

Delineation of Mitochondrial Genome Expression in Colorectal Adenoma Progression

LASHANALE MONIQUE WALLACE

PhD Candidate

Under the direction of

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Associate Professor, Department of Medicine

In partial fulfillment of the requirements for the degree

Doctor of Philosophy in Biomedical Sciences



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Graduate Education in Biomedical Sciences



Graduate Education in Biomedical Sciences

Final Examination of

LaShanale M. Wallace

For the Degree

DOCTOR OF PHILOSOPHY IN BIOMEDICAL SCIENCES

DISSERTATION COMMITTEE

Felix O. Aikhionbare, MS, Ph.D., Research Advisor

Associate Professor, Department of Medicine
Morehouse School of Medicine

Jason DeBruyne, Ph.D.

Associate Professor, Department of Pharmacology and Toxicology
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Assistant Professor, Department of Medical Education
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Xuebiao Yao, Ph.D.

Professor, Department of Physiology
Morehouse School of Medicine

PROFESSOR IN CHARGE OF RESEARCH

Felix O. Aikhionbare, MS, Ph.D.

Associate Professor, Department of Medicine
Morehouse School of Medicine

FIELDS OF STUDY

Major Subject: Biomedical Sciences

Basic Bioinformatics
Biochemistry
Biochemistry Laboratory
Biomedical Genetics
Biomedical Genetics Laboratory
Biomedical Science Presentation I & II
Cancer Biology
Critical Thinking and Scientific Communication I & II
Dissertation Research
Human Biology
Human Biology Laboratory
Integrated Biomedical Science
Laboratory Rotation I & II
Population/Evolution Genetics
Research Data Analysis
Scientific Integrity in Research
Seminar in Biomedical Sciences I - VI
Special Topics in Science Education

Research Focus: Mitochondrial Genome Variations in Colorectal Tumors

BIOGRAPHICAL SKETCH

Undergraduate Study:

B.S, May 2012; North Carolina Agricultural and Technical State University, Greensboro, North Carolina.

Major: Biology

Graduate Study:

Ph.D. Candidate, Morehouse School of Medicine (MSM), Atlanta, GA, 2013-present; *Biomedical Science*

Professional Memberships

2016-present American Society of Clinical Oncology interest Group
2016-present Minorities in Cancer Research
2016-2017 BioMed Talkers: Toastmaster International
2015-present American Association of Cancer Research

Professional Service

2016-present American Society of Clinical Oncology Interest Group-PhD Liaison
2016-2017 BioMed Talkers: Toastmaster International-Treasurer
2014-2016 Graduate Education in Biomedical Science Tutor, MSM
2014-2015 Graduate Education in Biomedical Science Student Association -Treasurer
2014-2014 Human Biology Lab Teaching Assistant, MSM

Recent Fellowships & Awards

2018 AACR Minority Scholar in Cancer Research Awardee, Chicago, IL. (Apr. 2018)
2017 Research Centers for Minority Institutions 2017 Conference Second Place Student Poster Competition, Washington, DC. (Nov. 2017)
2015 Student Mentor of the Year Award- Morehouse School of Medicine Graduate Education and Biomedical Science Student Association, Atlanta, GA. (May. 2015)

Selected Abstracts/ Presentations

Wallace L, Cherian AM, Aikhionbare F. Differential expression of MT-ATPase and COXIV genes in Colorectal Adenopolyps (April 2018). Poster Presentation, 110th Annual Meeting of the American Association for Cancer Research; Chicago, IL.

Wallace L, Cherian A, Grizzle W, Aikhionbare F. Mitochondrial influence on colorectal adenoma-tumor sequence (November 2017). Poster Presentation, Research Centers for Minority Institutions 2017 Conference, Washington, DC.

Adamson P, Cherian AM, **Wallace LM**, Bond VC, Aikhionbare FO. Alterations in mitochondrial genome and colorectal adenomas (November 2017). Poster Presentation, Research Centers for Minority Institutions 2017 Conference, Washington, DC.

Wallace L, Mehrabi S, Yao X, Aikhionbare F. Gene expression and mitochondria mutation analysis in Colorectal Adenomas (February 2017). Poster Presentation, Curtis L. Parker 29th Annual Student Research Symposium, Morehouse School of Medicine, Atlanta, GA.

Cherian AM, **Wallace L**, and Aikhionbare FO. Expression of mitochondrial genome alteration as a potential biomarker for colorectal Adenopolyps in relative to age and race (Abstract), *Georgia Journal of Science*, Vol 75, 2017

Cherian AM, **Wallace L**, and Aikhionbare FO, Mitochondrial Gene Expression in Colorectal Cancer: Its effect on Race and Age P-09, (February 2017). Poster Presentation, Curtis L. Parker 29th Annual Student Research Symposium, Morehouse School of Medicine, Atlanta, GA.

Millingen S, **Wallace L**, Cohen S, Mehrabi S, Aikhionbare F. Mitochondrial Gene Expression and Racial Disparities in Epithelial Ovarian Cancer (July 2016). Poster Presentation, Morehouse School of Medicine 2016 Summer Research Experience for Medical Students, Atlanta, GA.

