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Identification of early neurodegenerative pathways in progressive multiple sclerosis

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ABSTRACT:

Progressive multiple sclerosis (MS) is characterized by unrelenting neurodegeneration, which causes cumulative disability and is refractory to current treatments. Drug development to prevent disease progression is an urgent clinical need yet is constrained by an incomplete understanding of its complex pathogenesis. Using spatial transcriptomics and proteomics on fresh-frozen human MS brain tissue, we identified multicellular mechanisms of progressive MS pathogenesis and traced their origin in relation to spatially distributed stages of neurodegeneration. By resolving ligand–receptor interactions in local microenvironments, we discovered defunct trophic and anti-inflammatory intercellular communications within areas of early neuronal decline. Proteins associated with neuronal damage in patient samples showed mechanistic concordance with published in vivo knockdown and central nervous system (CNS) disease models, supporting their causal role and value as potential therapeutic targets in progressive MS. Our findings provide a new framework for drug development strategies, rooted in an understanding of the complex cellular and signaling dynamics in human diseased tissue that facilitate this debilitating disease.

STATEMENT:

This study systematically investigated disease mechanisms of multiple sclerosis (MS) in human post-mortem brain tissue. Applying state of the art sequencing and proteomics techniques to MS patient brains, Kaufmann et al. tracked a large number of molecular disease pathways in parallel and for the first time in direct relation to the progression of neurodegeneration. As a result, the authors uncovered a previously unknown relation between growth factor disturbances and neuronal decline in the progressive phase of MS, where current therapeutics are ineffective. Thus, the study lays important groundwork for the development of future MS therapeutics.

BACKGROUND:

The project was a fruitful collaboration between the Institute of Neuroimmunology and Multiple Sclerosis (INIMS) headed by Prof. Manuel Friese and teams from the University of Oxford (Prof. Lars Fugger) and the Max-Planck-Institute of Biochemistry (Prof. Mathias Mann).

The first author, Dr. Dr. Max Kaufmann, is a clinician-scientist working as a medical doctor at the UKE Department of Neurology and as a researcher with a sequencing and data science expertise in the lab of Prof. Friese. Funded by the Stifterverband (MS Clinician Scientist Program) and the DFG Walter Benjamin Program, Max performed his work on the project at the INIMS and during a postdoctoral research stay at the University of Oxford (Prof. Lars Fugger).