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Epigenetic Mechanisms of Inflammation and Fatigue in Patients With Cancer

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Purpose:

In this abstract, we present preliminary data from a research project related to epigenetic modifications as the use of omics in cancer symptom assessment, diagnosis, and potentially intervention. Fatigue, one of the most frequently reported symptoms in patients with cancer, can profoundly affect a cancer patient’s quality of life, treatment adherence, and health care utilization. Currently, there is no Food and Drug Administration (FDA)-approved pharmacological agent that effectively prevents or treats fatigue. Understanding the molecular mechanisms of fatigue is critical to its successful management and development of targeted therapies. Recent studies have linked cancer-related fatigue with inflammation even long after the completion of cancer treatment. However, the mechanisms for the persistence of inflammation and fatigue long after treatment completion have yet to be understood. Epigenetics refers to the regulation of gene activities that does not involve alteration of DNA sequence. Environmental stimuli, such as diet, pollution, infections, or cancer treatment, have profound effects on epigenetic modifications that can, thereafter, trigger susceptibility to disease or symptoms. Therefore, one potential explanation could be that cancer and its treatment leads to acute, but long-lasting epigenetic changes that may predispose to persistent inflammation and fatigue. DNA methylation is the well-studied epigenetic modification, and has been characterized in various disease processes including cancer, psychiatric symptoms, and inflammation. This study sought to explore DNA methylation changes associated with inflammation and fatigue in patients undergoing chemoradiotherapy for head and neck cancer (HNC). The reported methods and preliminary data were from our ongoing study. This presentation may also provide how we, as nurse scientists, design our studies to link the epigenetic changes to biological pathways that may help us to understand the mechanisms and potential intervention targets for patient-reported symptoms.

Methods:

Data were collected at pre- and one-month post radiotherapy. Patients were enrolled at the Radiation Oncology Clinics of Emory Healthcare. The main inclusion criteria were: histological proof of squamous cell carcinoma of the head and neck region; any clinical stage with no distant metastasis; and no major organ disease. Main exclusion criteria were: evidence of metastases; simultaneous primaries; previous invasive malignancies; and patients with major psychiatric disorders or those who cannot understand English.
Demographic and clinical variables were collected at baseline and/or follow up as appropriate through administration of standardized patient reported questionnaires. Fatigue was measured by using the Multidimensional Fatigue Inventory (MFI)-20, with a well-established validity and reliability (α=0.84) in use with patients with cancer. Blood samples were collected at the same day as the questionnaires using EDTA tubes. DNA was isolated from peripheral blood monocyte cells (PBMCs) according to the manufacturer’s protocol. The HumanMethylation450K BeadChip (Illumina; San Diego, CA) was used to test >480,000, methylation sites quantitatively across the genome.

Results:

Pilot data was generated from 12 HNC patients, 6 of whom had a significant increase in fatigue (defined as an increase of more than 25 points out of 100 from pre-to one-month post-chemoIMRT) and another 6 that had less than a 15 point increase over time). These data showed a promising link between fatigue status and DNA methylation changes. We evaluated DNA methylation changes across the genome before and after chemoIMRT. DNA methylation of CpG sites in 643 genes changed more than 10%. Genes whose methylation levels changed in response to chemoIMRT were enriched for 338 specific Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (6.73x10^{-22}<p_{corr}<.05) including immune response and cancer pathways. We next evaluated whether methylation of CpG sites that changed before and after chemoIMRT associated with differences in fatigue. Recognizing that a study of 12 subjects is unlikely to have the power necessary to achieve significance after multiple test correction, we concentrated on the 1199 CpG sites that changed in response to chemoIMRT. Overall, 306 chemoIMRT-responsive CpG sites (25.5%) associated with fatigue (p<.05), which is more than 5x what would be expected by chance (p<.0001). Among the top 5 CpG sites that most associated with fatigue, RNASET2, the gene containing the most associated CpG site (cg11301670), has been implicated in chromosomal rearrangements and tumor malignancy CITE. In addition, CpG sites in the interleukin (IL)-6 receptor (cg21262032) and a Tumor Necrosis Factor (TNF) Ligand (cg12045829), both of which are inflammatory markers, were also among the top five that most associated with fatigue.

