Is Parkinson’s disease the result of autoimmunity arising from Influenza A infection of the brain?

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Purpose/Objective: The mechanism of dopaminergic neuronal cell death remains a mystery in Parkinson’s disease. Compelling epidemiological evidence links Parkinson’s disease with Influenza A infection, with 5 million people developing the Parkinson’s associated disease, was also examined. Mice were primed against alpha synuclein by intranasal delivery of the neurotropic H1N1 A/WSN/33 Influenza strain. Following infection, brains were harvested and examined for the presence of the virus, T cell infiltrate and dopaminergic neuronal loss by immunohistochemistry and flow cytometry. Murine behaviour was also examined for Parkinsonian symptoms. A potential autoantigen, alpha synuclein; a protein central to the pathology in Parkinson’s disease, was also examined. Mice were primed against alpha synuclein in CFA and T cell behaviour examined.

Results: Preliminary data using our murine model has shown that the Influenza virus was detected in the midbrain as late as 21 days post infection. T cell subsets were also detected in the brain following infection. In addition to this, we were able to generate alpha synuclein reactive T cells, and these cells were able to traffic to the brain.

Conclusions: Identifying autoimmune mediated dopaminergic neuronal loss would radically change therapeutic approaches and may thus provide new targets to prevent the disease or preserve the quality of life of the patients. We thus need to further examine the aberrant immune response in Parkinson’s disease.

Materials and methods: The expression of IL-33 and its receptor ST2 on retinal pigment epithelial (RPE) cell line was examined by immunohistochemical staining. Next the severity of IRBP peptide induced-EAU was assessed in C57BL/6 mice treated with recombinant IL-33 or PBS. Cytokine secretion and production by the draining lymph nodes (DLNs) or spleen cells were measured at day 26 after immunization.

Results: We demonstrate that RPE cells expressed high levels of both IL-33 and ST2. Administration of IL-33 cytokine to EAU mice led to reduced disease severity. In line with the reduced inflammation in the retina of IL-33 treated mice, the percentage of IFN-γ+ or IL-17+ cells in the DLNs and spleen was markedly lower, while IL-5+ or IL-4+ cell percentage was increased. Furthermore, antigen specific production of IFN-γ, IL-17 and IL-6 by the DLN cells from IL-33 treated mice was also significantly reduced.

Conclusions: Our results suggest that IL-33 may play a protective role in the development of EAU possibly via its known role in promoting the function of alternatively activated macrophages.

Is there a functional role for KCNM1 in the multiple sclerosis?

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Purpose/Objective: A more detailed insight into disease mechanisms of multiple sclerosis (MS) is crucial for the development of new and more effective therapies. MS is a chronic inflammatory autoimmune disease of the central nervous system. The aim of this study is to identify novel disease associated proteins that are functionally involved in the MS brain pathology.

Materials and methods: In a previous proteomics study, brainstem proteins were obtained from Lewis rats with MBP induced acute experimental autoimmune encephalomyelitis (EAE), a well characterized disease model of MS. Samples were collected at different time points: just before onset of symptoms, at the top of the disease and following recovery. To analyze changes in the brainstem proteome during the disease course, a quantitative proteomics study was performed using two-dimensional difference in-gel electrophoresis (2D-DIGE) followed by mass spectrometry.

Results: We identified 75 proteins with a significant abundance difference between the different disease stages. Regulated proteins were mapped to existing biological networks by Ingenuity Pathway Analysis (IPA). Post-synaptic density protein 95 (DLP4), a key player in neuronal signalling and calcium-activated potassium channel alpha 1 (KCNM1), involved in neurotransmitter release, are 2 putative regulators connecting 64% of the proteins identified. The involvement of KCNM1 in macrophage functionality was studied in vitro by using a specific functional blocker for KCNM1, paxillin. We show that blocking of KCNM1 altered myelin phagocytosis and proinflammatory cytokine cytokine release, disease mechanisms which are highly involved in EAE and MS pathology. We are currently investigating possible influences of this blocker on functionality of other disease relevant cells and processes using in vitro and in vivo models.

Conclusions: This study will elucidate to what extent modulation via this ion channel affects disease processes in the context of EAE/MS.