Aging, sperm proteome, and neurodegenerative diseases: incidental observations or a little bit more than meets the eye?

Mohd A. Beg[1,*], Abrar O. Ismail[1], Firdous A. Khan[2], Ayodele A. Alaiya[3], Ishfaq A. Sheikh[1], Taha A.A. Hamoda[4], Badrah S. Alghamdi[1], Adel M. Abuzenadah[1], Jean M. Feugang[5]

[1]King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia.

[2]Department of Large Animal Medicine and Surgery, School of Veterinary Medicine, St. George's University, Grenada, West Indies.

[3]Stem Cell and Tissue Re-Engineering Program, King Faisal Specialist Hospital and Research Centre, Saudi Arabia.

[4]Department of Urology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

[5]Department of Animal and Dairy Sciences, Mississippi State University, Mississippi State, Mississippi, USA.

[*]Correspondence: Prof. M. A. Beg (E-mail: mabeg51@gmail.com; Tel.: +966-552822451).

Aging associated wellbeing is of considerable importance due to the increasing aging population with related health issues including fertility problems and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Alzheimer's disease involves amyloid plaque accumulation and synaptic pathology, while Parkinson's disease is characterized by the presence of pathological intracellular misfolded α-synuclein aggregates in the aging brain. The clinical signs of these neurological diseases are manifested later in life, but the underlying indicators that might be present much earlier remain unknown. Understanding the underlying pathobiological mechanisms of age-related diseases is crucial for addressing health challenges in the aging human population. Our recent investigations on human semen proteome revealed deregulation of several proteins and pathways that are potentially associated with neurodegenerative disorders. Briefly, we examined semen samples from healthy fertile Arab/Saudi men across three age groups: a Young Adult group (21–30 years, n=6), a Late Adult group (31–40 years, n=7), and an Advanced Age group (40–51 years, n=5). The semen samples were centrifuged to separate seminal plasma and spermatozoa. Following separation, the spermatozoa were gradient purified, and both spermatozoa and seminal plasma were subjected to LC-MS/MS proteomic analysis. Total detected proteins were filtered for altered proteins among the groups and enriched annotations (ontologies and pathways) of differentially expressed proteins (≥2-fold change) were analyzed. A total of 595 and 463 proteins, respectively, were identified in the spermatozoa and seminal plasma of the three age groups. Of these, 287 and 116 proteins were differentially expressed in spermatozoa and seminal plasma, respectively, in Advanced Age group compared to Young Adult group. In addition to sperm function-related processes, the functional and pathway analysis of these differentially expressed proteins indicated enrichment of pathways for neurodegenerative diseases such as Alzheimer's disease-presenilin pathway, Parkinson's disease pathway, Wnt signaling pathway, and Huntington's disease pathway. Specifically, in the Advanced Age group the differential changes were observed in the expression of Wnt2, ACTRT3, ACTA1, ACTB, ACTBL2, ACTG1, ACTG2, MMP7, PSMA3, PSMA5, PSMA6, PSMA7, PSMB1, PSMB3, PSMB4, PSMB7, PKLR, HSPA1A, HSPA1L, HSPA2, HSPA5, HSPA6, HSPA8, SEPTIN4, YWHAQ, DYNLL, AR4, TUBB1, TUBB8, GAPDH, CAPNS1, and RAC1. Wnt signaling is a prominent pathway required

for synaptic plasticity and maintenance in adult brain and is deregulated in aging brain and Alzheimer's disease. Similarly, the other differentially expressed proteins have been associated with the molecular portraits of the pathogenesis of Alzheimer's, Parkinson's, and Huntington's diseases. These interesting preliminary observations in the age-related proteomic profile of spermatozoa and seminal plasma made us wonder if there is any underlying consequential relationship with pathophysiology of neurodegenerative disorders. However, the fact that these might be incidental observations of overlapping proteomic pathways of sperm fertility and neurodevelopmental/degenerative pathways cannot be overlooked. Further studies in this area might help clarify this conundrum.

Acknowledgement: The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through project number 1132.