Causal Epigenetic Mechanism Underlying Arteriosclerosis in African Americans

Arteriosclerosis of the cardiac, cerebral, renal and peripheral arteries are often caused by high blood pressure and can lead to target organ damage and clinical sequelae such as heart attack, stroke, dementia and chronic kidney disease. While arteriosclerosis affects all human populations, it imposes greater health risks in underrepresented population such as African Americans. Indeed, greater progression of coronary atherosclerosis was observed in African-American patients, suggesting a more aggressive form of disease that requires intensification of secondary prevention strategies in African Americans. Here, we propose to investigate the epigenetic mechanism underlying the risk of arteriosclerosis in the underrepresented population of African Americans. We will do so by identifying DNA methylation sites that are causally associated with arteriosclerosis related clinical phenotypes in African Americans (N=1,848) from a predominately hypertensive cohort -- the Genetic Epidemiology Network of Arteriopathy (GENOA). We have already collected the whole genome sequencing data through the Trans-Omics for Precision Medicine initiative (TOPMed) on these individuals. We have collected genome wide methylation data in peripheral blood leukocytes based on the Infinium Human Methylation EPIC BeadChip on these individuals. We have also collected phenotypic measurements for arteriosclerosis that include coronary artery calcification, leukoaraiosis, microvascular arteriopathy of the kidneys, as well as peripheral arterial disease on these individuals. In this proposal, we aim to pair the DNA sequencing data, methylation data as well as the arteriosclerosis related phenotypic data in the GENOA cohort to investigate the causal epigenetic mechanism underlying arteriosclerosis. Specifically, we propose to (1) adapt the recently developed transcriptome wide association studies (TWAS) statistical method that has been widely used in transcriptomic analysis setting to methylation analysis settings. While the adaptation is straightforward, we will explore the connection of existing TWAS approach to the Mendelian randomization framework that are commonly used for causal inference in association studies to facilitate results interpretation. (2) With existing or adapted tools, we will perform an in-depth methylome wide association study, by treating cis-SNPs of each methylation site as instrumental variables, to identify methylation sites that are causally associated with each of the arteriosclerosis related phenotypes. In the analysis, we will carefully control for batch effects and various confounding factors. (3) When necessary, for the identified top candidate methylation sites, we will perform an experimental validation by adding methylation to the targeted regions and examining the consequence of these targeted methylation in cultured human cell lines. Targeted region methylation will be performed by using existing Type I CRISPR-Cas system based methylation tool to add methylation precisely and robustly on a specified region of the genome. The success of these proposed interdisciplinary aims will allow us to identify and validate DNA methylation sites that causally associated with arteriosclerosis, potentially providing novel epigenetic targets and facilitating translational research on arteriosclerosis.

The three cube collaborators consist of three faculty members from both School of Medicine and School of Public Health. Xiang Zhou ([xzhousph@umich.edu](mailto:xzhousph@umich.edu)) is a John G. Searl Assistant Professor in the Department of Biostatistics at the School of Public Health. He is an expert in developing and applying integrative statistical methods and computational tools for genetic and genomic studies. Yan Zhang ([yzhangbc@umich.edu](mailto:yzhangbc@umich.edu)) is an Assistant Professor in the Department of Biological Chemistry at the School of Medicine. She is an expert in developing and applying biochemical tools based on the CRISPR-Cas system. Wei Zhao ([zhaowei@umich.edu](mailto:zhaowei@umich.edu)) is an Assistant Research Scientist in the Department of Epidemiology at the School of Public Health. She is an expert in methylation and epidemiology analysis. She is an Investigator on the GENOA study and has involved in all aspects of the study. Our proposal requests a grant amount of 60K to adapt and apply existing statistical methods to methylation analysis setting, to perform in-depth analysis in the study cohort, and to validate analysis results using existing CRISPR-Cas tools. If successfully funded, the cube will cultivate the interdisciplinary collaboration among three junior faculty from three diversity research background that include epidemiology, biostatistics and biochemistry. The proposal has the potential to produce synergistic efforts across multiple research disciplines to benefit the translational research of cardiovascular disease and improve patient outcomes.