Institutionen för Klinisk Neurovetenskap

Genetic and Immunological Mechanisms Regulating Neuroinflammation

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Föreläsningssalen CMM L8:00.

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av
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ABSTRACT
Multiple Sclerosis (MS) is the most common neurological disorder in young adults and imposes both health and socioeconomic burdens on society. The cause and aetiology of MS are incompletely understood and current treatments are inadequate. Pathologically, prolonged chronic inflammation and widespread demyelination in the central nervous system leads to atrophy and progressive worsening of disease. This thesis combined use of in vivo animal models, in vitro cellular assays and in silico computational methods to characterise pathogenic mechanisms and translate findings from models to human disease.

The animal model of MS, experimental autoimmune encephalomyelitis (EAE), was evaluated in light of novel findings in MS aetiology and further analyzed to explore differences in strain susceptibility. Susceptible rats had increased interleukin 7 receptor (Il7r) and Il2ra expression as well as altered isoform signatures in naïve lymphoid tissue, setting the stage for T cell differentiation towards pathogenic T helper 1 (T\(_{H1}\)) and T\(_{H17}\) subtypes. Moreover, increased Il18r1 expression described in susceptible rats was explored in MS. Dysregulation of this receptor can mediate disease initiation through T cell differentiation as well as T cell and macrophage activation. IL18R1 levels were increased in peripheral immune and central nervous tissues in MS. Inflammatory molecules that are dysregulated in EAE likely represent true pathogenic mechanisms in humans.

Multiple approaches were used to define tumour necrosis factor (TNF) regulation of disease severity. A region on chromosome 4 in the rat regulated TNF production in macrophages following innate inflammatory stimulation. Additional inflammatory molecules were also genetically regulated, modifying the cellular phenotype and severity of multiple diseases. This specific inflammatory control provides insight into disease pathogenesis and future treatment options.

The approach of combining genetic and immunological approaches in both models and human samples will continue to improve disease understanding and provide novel therapeutics through identification of key regulators and general immune and non-immune pathways.