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Chitotriosidase – shucking the role of microglia in amyotrophic lateral sclerosis

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Cerebrospinal fluid chitotriosidase concentration reflects microglial activation in the spinal cord of in amyotrophic lateral sclerosis patients.

Chitin is a long chain insoluble carbohydrate polymer that is one of the most abundant organic materials in the biosphere, second only to cellulose.[1] It occurs as a key structural molecule in the exoskeleton of invertebrates and cell walls of fungi. It builds up the shells of oysters and clams. Its durable properties are the subject of intense study in biotechnology and materials science. There has been a long-standing assumption that chitin plays no role in vertebrate biology, but this is starting to change; expression of chitin in vertebrate tissues has been verified and potential biological functions of the polymer in higher organisms are just being unravelled.[1]

Chitinases constitute a widely expressed family of hydrolases that cleave chitins. Insects produce chitinases to facilitate moulting. Microorganisms produce them to digest nutrients. The function of chitinases in vertebrates remains unclear, but potentially they play a role in the innate immune system defense against, *e.g.*, fungi and bacteria. The first human chitinase to be cloned and characterised was chitotriosidase, also known as chitinase 1, CHIT1 or ChT. The gene (*CHIT1*) is found on chromosome 1 and encodes a neutral-acting glycosyl hydrolase that is expressed in monocytes and macrophages and, hence, also in miroglia (the resident macrophages of the central nervous system [CNS]). Activation of macrophages and microglia results in increased expression and secretion of chitotriosidase. There are also chitinase-like proteins that bind chitin but lack enzymatic activity. A well-studied member of the chitinase-like protein family is YKL-40.

Although the biological function of chitotriosidase in humans remains elusive, the enzyme has been explored as a potential biomarker for macrophage and/or microglial activation. Patients with Gaucher's disease, an inherited lysosomal storage disease, have macrophages engorged with lysosomal glucocerebroside. In response to this, the macrophages secrete enormous amounts of chitotriosidase; a patient with Gaucher's disease may have a 1000-fold increase in the blood level of the protein compared with normal controls. This can be used both as a diagnostic biomarker and as a marker to follow the effect of treatment.

In neurodegenerative diseases, most studies on microglial biomarkers have been performed in Alzheimer's disease (AD). Recent reports suggest that the cerebrospinal fluid (CSF) concentration of the secreted ectodomain of triggering receptor expressed on myeloid cells 2 (Trem2), a molecule that is selectively expressed on microglia in the CNS and genetically linked to AD, is increased in AD and correlates with CSF tau protein concentration (a marker of axonal degeneration in AD) (http://www.alzforum.org/alzbiomarker/meta-analysis/alzheimers-disease-vs-control-strem2-csf). These results are backed by an extensive literature showing increased CSF concentrations of other microglia- and/or macrophage-derived proteins, including chitotriosidase and YKL-40.[2] When measured in blood, the concentrations of most of the microglia-related proteins are higher than in CSF and probably reflect release from monocytes and macrophages in peripheral blood rather than CNS-related changes.

In the current issue of *JNNP*, Steinacker *et al*. report on chitotriosidase concentrations in CSF and serum from patients with amyotrophic lateral sclerosis (ALS) compared with results obtained from patients with a broad range of other neurodegenerative diseases, including frontotemporal dementia, AD, Parkinson's disease and Creutzfeldt-Jakob's disease (CJD), as

well as both neurologically healthy controls and ALS mimics.[3] There was a striking increase in CSF chitotriosidase concentration (measured by enzyme-linked immunosorbent assay; there are also assays for chitotriosidase activity but for those one needs to take a common *CHIT1* polymorphism that renders the enzyme inactive into account[4]) in ALS compared with all other diagnostic groups, except CJD. The highest concentrations were seen in patients with rapidly progressive ALS and there were positive correlations with both neurofilament light and heavy concentrations (classical markers of axonal degeneration in ALS), suggesting that CSF chitotriosidase concentration could be a disease activity marker in ALS. Additionally, the authors verified that chitotriosidase expression in the spinal cord was confined to cells that stained positively with microglia and macrophage markers (the staining was particularly strong in the spinal cord from ALS patients). No robust changes in chitotriosidase concentration were detected in blood, suggesting that a large proportion of blood-based chitotriosidase is derived from non-CNS sources, similar to what has been seen in studies of AD.

Taken together, Steinacker *et al*. demonstrate prominent microglial activation in the spinal cord of ALS patients. This activation correlates with clinical and biochemical markers of disease activity and can be quantified using an assay for CSF chitotriosidase. The results point towards microglial activation as an important feature of ALS pathophysiology and a potential therapeutic target. However, before such a conclusion can be drawn, longitudinal studies with repeated samplings are needed to elucidate when, during the disease course, the microglial activation signal becomes apparent and how CSF chitotriosidase concentration changes with disease progression. Are patients with the highest increase in CSF chitotriosidase concentration over time better or worse off in terms of disease progression than individuals with no or only a modest increase?

Declaration of Conflicting Interests

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