A164 RAPAMYCIN-INDUCED ALTERATION OF THE DC MATURATION PROCESS SUSTAINS THEIR CAPACITY TO INDUCE REGULATORY T CELLS

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Background Dendritic cells (DC) are professional antigen-presenting cells which have unique properties to steer the outcome of immune responses. The authors previously demonstrated that repetitive injection of immature DC (iDC) was able to protect mice from collagen-induced arthritis (CIA). Rapamycin (Rapa) is a macrolide antibiotic with potent immunosuppressive properties that have been ascribed primarily to its inhibitory effects on T cells. More recently the effect of rapamycin on differentiation, antigen uptake and the immunostimulatory capacity of human DC were examined. In the present study the authors investigated the effect of rapamycin on the phenotype as well as the immunogenicity of iDC, and evaluated the tolerogenic potential of such rapamycin-treated DC in CIA.

Methods Bone marrow-derived DCs were generated in the presence of 10 ng/ml of rapamycin during 6 days. Maturation of DCs was induced or not by addition of lipopolysaccharides ± interferon or interleukin 12 (IL-12). Phenotype of iDC and mature DC were characterised by FACS analysis and their cytokine secretions were quantified by ELISA. Repetitive injections of 5×10^5 rapamycin-treated DC were performed in naïve mice and regulatory populations were monitored in various lymphoid organs. In the CIA mouse model, injections of DCs were performed at days 21, 23 and 25 after immunisation.

Results The addition of rapamycin has an impact on the basal and induced expression of major histocompatibility complex class II and co-stimulatory molecules, with a major impact on CD86 expression. These results suggest that the rapamycin alters the maturation process of murine DC. The secretion profiles of the mDCs were also altered by the addition of rapamycin. The decrease of the immunogenicity and antigen-presentation abilities of rapamycin-treated DCs were confirmed in mixed lymphocyte reaction and antigen presentation assays respectively.

In vivo, the repetitive injections of rapamycin-treated or control DCs were able to induce the expansion of IL-10-secreting CD4 CD49b regulatory T cells, but not FoxP3⁺CD25 Treg cells in naïve mice. To evaluate the tolerogenic potential of rapamycin-treated DCs, they were repetitively injected in arthritic mice. The authors observed that mice vaccinated only with Rapa-iDC were protected from arthritis whereas those that received CTL-DC showed highest severity. A specific decrease of IgG2a antibody response was observed in the sera as well as an expansion of IL-10 secreting CD4 CD49b regulatory T cells in the liver of the protected mice.

Conclusion This results suggest that the DC maturation is altered by Rapamycin, improving their tolerogenic potential in vivo. The therapeutic potential of such a cell-based immuno-modulatory strategy might be assessed in rheumatoid arthritis.