Wallace L, Mehrabi S, Yao X, Aikhionbare F. Mitochondrial mutations and gene expression analysis in colorectal adenopolyps (April 2016). Poster Presentation, 107th Annual Meeting of the American Association for Cancer Research; New Orleans, LA.

Wallace L, Mehrabi S, Yao X, Aikhionbare F. Mitochondrial alterations in Colorectal Adenopolyps (February 2016). Poster Presentation, Curtis L. Parker 28th Annual Student Research Symposium, Morehouse School of Medicine, Atlanta, GA.

Wallace L, Mehrabi S, Yao X, Aikhionbare F. Specific mtDNA variants and colorectal adenopolyps. (April 2015). Poster Presentation, 106th Annual Meeting of the American Association for Cancer Research; Philadelphia, PA.

Wallace L, Mehrabi S, Cohen S, Aikhionbare F. Elevation of oxidative expression proteins in Colorectal Adenomatous polyps (November 2014). Poster Presentation, 7th Annual AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved; San Antonio, TX.

Wallace L, The effects of PI3K/AKT/MTOR inhibitors on the MEK/ERK pathway in AML cell types (November 2012). Poster Presentation, Annual Biomedical Research Conference for Minority Students; San Jose, CA.

Publications

Wallace L, Mehrabi S, Bacanomwo M, Yao X, Aikhionbare F. Expression of mitochondrial genes MT-ND1, MT-ND6, MT-CYB, MT-COI, MT-ATP6, and 12S/MT-RNR1 in colorectal adenopolyps. *Tumor Biology*. Sep 2016. PubMed PMID: 27333991.

Mehrabi S, **Wallace L**, Cohen S, Yao X, Aikhionbare F. Differential Measurements of Oxidatively Modified Proteins in Colorectal Adenopolyps. *International Journal of Clinical Medicine*. 6 Apr 2015. PubMed PMID: 26069854.

Rahmani M, Aust MM, Benson EC, **Wallace L**, Friedberg J, Grant S. PI3K/mTOR Inhibition Markedly Potentiates HDAC Inhibitor Activity in NHL Cells through BIM- and MCL-1-Dependent Mechanisms In Vitro and In Vivo. *Clin Cancer Res*. 2014 Jul 28. PubMed PMID: 25070836.

Manuscripts in Preparation/submitted

Wallace L, Grizzle W, Yao X, Banerjee S, Aikhionbare FO. Roles of Mitochondrial miRNAs in Early Stages of Colorectal Tumor Progression. *Cancer Research*, 2017 (Manuscript: *in preparations*).

Wallace L, Cherian AM, Adamson P, Bari S, Banerjee S, Floor M, Simien M, and Aikhionbare FO. Differential Expression of MT-ATPase and COXIV genes in Colorectal Adenopolyps (Submitted to *Journal of Diagnostic Pathology*)

DISSERTATION ABSTRACT

Wallace, LaShanale; Ph.D., Morehouse School of Medicine, May 2018 Delineation of Mitochondrial Genome Expression in Colorectal Adenoma Progression, Chair of Committee: Felix O. Aikhionbare, MS, PhD.

Colorectal cancer (CRC) is the most common gastrointestinal malignancy in the United States diagnosed in both men and women. Patients with colonic adenomatous polyps have a threefold higher risk of CRC over the general population. Moreover, a great deal of differences has been observed among patients with colonic adenomatous polyps during the course and outcome of the disease making application of appropriate therapies difficult. Given that CRC is considered an age related disease, the accumulation of reactive oxygen species (ROS) and oxidative DNA damage within mitochondrial genome during the course of a lifetime may be deleterious and involved in the development and progression of colorectal adenomatous polyps. Recent studies suggest the mitochondrion encodes miRNA sequences which may regulate different pathways involved in oxidative phosphorylation, apoptosis, and oxidative stress, all of which are pathways frequently deregulated in cancer. This study analyzed mitochondrial genome variations in 50 pairs of colorectal precancerous polyps (tubular, tubulovillous, villous) and adenocarcinoma tissues. Our hypothesis states that aberrant mitochondria genome expression contributes to the progression of colorectal adenomatous polyps to CRC. Variations within these different tissues were tested through the following experiments: (I) Direct sequencing and high resolution restriction digestion to evaluate specific DNA variants (II) Gene expression analysis of mitochondrial encoded genes using reverse transcription quantitative PCR, Western blot and (III) Pathway Studio and RT-qPCR analysis to determine MitomiRs expressed in colorectal polyp and carcinoma tissues. Of the 326 variants identified, those predicted to be disease causing were predominately found in complexes IV and V of the electron transport chain. Additionally five mt-genes and one rRNA were differentially expressed among the colorectal adenopolyps compared to their paired adjacent normal tissue. Protein analysis results showed an increased expression of complexes I and III as well as elevated carbonyl content among the studied colorectal tumors. More importantly miRNAs targeting genes in these complexes significantly increased from early adenomas to late stage adenomas. These findings provide insight into the significant role the mitochondria plays during early progressive stages of CRC development. Therefore, further mitochondrial expression studies could render an alternate target for CRC biomarker discovery and novel therapeutics.

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