Research on neuron-glia interactions in the discovery of novel theranostic exosomal targets of Alzheimer's disease (AD)

關於研究腦神經元與膠質細胞之相互作用及探索其應用於阿茲海默症的外泌體生物治療診斷標記

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AD is a prevalent neurodegenerative disease which occupies around 25 million people world-wide. However, there is no effective drugs to treat AD in general, although a recent new drug has been released in the market. The drug has raised the debate about the efficacy and side effect. One of the reasons is that drug treatment for late stage of AD is not much efficient. Therefore, the development of early diagnostic methods for AD has been highly in demand for the effective therapy of AD patients.

In the first year of the project (February 28, 2021 to now), we have been conducted to establish various techniques in vitro and to further identify diagnostic exosomal biomarkers before the application of the liquid biopsy method in rodents' model of AD and human patients.

(1). Neuroinflammation is a key factor for AD pathogenesis. Glia, including microglia and astroglia, is the major cell type associated with neuroinflammation. Therefore, we established primary culture method of astroglia and microglia. Furthermore, we induced and characterized inflammation-related M1 microglia and A1- astroglia which may highly related with neuroinflammation in neurodegenerative disease, such as AD.

(2). Neuroglia metabolic coupling is altered during neurodegeneration. One of important metabolite transporter are monocarboxylate transporter 1(MCT1) and its binding protein, CD147. MCT1 and CD147 in cultured microglia and astroglia were identified.

(3). We established and validated the isolation and characterization method of exosomes from microglia and astroglia. The techniques include ultracentrifuge isolation method, nanoparticle tracking analysis (NTA), Transmission electron microscopes (TEM), and immunogold-EM.

(4). MCT1 and CD147 were also identified in exosomes from cultured microglia and astroglia.

(5). To establish the co-culture system of neurons and glia (AD co-culture model in microfluidic compartment model), the protocol was established to make neuroblastoma differentiating neurons with neurites.

(6). To establish the minimally invasive label-free liquid biopsy methods for AD diagnostic and prognostic exosomal biomarkers, we had established various techniques using localized surface plasmon resonance (LSPR) and atomic force microscopy (AFM) biosensors. This technique has been developed and utilized in our on-going interdisciplinary brain cancer project.

In conclusion, we established various protocols and the techniques for the progress of the grant proposal in the first year. Next year, we will determine the in vivo applicability of the liquid biopsy method using an AD mouse model or other disease mouse model.

Outcome: Indirectly related one manuscript in terms of the optimization of biosensing AD biomarkers (MCT1, CD147, and APP C-99) in exosomes written in this project is published (Liu L#, Thakur A#, Li WK#, Qiu G, Yang T, Bing H, Lee Y*, Wu CML*. 2022 Site specific biotinylated antibody functionalized SAM Ag@AuNIs LSPR biosensor for the ultrasensitive detection of exosomal MCT4, a glioblastoma progression biomarker. Chemical Engineering Journal. 137383), and another manuscript is preparing to submit with Acknowledgement of this grant supporting. A few patents are prepared to submit (indirectly related). Biosensing Device for Detecting Cancer (Jan 11, 2022) is submitted to obtain a USA patent.