Conclusion:

The preliminary data from the pilot study suggested that epigenetic regulation of immune mediators may contribute to inflammation and persistent fatigue in these patients. Larger data are needed to verify the findings. As nurse scientists, we may be able to identify epigenetic modifications and to use them as predictive and prognostic biomarkers for symptoms and as interventional targets for the management of these symptoms.

Title:
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References:


Abstract Summary:
In this abstract, we present preliminary data from a research project related to epigenetic modifications as the use of omics in cancer symptom assessment, diagnosis, and potentially intervention.

Content Outline:
I. Introduction
   A. Understanding the mechanism of cancer-related fatigue is critical for symptom management.
   B. Epigenetic modifications provide a potential explanation for the associations between cancer-related fatigue and inflammation.
   C. This presentation also provides an example of designing nursing studies to link the epigenetic changes to patient-reported symptoms.

II. Body
   A. Introducing cancer-related fatigue and mechanisms
      1. Concept of cancer-related fatigue
         a) Definition of cancer-related fatigue
         b) Impact of cancer-related fatigue
         c) Management of cancer-related fatigue
      2. Mechanisms of cancer-related fatigue
         a) Inflammation
         b) Persistent inflammation and fatigue
   B. Introducing epigenetic modifications
      1. Concept of epigenetics
         a) Definition of epigenetics
         b) Types of epigenetic modifications
         c) Epigenetic agents for cancer treatment
      2. DNA methylation
         a) Definition of DNA methylation
         b) DNA methylation and inflammation
   C. Presenting a study design and preliminary data
1. Presenting the study design
   a) Sample and setting
   b) Measurements and assays
2. Presenting preliminary data
   a) Fatigue and DNA methylation changes overall
   b) DNA methylation changes associated with inflammation and fatigue

III. Conclusion
A. The preliminary data suggested that epigenetic regulation of immune mediators may contribute to inflammation and persistent fatigue
B. As nurse scientists, we may be able to identify epigenetic modifications and to use them as predictive and prognostic biomarkers for symptoms and as interventional targets for the management of these symptoms

First Primary Presenting Author
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Canhua Xiao, PhD
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**Professional Experience:** Dr. Xiao is a PhD-prepared nurse whose research focuses on fatigue in patients with cancer. She is the awardee of two active NIH grants in this area of science.

**Author Summary:** Dr. Xiao joined Emory University’s Nell Hodgson Woodruff School of Nursing as an Assistant Professor in 2014. Prior to that, she received a PhD from University of Pennsylvania in 2011, finished her postdoctoral training at Emory University in 2013. Dr. Xiao’s research interests focus on patient-reported outcomes, cancer-related symptoms/symptom clusters, and cancer related fatigue and its biological mechanisms.

Second Author
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**Professional Experience:** Dr. Alicia Smith is an Assistant Professor of Psychiatry and Behavioral Sciences at Emory University School of Medicine. She is also the Principal Investigator of the Human Psychiatric Genetics Laboratory, and the Director of the Psychiatric Genetics Core at Emory.

**Author Summary:** Dr. Smith studies the role of genetic and environmental factors in the development and symptoms of stress-related disorders across the lifespan. She uses a number of complementary approaches including bioinformatics and genome-wide evaluations of sequence variants, DNA methylation and gene expression to explore developmental and behavioral problems.

Third Author
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Professional Experience: Dr. Conneely is an Associated Professor at Emory University School of Medicine Department of Human Genetics. She received her PhD in biostatistics at University of Michigan in 2008.

Author Summary: Her research focuses on statistical methods for genetic association studies and large-scale studies of DNA methylation. Dr. Conneely are currently involved in GWAS, candidate gene studies, and methylation studies involving psychiatric outcomes, environmental stressors, and aging.

Fourth Author
Jonathan Beitler, MD
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Professional Experience: Dr. Beitler is a professor of radiation oncology at Emory University, and Georgia Cancer Coalition Distinguished Scholar. He has more than 20 years clinical experience in radiation oncology and in treating patients with head and neck cancer.

