

Demyelination during multiple sclerosis is associated with combined activation of microglia/macrophages by IFN- γ and alpha B-crystallin.

Bsibsi, M.¹, Peferoen, L.A., Holtman, I.R., Nacken, P.J., Gerritsen, W.H., Witte, M.E., Van Horssen, J., Eggen, B.J., Van der Valk, P., Amor, S., Van Noort, J.M.

¹Delta Crystallon, Zernikedreef 9, 2333, CK Leiden, The Netherlands.

Research question and background

Activated microglia and macrophages play key roles in driving demyelination during multiple sclerosis (MS), but the factors responsible for their activation remain poorly understood. Associated with areas of damage in MS is the widespread, up to 20-fold enhanced expression of the glial stress protein HSPB5 that is selectively induced in glial cells by oxidative stress, and serves to limit the potentially deleterious effects of such stress. We have recently shown that extracellular HSPB5 acts as a TLR2 agonist with a specific requirement for CD14 as co-receptor, which limits its signalling function to microglia and macrophages. The HSPB5-induced microglia/macrophage response is typified by production of large amounts of IL-10, modest amounts of TNF- α and IL-6, and absence of any IL-1 β or IL-12 release. This response profile is characteristic for an immune-regulatory phenotype. The inherent plasticity of innate responses by microglia and macrophages, however, renders their protective regulatory response to HSPB5 susceptible to re-programming. Given that IFN- γ can be secreted by infiltrated T cells in areas of active demyelination during MS we examined its effect on the HSPB5-induced response of microglia and macrophages.

Methods and tissues used

Cultured human microglia and macrophages were exposed to HSPB5 in the presence or absence of IFN- γ . Microarray studies were performed on the activated cells at different time points. The markers unregulated by IFN- γ were examined using immunohistochemistry on tissues sections of post-mortem brain tissue samples obtained from patients without neurological disorders and patients with MS with a focus on normal appearing white matter, and preactive and active lesions.

Results and conclusion

Exposure of cultured microglia and macrophages to IFN- γ abrogated subsequent IL-10 induction by HSPB5, and strongly promoted HSPB5-triggered release of TNF- α , IL-6, IL-12, IL-1 β and reactive oxygen and nitrogen species. In addition, high levels of CXCL9, CXCL10, CXCL11, several guanylate-binding proteins and the ubiquitin-like protein FAT10 were induced by combined activation with IFN- γ and HSPB5. As immunohistochemical markers for microglia and macrophages exposed to both IFN- γ and HSPB5, these latter factors were found to be selectively expressed in inflammatory infiltrates in areas of demyelination during MS. In contrast, they were absent from activated microglia in normal-appearing brain tissue. Together, our data suggest that inflammatory demyelination during MS is selectively associated with IFN- γ -induced re-programming of an otherwise protective response of microglia and macrophages to the endogenous TLR2 agonist HSPB5.

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