Early changes in astrocytes are associated with neurodegeneration in Parkinson's disease

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Background and aim: Neuroinflammation is a well-known contributor to the alpha-synucleinopathy in Parkinson's disease (PD), in which astrocytes appear to be key mediators and collaborate with activated microglia. The main function of astrocytes is to support neurons. Animal and cell culture studies indicate that astroglia dysfunction may trigger the pathogenesis of PD, particularly, the demise of dopaminergic neurons. The aim of this study was to investigate specific astrocytes changes related to early-stage PD in post mortem human tissue.

Materials and Methods: The study has been conducted on formalin fixed paraffin-embedded anterior cingulate cortex sections of 10 PD cases and 5 controls. Ethics was approved by Human Research Ethics Committee at the University of Sydney. Three astrocytic markers and one pathology marker (S129 phosphorylated alpha-synuclen) were used to study astroglial morphology, reactivity, function and pathology load using immunohistochemistry and immunofluorescence methods. Results: Immunofluorescence revealed no phenotype change in astrocytes in PD, with Aldh1l1 labeling astrocytic cell bodies and GFAP their processes in all cases and controls. In the brainstem stage of PD when biochemical changes occur in limbic regions, astrocytes (S100B and GFAP) appear to be quiescent, whereas when neuronal alpha-synuclein structural pathology appears in limbic cortices, they display a reactive morphology. Quantification of Aldh1l1 immunoreactive astrocytes revealed a loss of astrocytes prior to obvious structural pathology compared to controls.

Current treatments for PD act to alleviate the symptoms of the disease and do not alter disease progression. Deep brain stimulation (DBS) is one such treatment that can be used to successfully alleviate the motor symptoms of PD, and it has been demonstrated that its mechanism of action may include the activation of astrocytes. Furthermore, clinical trials have been conducted to determine whether the delivery of GDNF, to promote dopaminergic neuron survival in the SNc, would be a suitable treatment for the disease. Results so far have been mixed, with some studies showing improvements in patients compared with controls and others showing no difference. It will be important to determine whether small molecules, such as GDNF, can be successfully used to mimic the presence of healthy astrocytes, or whether treatment of astrocytic dysfunction or replacement of the astrocytes themselves will be necessary.

Lipid rafts also have an important role in astrocyte immune response to lipopolysaccharide (LPS). It has been shown that the disruption of lipid raft assembly that occurs in the absence of DJ-1 results in impaired TLR3/4-mediated endocytosis. It has also been shown that Park7-KO astrocytes display alterations in inflammatory cytokine production which could indicate a failure to terminate TLR4 surface signalling. The role of DJ-1 in astrocyte immune function has been further investigated by treating Park7-KO astrocytes with IFN-γ [22]. It was found that DJ-1 regulates astrocyte inflammatory response to IFN-γ by facilitating the formation of a complex of p-STAT1 with its phosphatase SHP1, leading to dephosphorylation of p-STAT1 and termination of signalling. This process was shown to be neuroprotective; IFN-γ treatment resulted in increased neuronal toxicity in Park7-KO brain slices compared with wild-type

Previous studies have shown some benefit of transplanting human foetal midbrain tissue into the brains of patients. Due to practical and ethical implications of conducting such studies on a larger scale, grafts of stem cell-derived dopaminergic progenitor cells are now being developed. If astrocyte dysfunction is key to the development of PD pathology, merely replacing the lost dopaminergic neurons alone may not be successful. Therefore, it will be important to ensure that stem cell-derived grafts have the capacity to produce astrocytes alongside dopaminergic neurons to promote their ongoing survival.

Glia account for over 50% of the cells in the brain and can be divided into various subtypes, of which astrocytes are the most populous. Although the existence of astrocytes was first documented over 100 years ago, relatively few studies are conducted into their roles in neurological disorders and diseases. PD is a common neurodegenerative disease, pathologically characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). The mechanisms of this neuronal degeneration have not yet been clearly elucidated, although astrocytes have been implicated in the pathogenesis of PD. A key aspect of PD pathophysiology is neuroinflammation in the SNc, including the presence of reactive astrocytes. This neuroinflammation has long been considered a downstream response to the death of dopaminergic neurons. However, evidence is building to suggest that astrocytes have an initiating role in PD pathophysiology.

Astrocytes have a range of functions, many of which are essential for maintaining neuronal health. They provide structural and metabolic support, and regulate synaptic transmission, water transport, and blood flow within the brain. They produce various neurotrophic molecules, including glial-derived neurotrophic factor (GDNF), which is especially important for the development and survival of dopaminergic neurons. Astrocytes also contribute to the blood–brain

barrier, which has been shown to be disrupted in patients with PD. Additionally, when an immune response is initiated by microglia, astrocytes surround the area, creating a barrier to prevent the spread of toxic signals into the surrounding healthy tissue.

Evidence is emerging to suggest that disruption of astrocyte biology is involved in dopaminergic neuron degeneration in PD. Although most PD cases are idiopathic, monogenic mutations in 17 genes have been identified and implicated in the development of the disease. A recent study comparing the transcriptome of different human and mouse brain cell subtypes demonstrated that many of the genes where monogenic mutations have been identified are expressed in astrocytes at levels comparable to, or in some cases higher than in, neurons. So far, proteins encoded by eight of these genes have been shown to have a role in astrocyte biology. Here, we review these new findings and discuss their implications in the development of the disease.

Conclusions: The early loss of certain astrocytes may facilitate structural pathology that stimulate a neuroinflammatory reaction in remaining astrocytes.

Note: This work is partially presented at World Congress on Neuroscience and Epilepsy which is held during November 16-17, 2018 at Tokyo, Japan