Multi-epitope-engineered tolerogenic dendritic cells effectively dampen EAE

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Background: Although effective in reducing relapse rate, currently available therapies for multiple sclerosis (MS) do not halt disease progression. Whereas several mechanisms underlie this process, epitope spreading potentially is one of the driving forces. Hence, targeting a variety of disease-associated antigens, for instance by the use of myelin antigen-presenting tolerogenic dendritic cells (tolDC), is a promising strategy to re-establish tolerance in a myelin-specific manner. Electroporation with mRNA encoding full-length myelin proteins is an innovative technique to load tolDC with a variety of naturally-processed myelin epitopes.

Aim: To evaluate the efficacy of myelin oligodendrocyte glycoprotein (MOG) mRNA-electroporated tolDC to dampen pathogenic T cell responses in experimental autoimmune encephalomyelitis (EAE).

Materials/methods: 1α,25-dihydroxyvitamin D_3-treated tolDC were electroporated with MOG mRNA to generate MOG-presenting tolDC. MOG_{35-55}-immunized C57BL/6 mice were injected intravenously at days 13, 17 and 21 post-induction with MOG mRNA-electroporated tolDC, MOG_{35-55}-pulsed tolDC, unpulsed tolDC or PBS. From day 7 post-induction onwards, mice were scored daily for signs of paralysis. At day 25, myelin reactivity was evaluated upon restimulation of splenocytes with MOG_{35-55} and other immune-dominant myelin-derived epitopes.

Results: Mice treated with MOG mRNA-electroporated or MOG_{35-55}-pulsed tolDC displayed clinical stabilization, as evidenced by a significantly reduced mean clinical score as compared to PBS-treated mice. Treatment with unpulsed tolDC did not improve the clinical score. Whereas splenocytes from untreated and PBS-treated mice exhibited a strong pro-inflammatory cytokine secretion profile upon restimulation with MOG_{35-55}, this was effectively suppressed in tolDC-treated mice. Interestingly, although EAE was induced using MOG_{35-55}-immunization, epitope spreading could be detected in untreated and PBS-treated EAE mice, but not in tolDC-treated mice.

Conclusion: Treatment with MOG mRNA-electroporated tolDC has a beneficial effect on the clinical course of EAE. Additionally, we demonstrated the need for MOG presentation for optimal clinical efficacy of tolDC treatment, underlining the importance of a disease antigen-specific therapeutic approach.