Cell-autonomous and non-cell autonomous protection of DNAJB6 in Huntington’s disease

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DOI: 10.33612/diss.101925993

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Document Version
Publisher's PDF, also known as Version of record

Publication date: 2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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CHAPTER 1

OUTLINE OF THE THESIS
Several neurodegenerative diseases are initiated by protein aggregation in neurons and are associated with a multitude of responses in non-neuronal cells in the brain, in particular glial cells like astrocytes.

These non-neuronal responses have repeatedly been suggested to play a disease-modulating role, but how these may be exploited to delay the progression of neurodegeneration has remained unclear.

Interestingly, one of the molecular changes that astrocytes undergo includes the upregulation of certain Heat Shock Proteins (HSPs or chaperones) that are classically considered to maintain protein homeostasis and protect cells from proteotoxic stress.

The aim of my research project was to explore if and how a specific HSP (DNAJB6) expressed either exclusively in neurons or exclusively in astrocytes can provide in vivo protection against protein aggregation and toxicity of Polyglutamine (PolyQ) huntingtin, the mutant protein associated with Huntington’s disease.

Chapter 2 of this Thesis provides a general overview on neurodegenerative diseases, including PolyQ diseases that are characterized by the aggregation of mutant proteins (e.g. huntingtin), neuronal degeneration and astrocyte reactivity. The role of the different HSP families and how they contribute to the protein quality control in the cells are presented. I explain the mechanisms underlying protein aggregation, why protein aggregates are toxic for cells, and why neurons are particularly vulnerable. I also provide an overview of the prion-like processes observed for different disease-causing aggregate species. Next, the roles that astrocytes are thought to play in the healthy brain and in the brain affected by neurodegenerative diseases are presented. I focus on how the astrocytes react to protein aggregation and protein aggregates and how they differ in this when compared to neurons. Moreover, it is discussed how astrocytes may intervene in the process of prion-like spreading of aggregates. Next, a systematic review is provided on what is known about expression of HSPs in astrocytes in neurodegenerative diseases, using data from patients and animal models. Based on all this information our hypothesis is presented in which we propose that the expression of specific chaperones in astrocytes during disease might be not only a “marker of stress” of reactive astrocytes, but instead an important mechanism of non-cell autonomous protection mediated by astrocytes towards neurons.

In Chapter 3, I next describe the in vivo D.melanogaster models that was generated for this research project. To fully explore whether and how the neuronal or astrocytic expression of HSPs contributes to neuroprotection in neurodegenerative diseases, I generated D.melanogaster models that exclusively express a mutant toxic protein in neurons, whilst co-expressing a protective chaperone either in the same neurons or in astrocytes. To do so, we used two different binary expression systems (GAL4-UAS and LexA-LexO) combined with cell-type specific promoters to express the transgenes in all neurons (using the driver elav), in all glial cells (using repo), or specifically in astrocytes (using alrm). Moreover, D.melanogaster models expressing the transgenes in ommatidia cells (using the driver gmr) have been also settled to perform other additional
experiments. Next, I present the data from these *D. melanogaster* models that exclusively express a mutant toxic PolyQ protein in neurons, whilst co-expressing a protective chaperone (DNAJB6) either in the same neurons (to study cell autonomous effects, **Chapter 4**) or in astrocytes (to study non-cell autonomous effects, **Chapter 5**).

Our data show that DNAJB6 can provide cell autonomous protection against PolyQ-mediated neurodegeneration in *D. melanogaster*, which is associated with a reduction in the PolyQ-protein aggregate load in the fly brains (**Chapter 4**). Intriguingly, the exclusive expression of DNAJB6 in astrocytes also provides non-cell autonomous protection against progressive neuronal degeneration and prolongs organismal lifespan (**Chapter 5**). However, this is not accompanied by a reduction in the PolyQ-HTT aggregate load in the fly brains. Rather, under these conditions, a high fraction of astrocytes now contains neuronal-derived PolyQ-HTT aggregates, in line with the suggestion that astrocytes might take up PolyQ-HTT aggregates species to halt neuron-to-neuron spreading, a capacity that is enhanced by DNAJB6 expression. Therefore, our data indicate that astrocytes play a role in the prion-like processes of PolyQ diseases and that the overexpression of specific protective HSPs - such as DNAJB6 - can boost the non-cell autonomous functions of astrocytes in protecting neurons (**Chapter 5**).

In **Chapter 6**, I discuss on how DNAJB6 can lead to neuroprotection in a non-cell autonomous manner. I discuss the mechanisms of prion-like propagation in PolyQ diseases and the possible role of astrocytes in each of these processes. Moreover, I provide ideas on whether and how astrocytes could be used as target for therapy, by boosting their capacity to handle toxic aggregates through the potentiation of their chaperonome and therefore by potentiating their non-cell autonomous protective functions.