TLR2 Ligation Modulates the Balance between Regulatory and Th17 Function in Human T-Cells: Implications for Multiple Sclerosis

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Background

By maintaining immunological self-tolerance, a subset of lymphocytes known as regulatory T cells (Tregs) play a key role in preventing the development of autoimmunity. These Tregs express a host of receptors, including pathogen recognition receptors (PRRs) of the innate immune system known as Toll-like receptors (TLRs). Ligation of these TLRs with pathogenic antigens known as pathogen associated molecular patterns (PAMPs) has been reported to modulate Treg function. Ligation of TLR2 in particular, has been reported to reduce the suppressive capacity of murine and human Tregs by unknown mechanisms. However this was recently elucidated upon when ligation of the TLR1/2 heterodimer was observed to enhance interleukin (IL)-6 and transforming growth factor (TGF)-â expression by Tregs. These cytokines have a vital role in regulating the reciprocal and mutually inhibitory relationship between Tregs and T-helper (Th) 17 cells- a subset of lymphocytes which are key in the pathogenesis of autoimmune diseases and protection against bacterial infections. The presence of IL-6 can alter the balance between Tregs and Th17 cells in favour of the latter by inducing differentiation of naïve T cells towards the Th17 lineage, whilst also inducing concomitant inhibition of Treg differentiation.

Aims & Objectives

To study the effects of different TLR2 ligands on the phenotype of Tregs.

Material & Methods

We examined the effect of different TLR2 ligands on the phenotype of Tregs isolated from HS and RR-MS patients.

Results

With this in mind, it was interesting to observe TLR1/2 ligation of human Tregs resulted in not only abrogation of their suppressive capacity, but also their differentiation towards the Th17 lineage. Based on these findings, we hypothesised that Tregs from relapsing remitting multiple sclerosis (RR-MS) patients are more susceptible to TLR2-induced differentiation towards the Th17 lineage, compared with healthy subjects (HS). We examined the effect of different TLR2 ligands on the phenotype of Tregs isolated from HS and RR-MS patients. We found that ligation of the TLR1/2, but not TLR2/6 heterodimer, increased the differentiation of Tregs from RR-MS patients towards the Th17 lineage, compared with HS.

Conclusions

Though such TLR2-induced modulation of Treg activity may lead to effective clearance of some pathogens, it could potentially increase the risk of autoimmunity, or even exacerbation of ongoing disease activity in RR-MS patients. With this in mind, it may be important to revaluate the idea of using autologous Tregs as cell-based alternative to conventional immunosuppressants.