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The effect of dietary tryptophan deprivation on autoreactive T cells and the gut microbiome

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Multiple sclerosis is one of the most common autoinflammatory neurological disorders among young adults leading to disability and is so far incurable. A complex interplay between environmental, genetic and autoimmune factors lead to demyelination, axonal damage and neurodegeneration in the central nervous system. Although treatment options with immunomodulatory drugs are advancing, they still come with severe side effects and are not curative. Thus, a better understanding of the underlaying mechanisms of the disease is essential.

There are already different mouse models of the so-called experimental autoimmune encephalitis available that each depict different aspects of the disease. The most used one is based on the widely accepted assumption of autoreactive T cells migrating to the central nervous system and attacking its myelin sheaths.

Interestingly, the essential amino acid tryptophan and its downstream metabolites have been identified to modify immune responses. Moreover, the gut microbiome composition is assumed to play a role in mediating autoimmunity. So as on one hand, autoreactive T cells are known to play a crucial role in the pathogenesis of multiple sclerosis and on the other hand, it has been previously shown that dietary tryptophan depletion inhibits disease induction in the mouse model of the primary progressive form of multiple sclerosis, in this thesis I further investigated that interplay.

Identifying encephalitogenic properties of T cells in response to dietary tryptophan restriction, the results were in line with previous findings of a reduced encephalitogenic phenotype of autoreactive T cells in the mouse model of primary progressive multiple sclerosis. Further experiments on myelin oligodendrocyte glycoprotein-reactive autoantibodies showed no effect of dietary tryptophan restriction on those antibodies. As suggested earlier in my group, dietary tryptophan depletion resulted in mild gut inflammation. The same grade of inflammation in a colitis mouse model though could not prevent from the experimental autoimmune encephalitis. So, I investigated the grade of gut inflammation affecting the susceptibility to experimental autoimmune encephalitis. I saw that severer intestinal inflammation could indeed lead to a similar effect as tryptophan deprivation, although the mechanism may not be the same. A priming effect as an underlaying mechanism of the dietary alteration or inflammation could not be found in my experiments.

To see if disease could also be prevented in the relapsing remitting form of multiple sclerosis, I performed additional experiments in the appropriate animal model. Here, I found not only that the result could not be reproduced, but also that pertussis toxin, used to break down the blood brain barrier in experimental autoimmune encephalitis, seems to have a further immunomodulatory effect. As suggested in literature, in my experiments the myeloid compartment was not altered by it.

In summary, in this thesis I could show that many different mechanisms contribute to the effect of dietary tryptophan deprivation on autoreactive T cells with the gut microbiome composition and the gut-brain-axis standing out as promising targets for future multiple sclerosis therapies. Another important result of my thesis is the unveiling of the limitations of the so far available animal models. My findings show that more comprehensive models are needed to fully depict the disease.