RUTGERS
School of Graduate Studies

Office of Student Affairs and Admissions
SGS at New Jersey Medical School
Rutgers, The State University of New Jersey
185 South Orange Avenue, MSB C-696
Newark, NJ 07103

http://njms.rutgers.edu/gsbs/
p. 973-972-4511
f. 973-972-7148

YOU ARE INVITED TO ATTEND THE DEFENSE OF THE DOCTORAL DISSERTATION

"Investigating Novel Epigenetic Biomarkers of Hepatocellular Carcinoma"

By
Aesis M. Luna

Molecular Biology, Genetics, and Cancer Program

BS, Microbiology 2002, University of Texas, Austin, TX

Thesis Advisors:

Dongfang Liu, Ph.D.
Associate Professor
Department of Pathology, Immunology and Laboratory Medicine

Chen Liu, M.D., Ph.D.
Professor
Dept of Pathology
Yale School of Medicine

Tuesday, May 23rd, 2023
10:30 AM
NJCC G-Level Auditorium, Zoom

Join Zoom Presentation:
https://rutgers.zoom.us/my/aml381?pwd=Wit3bFpma3A5UTNSU0xjblhnU2JiQT09

Meeting ID: 858 857 1873
Passcode:149597

ABSTRACT

Hepatocellular Carcinoma (HCC,) a primary liver cancer, continues to increase in mortality and incidence world-wide. Despite developing in long-term cirrhotic inflammation, HCC has a low frequency of genetic mutations (~2 per Mb), therefore no mutational treatment targets have been successfully identified. However, sequencing advancements have revealed conserved epigenetic signatures in liver cancer. While epigenetic targets have the potential to discover novel treatments and biomarkers, much is unknown about their mechanisms and links to cancer. Therefore, it is critical to research the promising area of epigenetic events in tumorigenesis. In our collaborative epigenetic publications with Mayo Clinic, computational analyses identified 10 gene targets in the liver including Catechol-O-Methyltransferase (COMT). COMT, traditionally researched for neurological diseases, transfers a methyl group to neurological chemicals such as dopamine and epinephrine, as well as opioid related drugs. This transfer neutralizes oxidative toxins, preventing cell damage and inflammation. COMT emerged as the gene of interest through in vitro screening of differential RNA and protein expression in cancer samples. This thesis tested COMT as a suspected tumor suppressor in hepatocytes.

First, this study established a pathology timeline of COMT expression using explant patient tissues. Transplant patient liver IHC slides were analyzed for protein expression. The results indicated that most HCC samples (n=30) had drastically low COMT expression compared to non-tumor tissues. Furthermore, there was lower COMT expression in the alcohol-related HCC (n=15) versus Hepatitis C Virus (HCV)-HCC as well as inversely correlated expression with HCC cancer stage. To examine the link in tumor formation and COMT function, a knock-out COMT mouse model was used. When treated with a five percent (5%) alcohol solution for one to three weeks, KO-COMT mice (n=18) experienced progressively significant necrotic liver damage compared to wild-type (WT) mice. Further phenotypic analysis shed light on prevention of risk factors affecting both genotypes. Interestingly, even after 6 months of recovery, the KO-COMT mice (n=2) had more necrosis than WT mice. Thus, indicating that COMT metabolism is critical to prevent long term hepatocyte injury, in toxic environments.

Finally, to find methylated-DNA biomarkers in blood serum, differentially methylated CpG's were examined. Primers were identified for future testing on human blood samples. Additionally, in collaboration with Yale University, human HCC and non-tumor samples were analyzed with several epigenetic aging clocks to assess cancer risk. It was discovered that HCC patients show an increased acceleration of epigenetic aging, known as PhenoAge, in tumor versus non-tumor tissues. Alcohol-related HCC patients also showed significant increase in PhenoAge when compared to HCV-HCC patients. These results reveal epigenetic aging as a novel biomarker for HCC and liver disease. Moreover, epigenetic clock data also clarified how several epigenetic-linked factors such as smoking and drinking alcohol, advance tumor onset.

Overall, these results offer novel HCC biomarkers and support the hypothesis that liver injury causes early epigenetic damage, and deregulation of potential tumor suppressors like COMT.