CASE STUDY

Comprehensive analysis of microglia across neuropathological stages of Alzheimer's disease (AD)

Who: Stefan Prokop, MD
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Stefan Prokop, MD, is a Neuropathologist and Research Fellow at the University of Pennsylvania School of Medicine. His work is focused on Alzheimer's disease (AD) with a specific interest in the role of the immune system in AD pathogenesis and progression.

NanoString Assay selection:

nCounter® Human Neuropathology Panel
nCounter® Human Neuroinflammation Panel
GeoMx™ Digital Spatial Profiler (DSP)

Project Summary:

The pathognomonic protein deposits in AD elicit an activation of microglia, but the role of this innate immune activation in the course of AD is controversial, in part because mouse models of AD pathology do not fully capture the complex human disease condition. To tackle this problem, we undertook a comprehensive analysis of microglia in different stages of AD in human brains to lay the groundwork for mapping the innate immune response towards extracellular and intracellular pathologies in human neurodegenerative disease.

Morphologic characterization of microglia in different stages of AD using immunohistochemical markers revealed increased microglial activation with advancement of AD neuropathological changes and an increase in dystrophic microglia in late disease stages. Our findings were corroborated with cell type and pathway specific gene expression profiling using the nCounter Human Neuropathology Panel, which demonstrated an increase in microglial activation with progression of AD neuropathological changes. This analysis also revealed distinct differences in gene expression profiles derived from patient samples carrying an AD associated risk variant of the microglia receptor Trem2. We further honed in on these differences by using the nCounter Human Neuroinflammation Panel to elucidate differentially regulated pathways in AD patients carrying Trem2 risk variants in comparison to disease stage matched patients with a normal variant of Trem2. Finally, we employed Digital Spatial Profiling technology, which enabled morphology-driven, multiplex protein expression analysis to analyze 35+ protein targets at increasing distances from amyloid plaques in these patient samples in order to assess the effects of pathology on microglia phenotype.

Our studies demonstrate that combining morphologic characterization of microglia cells with novel cell type and pathway specific gene expression analysis in human post mortem brain specimens allows for interrogation of the innate immune system in the complex environment of a coexisting multitude of different protein pathologies in AD and provides novel insight into the role of the immune system in AD pathogenesis and progression.

"The fact that [NanoString] allows for the use of FFPE tissue…combined with the speed of results generation are all key advantages over current sequencing platforms. Additionally, multiplexed quantitative protein analysis is one of the biggest needs in neuroimmunology research… and GeoMx DSP not only allows for the quantification of 35+ proteins in 1 sample, but also enables spatially resolved mapping of the quantified proteins."

Stefan Prokop, MD

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