DOI: 10.1002/alz70861_109037

BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

GENETICS

In-situ glial cell-surface proteomics identities pro-longevity factors in *Drosophila*

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Abstract

Background: Recently, much focus has shifted towards understanding how glial dysfunction may be contributing to age-related neurodegeneration. This is largely due to the many crucial roles glial cells play in maintaining healthy brain function, such as moderating cell-cell interactions, maintaining homeostasis, immune responses, etc. Cell-cell interactions, which are mediated by cell-surface proteins, control nearly all aspects of development and physiology; as such, dysregulation of glial cell-surface proteins in particular is hypothesized to play an important role in age-related neurodegeneration. However, it remains technically difficult to profile glial cell-surface proteins in intact brains, where many cell types intermingle within a very compact region.

Method: Recently, we worked alongside our collaborators to develop a platform to profile spatiotemporally resolved cell-surface proteomes from intact brains in *Drosophila*. Importantly, this enables us to fully profile cell-surface proteomes in-situ and preserve important global dynamics and cell-cell interactions that would otherwise be lost using more traditional proteomics methods. Applying this platform to aging-model (i.e., young and old) flies, we investigated how glial cell-surface proteomes change as during normal brain aging.

Result: We identified several candidate genes associated with neural development and wiring molecules not previously thought to be particularly active in glia or in normal brain aging, including DIP-β, which was associated with significant increases in lifespan when it was constitutively over-expressed in glia as adult flies aged.

Conclusion: Our study is the first to apply *in-situ* cell-surface proteomics to glial cells in *Drosophila*, and fully profile and characterize the glial cell-surface proteomes of aging-model (young and old) flies. Additionally, while DIP-β's role in precise neural circuit assembly during development has been studied extensively, ours is the first to identify DIP-β as a potential regulator of healthy brain function and aging in adult flies.