DOI: 10.1002/eji.202470200

European Journal of Immunology
Clinical-Basic-Translational

1134 – WS59.1

Blood Brain Barrier transmigration triggers inflammasome activation in Th lymphocytes during neuroinflammation

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Rationale: Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS), characterized by infiltration of immune cells into the brain. The disease is initiated when self-reactive T cells are activated in the periphery, after which they travel to the CNS through the blood brain barrier (BBB). Once inside, an inflammatory cascade is triggered, causing damage to neuronal tissue, which results in neurological disabilities. Up to now, the role of the inflammasome herein was mostly studied in innate immune cells. However, recently it was shown that inflammasome activation in adaptive immune cells plays a role in other autoimmune diseases. Here, we aim to identify whether inflammasome activation in T helper cells is increased in MS patients, and whether it contributes to disease pathogenesis and progression.
Methods/Results: RNA analysis of ex vivo samples of MS patients and healthy controls reveals that inflammasome related markers are upregulated in CD4 T cells of MS patients. To visualize inflammasome activation in vivo, we used a preclinical mouse model, experimental autoimmune encephalomyelitis (EAE), in ASC-reporter mice. Herein, we identified an increase in inflammasome activation in the CD4 T cell subsets Th17, Th17.1 and Tregs, over time **exclusively** in the CNS. Lightsheet microscopy of whole brains of healthy and EAE induced ASC-reporter mice show a clear increase in immune cells containing inflammasome activation during disease. In NLRP3 knock out mice, EAE induction resulted in significantly lower disease scores compared to WT mice. Importantly, this coincided with a decreased CNS infiltration of Th1 and Th17 subsets. Finally, using human in vitro BBB migration assays, we found that only Th cells show increased inflammasome activation after BBB transmigration. Also, inflammasome activation in Th cells increased their migration rate, linking the inflammasome to the propensity of Th cells to migrate across the BBB.
Conclusion: These results indicate that inflammasome activation in Th cells is crucially involved in autoimmune neuroinflammation. Importantly, it appears to be linked to BBB transmigration, which is an initiating player in EAE and MS. Therefore, inhibition of inflammasome activation specifically in Th cells could be a possible therapeutic modality to treat MS patients.

