



**Karolinska
Institutet**

Department of Clinical Neuroscience

Genetic Regulation of Autoimmunity in Experimental Neuroinflammation

THESIS FOR DOCTORAL DEGREE (Ph.D.)

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
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by

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M.D.

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease that affects the central nervous system causing axonal demyelination and leads to significant disabilities. MS affects mainly young adults and incidence of disease in Sweden is around 600 new cases/year. Genetic factors together with lifestyle/environmental influences contribute to MS pathogenesis, though their functional roles and mechanisms leading to disease are incompletely understood and current treatments exhibit modest effect and harmful side effects. Identification of risk genes and elucidation of molecular mechanisms will shed light on disease pathophysiology.

In this thesis, we used experimental autoimmune encephalomyelitis (EAE), an animal model mimicking clinical and pathological features of MS, to genetically dissect and study the role of antibodies (Abs) against myelin and neuronal antigens. Additionally, we attempted to pinpoint risk genes and investigate molecular pathways controlling antibody response and EAE.

Following a hypothesis-free approach, we identified that Ab response against myelin oligodendrocyte glycoprotein (MOG) was under polygenic control and *antigen-presenting lectin-like (APLEC)* genes, encoding C-type lectin receptors (CLRs), were the major regulators. Likewise, Ab response against neurofascin was also genetically regulated and correlated with EAE severity, encouraging further attempts to study MS genetics in relation to severity as well. Moreover, genetic regions controlling Ab response overlapped with EAE-regulating regions, implying common molecular pathways, and Ab titers correlated with disease susceptibility and severity implicating Abs in disease pathogenesis. We identified differential genetic regulation of Th2-related IgG1 isotype versus Th1-related IgG2b isotype. Moreover, the protective effect of IgG1/IgG2b ratio that we observed during EAE may have a potential significance in relation to therapeutic agents that promote Th2 predominance.

Functional studies were performed on congenic lines to elucidate the role of CLRs, able to sense also endogenous alarm signals, in EAE pathogenesis. We identified that macrophage C-type lectin (Mcl) and macrophage inducible C-type lectin (Mincle) receptors, mainly expressed on myeloid cells, are essential for the amplification of the inflammatory response in the CNS and are able to modulate EAE by skewing the immune response towards Th17 pathway. Unraveling molecular mechanisms underlying CLRs signaling is particularly important as these receptors may serve as novel therapeutic targets.

Combining genetic and immunological studies on experimental models is a promising approach that gives insight in disease mechanisms and facilitates the development of effective prognostic, diagnostic or therapeutic tools/agents.