

Expression and function of TLR5 on Human CD4+CD25+ T regulatory Cells.

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It has been suggested that a specific class of T cells, known as T regulatory (Tr) cells, could be used as a cell-based therapy to prevent rejection of organ transplants, without the complications of long-term immuno-suppression. In vivo studies have demonstrated that Tr cells are critical regulators of peripheral tolerance, however the factors which control their generation and function are poorly understood on a molecular level. One of the defining characteristics of human Tr cells is their profound unresponsiveness to polyclonal stimuli. Identification of methods to overcome this anergy will provide valuable information required for future Tr cell-based therapies.

Toll-like receptors, or TLRs, are germ line encoded pattern recognition receptors. Long considered critical to innate immunity, the recent observation that specific subsets of Tr cells selectively express certain TLRs is of considerable interest. Moreover, it appears that this differential expression of TLRs may result in functional consequences, such as inducing Tr cell activation and/or proliferation.

We investigated the effects of a bacteria-derived molecule, flagellin, on human Tr cells. Using quantitative PCR and flow cytometry, we first determined that resting human Tr cells express high levels of the flagellin receptor, TLR-5. This receptor was shown to be functional, as flagellin induced activation of ERK and p38MAPK. Moreover, co-stimulation with flagellin increased the expression of a critical Tr-cell-specific transcription factor, FoxP3. However, biological assays demonstrated that flagellin neither reversed the anergic state of Tr cells, nor improved their suppressive capacity, in either co-culture or pre-treatment conditions. Further experiments will investigate the role of flagellin as a survival and/or differentiation factor for Tr cells.

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