

University of Groningen

## The identification of cell non-autonomous roles of astrocytes in neurodegeneration

Li, Yixian

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2018

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Li, Y. (2018). *The identification of cell non-autonomous roles of astrocytes in neurodegeneration*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

## ENGLISH SUMMARY

Aging is a natural process for all living organisms. One consequence of aging is a decline in organ function, including the brain. Aging is a major risk factor for neurodegenerative diseases. Nowadays, the lifespan of the human population increases, resulting in an increased prevalence of neurodegenerative diseases. The pathogenesis of age-related neurodegenerative diseases is complex and multifactorial. A common feature of these diseases is the accumulation of misfolded or aggregated proteins in the brain. This is considered one of the contributory factors in neurodegenerative diseases. Normally, misfolded proteins can be broken down and removed, but in neurodegenerative diseases they accumulate and form aggregates that are toxic to neurons. Specific misfolded proteins are associated with specific neurodegenerative diseases. For example, beta amyloid peptides form the so-called plaques in Alzheimer's disease.

Neuronal function and health are supported by non-neuronal cells, glia. In the brain, there are different types of glial cells, including astrocytes and microglia. Astrocytes are star-shaped cells and are the most abundant glial cells. They have multiple roles in the brain and are involved in maintaining levels of neuronally released chemical signals, energy metabolism, inflammation as well as the repair of injuries. Activation of astrocytes can occur through signals from neurons and microglia, and this helps the astrocytes to support the well-being of neurons. However, chronically activated astrocytes are found in almost all neurodegenerative diseases and can contribute to their pathogenesis. It is now clear that this activation state during disease is distinct from activation in a healthy individual. The mechanisms by which astrocytes can influence neurodegeneration are not fully understood yet. Knowledge about these may ultimately help in the identification and development of therapeutic targets.

In this thesis, the aim is to understand how astrocytes can influence neurodegeneration. For this, we examined the effect of astrocytes on neurotoxicity of a specific misfolded protein that is associated with a neurodegenerative disease. One misfolded protein we used causes the inherited neurodegenerative disease SCA3 (Spinocerebellar Ataxia 3). We also used plaque-forming beta amyloid peptides, associated with Alzheimer's disease. As we cannot use humans as experimental models, we used an animal model that also has astrocytes, and in which neurodegeneration occurs upon the neuronal presence of human misfolded proteins. The model organism we used is the fruit fly, also known as *Drosophila melanogaster*. Although seemingly quite different from humans, 50% of fly genes are conserved in humans, and their astrocytes are functionally similar. Flies have a short lifespan (60-80 days), allowing quick analysis of the effect of a certain treatment. Moreover, the fruit fly can also be used to examine the effect of a large number of genes in specific cells in a short time frame. Research in flies has been very important for human biology and has resulted in the identification of the functions of genes associated with cancer,

neurodegeneration, and many other diseases.

We tested the effect of more than 150 conserved genes in a genetic screen in astrocytes on neurodegeneration by inhibiting individual genes. We identified 46 genes that could enhance or inhibit neurodegeneration. This shows that astrocytes are important modulators of neurodegeneration. When the activity of an enhancer gene, called NF- $\kappa$ B, which causes inflammation, was inhibited in astrocytes, flies lived significantly longer and were also more active, indicative of higher “quality of life”. Similar effects were found in “Alzheimer’s disease flies”, where human beta amyloid peptides were present in the brains. While inhibiting NF- $\kappa$ B in astrocytes is not a cure for neurodegeneration, it extends life and appears to enhance the quality of life. NF- $\kappa$ B-activated inflammation in the brain, however, did not influence the amount of aggregates. Possibly, a future therapy that targets genes in astrocytes can be combined with a therapy that targets aggregates for optimal effects.

So far, we only solved a small part of this puzzle and additional questions remain and arise. For example, what is the effect of other genes that we identified on lifespan? And more mechanistically: what molecular pathways in astrocytes influence neurodegeneration, and how? Will these observations in flies also be true in mammals? It will be of interest to reproduce our findings in mouse models, which more closely reflect humans.

All in all, the work done in this thesis underscores the importance of astrocytes in neurodegenerative diseases and provides insight into how they are influential in the pathogenesis of these diseases.

