Role of glial reactivity in α-synuclein-induced neurodegeneration in the Drosophila model

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Résumé

Parkinson's disease (PD) is a neurodegenerative disorder caused by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Although the majority of PD cases appear to be sporadic, the identification of genes associated with familial forms of PD has led to important insights into its pathogenesis. An abnormal accumulation of α-synuclein, encoded by the gene *SNCA*, triggers the formation of characteristic protein aggregates (Lewy bodies) and the loss of dopaminergic neurons, while mutant forms of this protein such as α-synA30P are associated to familial forms of the disease. However, the mechanism by which α-synuclein promotes toxicity and contributes to neuronal death remains unclear. *Post-mortem* analyses of brain and cerebrospinal fluid from PD patients showed the accumulation of proinflammatory cytokines, indicative of an ongoing chronic neuroinflammation in the affected brain regions. Several studies have confirmed inflammation and immune responses to be determinant factors in disease progression and responsible for pathogenic processes in onset of both familial and sporadic PD. This inflammation primarily mediated by glial cells could be induced by the presence of oxidized and aggregated forms of the α-synuclein or by neuromelanin released from degenerating neurons. It is characterized by the increased presence of activated microglia which are the macrophages of the brain, and circulating immune cells, as well as by the release by these cells of pro-inflammatory cytokines such as the tumor necrosis factor TNF-α, interleukin-1 (IL-1), nitric oxide (NO) and reactive oxygen derivatives. The importance of this inflammation in the pathogenesis has been confirmed recently in particular by the demonstration of the protective role of the glucocorticoid receptor (GR) expressed in microglial cells. A better understanding of the role of inflammation in PD will provide new insights into the pathological processes and help to establish effective therapeutic strategies. For this, animal models are essential to progress in understanding of the PD pathogenesis, more precisely during the pre-symptomatic stage. The first transgenic model of PD was developed in an invertebrate organism, the fruit fly *Drosophila melanogaster* in 2000 by Feany and Bender. These authors have shown that prolonged pan-neuronal expression of human α-synuclein led to progressive locomotor disorders, loss of dopaminergic neurons and the formation of inclusions similar to Lewy bodies. Moreover, it has been shown in our laboratory that the motor deficiencies in the Feany and Bender model correlate with the degeneration of a bilateral group of 15 dopaminergic neurons from the brain protocerebral anterior medial (PAM) clusters that are particularly sensitive to the toxicity of α-synuclein. The role of cellular interactions in neuronal dysfunctions induced by α-synuclein have not yet been studied with precision in the *Drosophila* model. Our project aims at studying the reactivity and the role of glial cells in the neurodegeneration induced by human mutant α-synuclein expression in the fly neurons. Our first results

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have shown that expression of genes encoding specific glial proteins are disrupted during the pathogenesis and that altering the expression of glial genes can significantly modulate the pathogenesis-associated phenotypes. This suggests that focusing on the signaling pathways involved in neuroinflammation in *Drosophila* could provide a better understanding of the molecular mechanisms involved in PD pathogenesis. This could open the door to targeted therapy for the prevention and treatment of this currently incurable disease.