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Epigenetic biomarkers for Alzheimer's disease using a transgenic porcine model

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UGP 2017: Epigenetic biomarkers for Alzheimer's disease using a transgenic porcine model.

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Project background

Alzheimer's disease (AD) is the most common cause of dementia, accounting for approximately 60~70% of dementia cases. AD afflicts more than 35.6 million individuals worldwide and is expected to increase to 65.7 million by 2030 and 115.4 million by 2050 [1]; AD is a serious public health problem that is causing increased health care costs worldwide. Typically, AD is a relentlessly progressive disorder that initially manifests as severe loss of memory, particularly episodic memory.[2] The disorder is not curable at present, and the mechanisms driving development of AD are not fully understood. Therefore, there is an urgent need to develop and characterize relevant AD transgenic animal models to facilitate translational research and preclinical testing of therapeutic agents.[3] Furthermore, it is imperative to discover the underlying mechanisms that exacerbate AD, which hinder mitigation efforts to reduce the health burden of this disease.

Studies have shown that epigenetic regulation (DNA methylation and miRNAs etc.), or heritable changes in gene expression that occur without directly altering the DNA sequence, offers a plausible mechanistic explanation, in addition to gene-environment interactions, for some of the molecular events linking disease onset and development.[4-6] While the role of epigenetic alterations in brain plasticity and disease has been discussed,[7-9] very few studies have examined the relation between epigenetic changes (miRNAs) and AD in a large animal-transgenic model. The goal of my laboratory, with expertise in epigenetic studies, is to define epigenetic mechanisms by which genetic and/or environmental exposures impact chronic diseases to improve overall health and treatment. Therefore, I proposed to define epigenetic alterations associated with AD development by profiling expression of miRNAs using an AD transgenic pig with a multi-cistronic vector system generated by Dr. Se-Pill Park at Jeju National University Stem Cell Research Center (JNUSCRC), South Korea.

Project progress

With the generous support of GRIP, I could visit JNUSRC in Korea to collaborate on research and initiate the experimental phase of this project. I visited Dr. Park's laboratory at JNUSRC in July 2017 and discussed the generation of several AD transgenic pig models with multi-cistronic vector systems as well as the best experimental design for measuring epigenetic alterations in AD. Consequently, I received brain tissues from two different aged AD transgenic pigs (7-week and 3-months old) and one control pig from Dr. Park at JNUSCRC in April 2018; I just completed profiling the expression of 134 miRNAs using the nCounter Analysis System. Currently, I am working on statistical analyses to identify specific miRNAs relevant to AD development, and I will further determine miRNA-mRNA target recognition and functional networks using the Ingenuity Pathway Analysis (IPA) tool this fall.

Impact of project and future direction

- *UM's internalization and collaboration:* This study will be completed through an international collaboration with Dr. Se-Pill Park at JNUSCRC, Korea, a well-known Korean scholar in stem cell research. As such, it will significantly advance the internationalization of UM. In addition, I plan further research collaborations with Dr. Sarjubhai Patel at the Department of Biomedical and

Pharmaceutical Sciences, UM using AD transgenic pigs from Korea; this in turn, will result in multiple collaborations within UM as well as Jeju National University in Korea that will be beneficial for both universities.

- *Student research and mentorship*: Through this GRIP support, I will expand my current epigenetic knowledge base and develop new research areas (i.e. AD). Furthermore, I instructed and supervised one graduate (Beth Cole) and two undergraduate students (Caroline Maughan and Minsun Koo) when performing the epigenetic analyses using the samples from Korea. The students will also be trained to work with IPA software to determine miRNA-mRNA relationships and their functional networks and pathways in AD development.

- *Manuscript in preparation*: I am working on a manuscript titled "miRNAs expression in Alzheimer's disease: using transgenic pigs with multi-cistronic vector system", and I will submit this to a high impact peer-reviewed journal (i.e. *Clinical Epigenetics*) this winter.

- *External Funding proposal under development*: I am currently generating preliminary data for grant applications, and this, combined with the expansion of my expertise, will improve my chances of acquiring outside funding. I plan to apply for external funding (i.e. Alzheimer's Association or NIH) by February 2020.

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