observed metabolic improvements. First, we sought to identify additional genes that are involved in this unique regulation. \( V_{gf} \) (non-acronymic) is highly expressed in the hypothalamus and had been shown to be induced by BDNF. Thus, we investigated hypothalamic-specific \( V_{gf} \) expression responding to environmental stimuli, its relationship with \( Bdnf \); its impact on metabolic function, and its involvement in the HSA axis. Our data showed that \( V_{gf} \) likely acts in the melanocortin pathway of metabolic homeostasis, downstream of \( Bdnf \), while having a minor role in the HSA axis. Following hypothalamus-specific depletion, mice experienced
elevated adiposity, decreased core body temperature, reduced energy expenditure, impaired glucose tolerance, and disrupted molecular features of adipose tissue. Therefore, we concluded that VGF plays an important role in energy balance and glycemic control.

Following this deepened characterization of the HSA axis and implication of a novel gene in metabolic regulation, we aspired to investigate the potential anti-breast cancer effects of EE. HSA axis activation has been shown to mitigate both colon cancer and melanoma progression; however, the effects of adiposity and leptin signaling within the unique microenvironment of the mammary adipose depot following EE have not been investigated. Thus, we explored the effects of EE on breast tumorigenesis in varied body mass states and also considered the role of leptin by utilizing obese models with varied leptin signaling. Our data indicated that the effects of EE on tumorigenesis were dependent on leptin signaling. EE inhibited mammary tumor growth when leptin signaling was intact, but increased tumor growth in its absence due to the elevated NE released in response to HSA axis and sympathetic activation. We concluded that microenvironment is critical in breast tumorigenesis, and that the drop in leptin following EE is the primary peripheral mediator of its anti-breast cancer effects, offsetting the pro-tumorigenic effects of NE.

It is clear that cancer onset and progression is dependent on both the macro- and microenvironments. Additionally, it is evident that cancer cells have redundant pathways to ensure their survival and growth. However, most conventional chemotherapies only affect one or two molecular targets within these pathways. Thus, the beneficial and pleiotropic effects of EE on multiple organ systems and pathways both in the local microenvironment and systemically represent an attractive strategy for more effective and enduring combination therapies. Success of these interventions will limit many obesogenic conditions as well as diminish relapse potential and reduce the likelihood of developing cancer in the first place; which together, will contribute to our goal of creating a healthier and cancer-free world.

2016 BSGP Annual Retreat, Columbus, OH. **Grant D. Foglesong**, Wei Huang, Kyle J. Widstrom, Lei Cao. Lifestyle improvements delay breast cancer onset and progression in obese mouse models.

2016 *Ignite* Research Reception, Columbus, OH. Jennifer Petrosino; **Grant Foglesong**; Anuradha Kalyanasundaram; Alan Flechtner; Paulo Fadda; Muthu Periasamy; Santosh Maurya; Ouliana Ziouzenkova*; Federica Accornero*. ADH1 ablation mediates pericardial adipose tissue accumulation.

2016 Great Lakes Breast Cancer Symposium, Pittsburgh, Pennsylvania. **Grant D. Foglesong**, Wei Huang, Lei Cao. Leptin mediates the anti-breast cancer effects of environmental enrichment.

2016 American Association for Cancer Research Annual Meeting, New Orleans, Louisiana. **Grant D. Foglesong**, Wei Huang, Lei Cao. Leptin mediates the anti-breast cancer effects of environmental enrichment.

2016 The 13th Annual Russell Klein Nutrition Research Symposium, Columbus, Ohio. **Grant D. Foglesong**, Wei Huang, Xianglan Liu, Andrew M. Slater, Jason Siu, Stephen R. J. Salton, Lei Cao. Role of hypothalamic VGF in energy balance and metabolic adaption to environmental enrichment in mice.

2015 The 14th Annual Ohio State University Wexner Medical Center Trainee Research Day, Columbus, Ohio. **G. D. Foglesong**, X. Liu, W. Huang, C. Wang, A. M. Slater, L.
Cao. Hypothalamus-specific knockdown of Vgf induces metabolic dysfunction.


2014 The Ohio State University Comprehensive Cancer Center – James 16th Annual Scientific Meeting. L. Xianglan, T. McMurphy, **G. Foglesong**, R. Xiao, A. Slater, L Cao. Cancer Prevention and Treatment by the Activation of a Brain Adipocyte Axis.

**RECENT PUBLICATIONS**

**Foglesong, G. D.,** Huang, W., Widstrom, K. J., Cao, L. Lifestyle Improvements Delay Breast Cancer Onset and Progression in Obese Mouse Models via Endocrine Signaling. *Manuscript in Preparation*


**AWARDS AND HONORS**

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FUTURE PLANS

Contributing to novel disease discoveries at the bench has been a fascinating, rewarding, and inspiring experience that has lead me to pursue post-doctoral research opportunities concentrating on the interactions between metabolism, adipose tissue, and cancer. Additionally, I have had the unique opportunity to work in a biomedically focused entrepreneurial environment to advance innovative discoveries towards commercialization. This has also been an eye-opening experience that has highlighted my passion to help breakthroughs come to life beyond the bench. Thus, I am also pursuing medical affairs positions within the biopharmaceutical industry. Ultimately, I hope to leverage my biomedical science research experience to pioneer translatable and clinically relevant interventions to enrich our world and the health of everyone in it.