



DAREMUS

Dansk Selskab for Forskning i Multipel Sklerose

Abstract form: Max 350 ord (punkt 3 – 6) på max én A4 side

Ønsker deltagelse i foredragskonkurrencen (4 abstracts udvælges): JA (X); NEJ ()

Navn Ruthe Dieu **Institution** Syddansk Universitet **Alder** 27 (hvis deltagelse i konkurrence)

Følgende struktur bedes fulgt:

1) Titel

Glial and immune regulation of inflammation in the central nervous system

2) Forfattere

Ruthe Dieu, Reza Khorrooshi, Stefan Lienenklaus, Ulrike Muscha Steckelings, Trevor Owens

3) Hypotese

CNS-resident glial and myeloid cells respond to innate stimuli by production of type I interferons (IFNs) that induce and act with anti-inflammatory cytokines to suppress multiple sclerosis (MS)-like disease.

4) Metoder

To study type IFNs in the CNS, I will administer agonists to receptor activator of NF- κ B (RANK), angiotensin 2 receptor (AT2R) and the type I IFN receptor, directly into the cerebrospinal fluid (CSF) of mice. IFN β induction in the CNS and the cellular sources will be investigated in IFN β -luciferase and IFN β -yellow fluorescent protein reporter mice, respectively. Bone marrow chimeric mice are being generated in collaboration with the department of radiation oncology at Odense Universitets Hospital, in order to discriminate between CNS-resident and blood-derived cellular sources of IFN β in the CNS. Flow cytometric sorting of microglia and astrocytes allows further analysis by quantitative real-time PCR. Genes of interest to be investigated include type I IFNs and cytokines. I will examine the effect of CNS-endogenous IFN induction by these agonists on development of experimental autoimmune encephalomyelitis (EAE), an MS-like disease in mice. I will also investigate how injections of IFN β/α directly into CSF affect EAE and to examine mechanism of action.

5) Resultater

Studies in MS and EAE have shown that peripherally administrated IFN β has a protective role. Furthermore, we recently showed that type I IFNs induced in the CNS of EAE mice by a toll-like receptor 3 ligand is

protective against EAE¹. In this present study, other potential IFN-inducing receptors are to be investigated. Preliminary data already show that RANK-signaling induces IFN β .

6) Diskussion

RANK belongs to the TNF-receptor superfamily and has shown to induce IFN β . AT2R activation has anti-inflammatory and neuroprotective effects. An AT2R-specific agonist C21 has shown to suppress EAE and attenuated T-cell and microglial response. An overall prediction is that these ligands can induce CNS-endogenous type I IFNs, which will a protective role in EAE. The findings of this study will increase understanding of normal CNS homeostasis as well as identify new targets for MS therapy.

¹ Khorrooshi, R., et al., *Induction of endogenous Type I interferon within the central nervous system plays a protective role in experimental autoimmune encephalomyelitis*. Acta Neuropathol, 2015.