THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Niran Hadad

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
Neuroscience

Friday, February 22, 2019 | 11:00 am
Robert M. Bird Library Auditorium, Room, 299

Neuroepigenetics of Aging

COMMITTEE IN CHARGE: Willard Freeman, PhD (Chair); Arlan Richardson, PhD, Jonathan Wren, PhD; David Sherry, PhD; Cecil Lewis, PhD

ABSTRACT: Decline in cognitive function is a characteristic of brain aging and may lead to the development of more severe neurodegenerative diseases. While aging has been implicated as the main risk factor for the development of these diseases, a gap remains in the understanding of the exact molecular and cellular mechanisms promoting the development of cognitive aging. DNA methylation is a malleable epigenetic mark required for CNS development and remains dynamically regulated in the adult brain. In neurons, DNA methylation occurs in both CpG and non-CpG context. Loss of epigenetic homeostasis is proposed as a hallmark of aging. Specifically, changes in DNA methylation are associated with aging and neurodegenerative disease. Nevertheless, the relationship between DNA methylation and brain aging remains associative with little knowledge on non-CpG methylation. Furthermore, the functional role of DNA methylation changes with aging is unknown and is constrained by the complexity of transcriptional regulation by DNA methylation.

Using bisulfite sequencing approaches and applying them to study the aging methylome of both male and female mice we demonstrate that age-related alteration in DNA methylation in the hippocampus occur at specific loci across the genome. Changes in methylation are sex-specific and are abundant in non-CpG context. By perturbing the aging process using calorie-restriction, an established anti-aging intervention, we show that age-related alteration to DNA methylation in the brain can be prevented and that calorie-restricted specific changes may contribute to maintaining epigenetic homeostasis by regulating the DNA methylation machinery. Lastly, the functional role of DNA methylation in regulating transcriptional changes with age was assessed using whole-genome bisulfite sequencing and RNA-sequencing. Changes in methylation in enhancers and gene body are anti-correlated with age-related transcriptional changes. Furthermore, a positive association between early life methylation patterns and age-related transcriptional changes is observed. These methylation patterns, in combination with other histone marks, can be used to classify up- and down- regulation of genes that change with age.

Taken together, our studies expands upon prior work in the field of epigenetics of aging by providing evidence that DNA methylation dynamics with age are sex-specific, occur in both CpG and non-CpG context, are responsive to anti-aging interventions, and potentially mark specific genes as more susceptible to change with aging.