Neuroinflammation accompanying glial mutations: pathogenetic aspects and similarities to progressive multiple sclerosis

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Previous studies by the group of Rudolf Martini have shown that low-grade secondary inflammation can be a highly pathogenic modifier and amplifier of CNS neuropathology in mouse models with primary neural perturbation. Initial studies in transgenic proteolipid protein 1-overexpressing mice, a model of leukodystrophy, revealed that demyelination and axonal damage are exacerbated by clonally expanded and antigen-specific CD8+ T-lymphocytes in a process dependent on T-cell receptor and the effector molecules perforin and granzyme B.

Additional studies in mouse models of inherited lysosomal storage disorders, in which the causative mutation is not restricted to oligodendrocyte function, demonstrated that CNS inflammation can also amplify disease in models of neurodegenerative diseases.

These observations could have important implications for subtypes of multiple sclerosis. Recent concepts postulate that the progressive forms of MS might have an underlying cytodegenerative cause that is modulated by superimposed inflammatory episodes. This hypothesis is supported by two case reports of multiple sclerosis patients with point mutations in the PLP1 gene.

In order to test the pathogenicity of these PLP1 point mutations, we introduced them into mouse models mimicking the exact genetic situation described in the patients. The newly generated models exhibit alterations in CNS myelin ultrastructure and develop a mild and diffuse demyelinating phenotype at advanced age. In addition, they show progressive damage of myelinated axons, degeneration of retinal ganglion cell neurons and CNS abnormalities as revealed by non-invasive imaging approaches such as OCT and MRI. These neuropathological features clinically manifest in impaired motor performance as assessed by rotarod analysis. Importantly, the progressive CNS abnormalities are also accompanied by low-grade inflammation, comprising increased numbers of CD8+ T-lymphocytes and microglial activation.

These observations suggest that glial mutations can lead to axonal perturbation and secondary inflammation with similarities to progressive MS. The newly generated models can be used to analyse the impact of secondary inflammation in progressive MS. Furthermore, the models are valuable tools for developing inflammation-related and -unrelated treatment options of the mostly therapy-resistent disorder.