Author Summary: Dr. Beitler's area of interest is head and neck cancer. He is an institutional principal investigator (PI) for NRG Oncology and a co-PI for the National Clinical Trials Network Lead Academic Participating Site.

Fifth Author
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Professional Experience: Kristin Higgins, MD, is board certified in radiation oncology and is a clinical member of the Winship Cancer Institute. In 2015, Dr. Higgins was named medical director of radiation oncology of The Emory Clinic at Winship Cancer Institute's Clifton campus location.

Author Summary: Dr. Higgins' research interests include using functional imaging in head and neck cancer to predict treatment outcomes. She also has a research interest in optimizing radiotherapy for locally advanced non-small cell lung cancer.

Sixth Author
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Professional Experience: Evi relocated to Atlanta in 2013 where she joined the Behavioral Immunology Program later that year. Prior to joining the lab, she was a microbiology laboratory analyst for a medical devices/supplies manufacturer. A graduate of the University of Central Florida, Evi obtained a Bachelor of Science degree in Molecular Biology and Microbiology.

Author Summary: Evi Wommack is the laboratory manager for the Emory Behavioral Immunology
Program. She oversees day-to-day laboratory operations, performs testing and analysis on clinical research samples and assists with interpretation of study data for research publications.

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**Professional Experience:** Dong Moon Shin, MD, FACP, is the Frances Kelly Blomeyer Distinguished Endowed Chair in Cancer Research, Professor of Hematology/Medical Oncology, Professor of Otolaryngology, Professor of Biomedical Engineering, Director of the Head and Neck Cancer SPORE Program and Georgia Cancer Coalition Distinguished Scholar at the Winship Cancer Institute at Emory University.

**Author Summary:** Dr. Shin's research focus is in head, neck and lung cancers. During the past 30 years his research has been in the following areas: establishing carcinogenesis models in preclinical and clinical settings for head, neck and lung cancer; developing biomarkers in animal and human carcinogenesis for head, neck and lung cancer; developing molecular targeted prevention and therapies; and developing novel therapeutics (clinical or translational protocols) for head and neck cancer, lung cancer, thymoma and mesothelioma.

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**Professional Experience:** Nabil F. Saba, MD, FACP, is a Professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine and Director of the Head and Neck Cancer Medical Oncology Program at Winship Cancer Institute of Emory University.

**Author Summary:** Dr. Saba's research is focused on clinical and translational work in head and neck, and esophageal cancer. He has been the recipient of several NIH and industry funded grant support to study these malignancies.

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**Professional Experience:** Dr. Bruner is the Robert W. Woodruff Professor of Nursing, Professor of Radiation Oncology at Emory University, and the Associate Director for Outcomes Research for both the Winship Cancer Institute and RTOG. Dr. Bruner is a preeminent researcher in cancer symptom science and is the first and only nurse to be a PI of a NCI sponsored clinical trials CCOP.

**Author Summary:** Dr. Bruner is currently leading a project to bring modern radiotherapy and quality assurance to Ethiopia, and Chairs the Advisory Board for the Emory University-Addis Ababa University (AAU) partnership in developing AAUs first doctoral program in nursing. Her most current research is focused on the role of the human microbiome in carcinogenesis and cancer treatment outcomes.

Tenth Secondary Presenting Author
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**Professional Experience:** Dr. Andrew Miller is William P. Timmie Professor of Psychiatry and Behavioral Sciences and Director of Psychiatric Oncology at the Winship Cancer Institute at the Emory University School of Medicine in Atlanta, Georgia. He is an internationally recognized leader in the area of brain-immune interactions as they relate to stress and depression.  

**Author Summary:** His work has demonstrated that during immune activation, inflammatory cytokines can access the brain and interact with the metabolism of dopamine and glutamate, while altering neurocircuits in the brain relevant to motivation and reward as well as anxiety and alarm. Dr. Miller has also studied the impact of cytokines on neuroendocrine regulation and sleep including the study of the specific signal transduction pathways involved.