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Combined neuropathology and in situ sequencing characterization of meningeal inflammation in progressive multiple sclerosis.

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Introduction:

Chronic compartmentalized inflammation in central nervous system niches, such as the leptomeninges, perivascular spaces and choroid plexus plays a key role in the pathogenesis of progressive multiple sclerosis (pMS). In particular, high levels of meningeal inflammation were found associated with a substantial "surface-in" gradient of neuronal loss and microglia activation in GML and NAGM with early and severe disease progression.

Objectives/Aims:

We aimed to better characterize the inflammation using immune-related gene profiling of meningeal infiltrates in pMS.

Methods:

Formalin-Fixed Paraffin-Embedded (FFPE) sections from 60 post-mortem MS progressive cases and 10 healthy donors were used for immunohistochemistry and morphometric count, phenotype and location analysis of immune cells in the meninges. 6 MS cases with substantial meningeal inflammation and 3 controls were selected to employ a new technology (CARTANA applied to Nikon Ti2-E microscope with single-cell resolution) allowing in situ gene sequencing (ISS) analysis of a selected pool of 157 immune-related genes. With this technique the mRNA is sequenced directly on the selected region of interest (ROI: meningeal infiltrate).

Results:

Detailed meningeal cell count analysis demonstrated significantly increased numbers of B cells in 26 out of the 60 examined MS cases (43%) characterized by the highest degree of meningeal inflammation (>50 cells/field). In particular, B cell numbers were higher than both macrophages ($p=6.218x10-13$) and T cells ($p=7.000x10-4$). ISS analysis revealed significant increases ($p<0.05$, fold change>1.5) of 85 out of the 157 examined genes in MS inflamed meninges compared to controls, including: CD209, CXCR5, CD19, CD8, LTBR, CD27, Granzyme B, TNFRSF1A and TSPO. KEGG pathway analysis suggested that these genes were mainly associated with viral protein interaction with cytokine/cytokine receptors, B cell receptor signaling, PD-L1 expression and PD-1 checkpoint pathways and TNF signaling. Gene ontology analysis revealed that most of the biological processes linked to these molecules involve regulation of the type 2 immune response, regulation of dendritic cell chemotaxis, membrane fusion involved in viral entry into host cell and regulation of T cell activation and polarization.

Conclusion:

Highly specialized immune and inflammatory responses, possibly involving anti-viral immunity, persist in the meninges of progressive MS and may sustain intrathecal chronic inflammation.

Disclosures:

nothing to disclose