Karolinska Institutet

Institutionen för klinisk neurovetenskap

From genetic associations to biologic implications in Multiple Sclerosis

AKADEMISK AVHANDLING
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ABSTRACT

Every year, 600 people in Sweden develop MS, making it the second most common cause of disability (after accidents) in young adults. The pathophysiology is characterized by inflammation of the central nervous system and impaired neuronal signaling. Although the cause of MS remains elusive, important environmental and genetic contributors to disease risk have been identified. In order to develop better treatment strategies these risk modifying elements need to be functionally understood in the context of MS. Since the vast majority of currently known genetic and environmental factors increasing MS susceptibility have only been discovered in the past 5 years, now is the time to elucidate their biological foundation. This thesis, as the title suggests, focuses on the genetics of MS and how it impacts pathology. In time and content, it straddles the shift between searching for genetic associations (paper I), and understanding their clinical and biological implications (papers II-IV).

The main scientific objective of my PhD project was to characterize the association between the gene encoding the IL-7 receptor α-chain (*IL7R*) and MS susceptibility. First, we show that *IL7R* genotype does not impact clinical characteristics of MS such as disease severity or age at onset (paper II). This suggests that the link to MS susceptibility is indeed due *IL7R*'s influence on disease triggering events rather than an effect of altered clinical manifestation. In paper III we confirm previous reports that the MS associated allele (*IL7*R*C) causes increased expression and production of an alternatively spliced, soluble receptor isoform (sIL7Rα). We show that this isoform has intermediate affinity for IL-7, but contrary to membrane bound IL7Rα, does not bind TSLP. Despite competing with cell associated IL7Rα, sIL7Rα prolongs and potentiates IL-7's bioactivity both *in vitro* and *in vivo* by limiting excessive IL-7 consumption. Furthermore, MS patients homozygous for *IL7R**C have a 2-fold increase in plasma IL-7 levels, consistent with decreased IL-7 consumption as a result of higher sIL7Rα. In order to further map the interface between MS and IL-7 we went on to screen patients' serum IL-7 levels under different treatment regimens (paper IV). We found that MS patients receiving IFNβ therapy have increased serum IL-7 levels compared to untreated patients and healthy controls. The elevated IL-7 levels are coupled with both lower peripheral blood lymphocyte counts during IFNβ treatment, and reduced IL7Rα expression on those lymphocytes. Considering the stable rate at which IL-7 is typically produced, and our data supporting reduced IL-7 consumption, the increase in serum IL-7 is likely a product of slower depletion rather than increased production. Since IL-7 is an immune stimulatory cytokine associated with several autoimmune diseases, therapeutic modulation of this axis may improve clinical outcomes of MS patients, particularly for those receiving IFNβ treatment.

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