

Title: Determining immunoglobulin G subclass profiles of tertiary lymphoid structures in a post-mortem multiple sclerosis case

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Abstract:

Multiple Sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS). The relative grade of meningeal inflammation and the presence of tertiary-lymphoid structures (TLS) in MS is associated with a more severe and progressive disease course. The immune cell composition of TLS in MS is unclear and it is not known whether the immune profiles of TLS are distinct in different CNS compartments that harbour inflammatory cells. This study aims to characterise the immunoglobulin profiles of TLS and other CNS inflammatory areas in post-mortem brain tissue.

Methods: Using formalin-fixed paraffin-embedded post-mortem tissue from the Dame Ingrid Allen Tissue Collection at Queen's University Belfast, in-depth molecular profiling of TLS and other CNS inflammatory compartments was undertaken. Nanostring digital spatial profiling whole transcriptome analysis was performed on 2 MS cases harbouring TLS. Selected RNA candidates were subsequently validated using the RNAscope multiplex assay. Immunohistochemical (IHC) staining of IgG4 and IgG3 was undertaken to determine if there is a distinction between these IgG subclasses in different inflammatory CNS compartments.

Summary of results: Highest expressed genes in TLS were IGHG4 and IGHG3. IHC analysis revealed that relative to other meningeal inflammatory sites there was a high expression of IgG4 within TLS. No IgG4 detection was observed in grey or white matter perivascular spaces. IgG4+ cells did not co-localise with CD138+ plasma cells which represented 10% of cells within TLS.

Conclusions: These findings demonstrate that TLS may have unique immune signatures in comparison to other areas of compartmentalised inflammation in MS. Determining the immune signatures of TLS and if there are distinctions between other inflammatory CNS spaces will be critical to increase our understanding of pathological mechanisms in progressive disease.

1. Trend S, Jones AP, Cha L, et al. Higher Serum Immunoglobulin G3 Levels May Predict the Development of Multiple Sclerosis in Individuals With Clinically Isolated Syndrome. *Front Immunol.* 2018;9:1590. doi:10.3389/fimmu.2018.01590