Unravelling SAA-mediated immune responses to bacterial-derived amyloids in the central nervous system

Aurélie Hofkens (1), Peter Verstraelen (1), and Winnok H. De Vos (1)
1) Laboratory of Cell Biology and Histology, University of Antwerp.

Recent studies indicate that gut inflammation can exacerbate the risk of developing Alzheimer's Disease (AD). Our lab found that bacterial amyloids act as potent immune inducers in the gastro-intestinal tract and its enteric nervous system (1). In this context, serum amyloid A3 (SAA3) emerged as a key regulator driving a pro-inflammatory feed-forward response, characterized by cytokine secretion and T-cell infiltration. Since SAAs are acute-phase proteins with pro-inflammatory and amyloidogenic properties, which are elevated in the brains of AD patients, we asked whether they play a role in pathogenic gut-brain communication in AD. To investigate this, we administered intraperitoneal injections of the bacterial amyloid curli in C57Bl6 mice. This caused a general increase in circulating SAA protein levels and a specific, restricted elevation of Saa3 expression at brain borders. As a more direct means to interrogating the putative function of SAAs in AD pathology progression, we stereotactically injected adeno-associated viral vectors that cause constitutive Saa3 expression into the hippocampus of one-month-old APP/MAPT mice. Through RNA-Scope and quantitative immunofluorescence staining, we will evaluate the impact on microglial activation and Aß load, respectively. Lastly, we are investigating whether this SAA loop is conserved in humans by exposing iPSC-derived microglia progenitor cells to curli and Aß. Preliminary results indicate that these cells produce SAA1/2 in response to curli, making them a good human model to further investigate. By uncovering the role of SAAs in early immune-driven mechanisms of AD pathogenesis, we aim to provide novel insights that contribute to the development of disease-modifying therapies for this devastating disorder.

(1) Verstraelen et al (2024). CMGH, 18(1), 89–104.