Selective filtering defect at the axon initial segment in Alzheimer’s disease mouse models

Yu Wu
Alzheimer’s Disease (AD)

Mouse models: APP/PS1, PS1δE9, APPswe, hPS1

MicroRNAs (miRNAs)

- Non-coding RNAs
- Over 1,000 identified miRNAs
- Interact with the complementary mRNA sequences
- Target degradation or translation repression
Upregulation of miR-342-5p in the Hippocampus of AD Transgenic Mice

- 7 miRNAs were upregulated
- 7 miRNAs were downregulated
- miR-342-5p showed an \sim 22\text{-}fold upregulation
Ankyrin G (AnkG) mRNA 3’UTR was a Target of miR-342-5p

Complementary sequences for miR-342-5p are present in the 3’UTR of AnkG mRNA in both mouse and human.
AnkG Plays a Critical Role at the Axon Initial Segment (AIS)

A Selective Filter for Cytoplasmic Transport at the Axon Initial Segment

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AnkG has been associated with the AIS filtering and protein trafficking.
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AnkG Downregulation Induces Impaired Selective Filtering Machinery at AIS

10kDa 70kDa dextran
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Impaired AIS Filtering Might Underlie Functional Defects in APP/PS1 Neurons
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Impaired AIS Filtering Induced Synaptic and Cognitive Defects in APP/PS1 Mice
Summary
Synapse

Synaptic Plasticity

Learning Memory etc.
Myelin Plasticity

Myelin Plasticity

Myelin Sheath

• Formed by oligodendrocytes in central nervous system (CNS)
• Important for the propagation of action potential along axon
• Naked at axon initial segment (AIS) and nodes of Ranvier
Myelin Plasticity

Myelin plasticity
- Structure of myelin
- Structure of nodes of Ranvier
- Length of internode
- Unmyelinated-axon

Motor skill learning requires active central myelination

Ian A. McKenzie,¹* David Ohayon,¹* Huiliang Li,¹ Joana Paes de Faria,¹† Ben Emery,² Koujiro Tohyama,³ William D. Richardson¹‡

Myelin-forming oligodendrocytes (OLs) are formed continuously in the healthy adult brain. In this work, we study the function of these late-forming cells and the myelin they produce. Learning a new motor skill (such as juggling) alters the structure of the brain’s white matter, which contains many OLs, suggesting that late-born OLs might contribute to motor learning. Consistent with this idea, we show that production of newly formed OLs is briefly accelerated in mice that learn a new skill (running on a “complex wheel” with irregularly spaced rungs). By genetically manipulating the transcription factor myelin regulatory factor in OL precursors, we blocked production of new OLs during adulthood without affecting preexisting OLs or myelin. This prevented the mice from mastering the complex wheel. Thus, generation of new OLs and myelin is important for learning motor skills.
Active CNS Myelination is Required for Motor Skill Learning

WT mouse  
Seven nights self-training

$P$-Myrf (-/-) mouse  
Seven nights self-training
Active CNS Myelination is Required for Motor Skill Learning
Running Stimulates OP Proliferation and OL Production
Relative Researches

Plasticity in gray and white: neuroimaging changes in brain structure during learning

Robert J Zatorre\(^1\,^4\), R Douglas Fields\(^2\,^4\) & Heidi Johansen-Berg\(^3\,^4\)

Human brain imaging has identified structural changes in gray and white matter that occur with learning. However, ascribing imaging measures to underlying cellular and molecular events is challenging. Here we review human neuroimaging findings of structural plasticity and then discuss cellular and molecular level changes that could underlie observed imaging effects. Greater dialog between researchers in these different fields would help to facilitate cross-talk between cellular and systems level explanations of how learning sculpts brain structure.
Longitudinal Studies of Structural Changes in Gray and White Matter with Learning
Thanks for your attention!
AnkG mRNA 3’UTR was a Target of miR-342-5p
AnkG mRNA 3’UTR was a Target of miR-342-5p
AnkG mRNA 3’UTR Direct Binds with miR-342-5p

RNase protection assay
Downregulation of AnkG in AD Transgenic Mice Associated with PS1 Mutant

The downregulation of AnkG was due to either accelerated degradation or reduced protein expression at the translation level.
AnkG mRNA 3’UTR was a Target of miR-342-5p

Luciferase Reporter Assays

www.biocat.com
$A\beta$ is derived from the APP after $\beta$- and $\gamma$-secretase cleavages

*Amyloid Hypothesis and Alzheimer’s Disease, Xiaqin Sun and Yan Zhang*
Upregulation of miR-342-5p in AD Transgenic Mice
Upregulation of miR-342-5p in AD Transgenic Mice Associated with PS1 Mutant