

Letter to the Editor: Autoimmune pathogenic mechanisms in Huntington's disease.

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Dear Editor,

with this letter we would like to describe the most recent evidences highlighting the role of autoimmunity in Huntington's Disease (HD) pathogenesis.

Huntington's disease (HD) is a inherited neurodegenerative disorder characterized by marked psychiatric, cognitive and motor impairments. The features of the disease are caused by a CAG codon/polyglutamine repeat expansion in the huntingtin gene, which leads to the expression of a mutated form of the huntingtin protein (mHtt) in cells of the central nervous system [1]. There is now emerging data providing compelling evidence for immune abnormalities in HD, which are central to the disease process.

At the cellular level, neuronal dysfunction has been proposed to be mediated by intermediate stages of polyglutamine aggregates [1] which lead to cytoplasmic and nuclear inclusions of aggregated mHtt that are already present at the onset of the disease . The specific mechanisms linking the abnormally expanded huntingtin with the pathogenesis of HD are not well understood, but experimental data suggest that excitotoxicity, metabolic impairment and oxidative stress are all involved in the neurodegenerative process [1]. The recent development of a transgenic mouse in which astrocytes were engineered to express the mHtt, has demonstrated that expressing the mutant protein only in this cell type can drive neurological impairments. The question on the specific role of astrocytes in immunity and HD needs to be addressed. In pathological conditions, astrocytes can be activated to produce cytokines, but are unlikely to behave as efficient antigen-presenting cells, because the upregulation of major histocompatibility complex class II molecules on this cell type is a rare event [2].

mHtt has been reported in monocytes, microglia and astrocytes of HD patients [3], but the detection of mHtt expression in cell populations outside the CNS has received only limited attention, with a single report describing nuclear inclusions in the postmortem muscle tissue of a HD patient [4]. Interestingly, there is increased complement biosynthesis (for example, C3 and C9) by microglia in the brains of HD patients, and so it has been proposed that the complement system is activated in

the membranes of neurons, thus inducing cytotoxicity, which may in turn contribute to neuronal death [5]. The I κ B kinase/nuclear factor- κ B signaling pathway that triggers IL-6 release is also upregulated by mHtt, potentially participating in neurotoxicity [6].

The correlation of mHtt and disease expression in various systems, originating in peripheral tissues, is proving very interesting and intriguing. Indeed it can be surmised that the soluble or aggregated forms of mHtt are released on neuronal cell death, and subsequently detected and captured by immune cells as immunogenic molecules. Misfolded mHtt could be sensed as an “infectious” protein triggering an immune response in much the same way as other proteins—for example, extracellular amyloid can be taken up by macrophages through a phagocytic or receptor-mediated endocytic process [7]. Remarkably, synthetic polyQ peptides can also be ingested by cells in culture, which can then translocate to the nucleus where they become cytotoxic [8]. Moreover, internalized fibrillar aggregates are able to interact with soluble cytoplasmic proteins [9].

Two hypotheses emerge from these concepts: the release of immunogenic molecules from dying neurons could trigger an immune response, or sensitize the immune cells to the inflammatory environment. Alternatively, the intrinsic microglial expression of the mHtt might compromise their physiological function and exacerbate the release of pro-inflammatory cytokines, quinolinic acid (QA) and oxygen species..

There is therefore accumulating evidence that the immune system is activated in HD, and two consequent mechanisms could be proposed to account for this. In the first instance, the altered immune profiles as detected in pre-symptomatic HD patients would suggest that immune activation takes place before neuronal degeneration. In an alternative scenario, the expression of mHtt could sensitize immune cells to overreact toward degenerating neurons.

Dissecting the contribution of the immune response to HD pathology, and fully understanding whether this phenomenon is a cause or a consequence of the disease, is still not clear.

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