Karolinska Institutet

Institutionen för Klinisk Neurovetenskap

Genetic and Immunological Regulation of Neuroinflammation

AKADEMISK AVHANDLING
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av

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ABSTRACT

Multiple Sclerosis (MS) affects young adults and is characterized by chronic inflammation and demyelination in the central nervous system that leads to progressive worsening of disease. The cause of MS is incompletely understood and there is a need for more specific and effective treatments.

This thesis aimed to characterize genetically controlled pathogenic mechanisms in the model of MS, experimental autoimmune encephalomyelitis (EAE), and to translate findings from experimental models to human disease.

We demonstrated that genetic risk factors and pathogenic mechanisms in EAE are similar to those of MS. The EAE-susceptible strain had increased expression of MS candidate genes *Il2ra* and *Il7r* among others and up-regulation of MS-associated immunological pathways such as T_H1 and T_H17. Expression of *Il18r1* was increased in both the susceptible strain and in periphery and cerebrospinal fluid of MS patients. This might contribute pathogenically to disease through T cell differentiation and activation. Clinically isolated syndrome (CIS) patients had elevated *IL18R1* expression, thus it could potentially serve as an early disease biomarker.

Using an expression quantitative trait loci (eQTL) approach we detected numerous *cis*-regulated positional candidate genes for EAE and defined several disease correlated gene networks enriched for pathways involved in cell-mediated immune mechanisms of relevance for both EAE and MS. *Mfsd4* was identified as a candidate gene for *Eae34* which conferred a functional effect on T cell proliferation and activation. The importance of autophagy related genes in the pathogenesis of neuroinflammation was investigated. *Atg7* expression was higher in the EAE-resistant strain and in MS patients it associated with remission and less severe symptoms.

Results presented in this thesis collectively demonstrate genetic regulation of known and novel mechanisms in EAE and MS and point to causal pathogenic pathways. Combining various research fields in both human cohorts and experimental models is a promising approach to increase our ability to define MS susceptibility genes and pathways to target for currently unfulfilled therapeutic needs.

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