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INVITED COMMENTARY

iTregs by vitamins: commentary on 'Retinoic acid attenuates acute heart rejection by increasing regulatory T cell and repressing differentiation of Th17 in the presence of TGF-β'

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Nowadays the CD4 network is a complex story. We all know that after stimulation naïve CD4+ T cells differentiate into T helper (Th)1 cells, mediating cellular immunity and into Th2 cells important for humoral immunity. The traditional view is that T cell populations secrete distinct sets of cytokines [1]. This model of CD4 differentiation has been replaced by a model, that includes a T cell subset that regulates immune responses, the Treg, which has its own master transcription factor, the forkhead transcriptional repressor, FoxP3 and a CD4+ T cell subset called Th17 cells that produce proinflammatory cytokines controlled by the transcription factor orphan retinoid receptor, Rorγt. The CD4 differentiation is a complex story because both Th17 and regulatory T cells are both under the influence of TGF-β. When naive peripheral CD4+ T cells are exposed to TGF-β and antigen they differentiate into induced iTreg but when also IL-6 and IL-23 are present they become IL-17 secreting Th17 cells [2]. Furthermore, identification of these new subsets showed that cytokine production is not as stable as once thought. It now seems that there is a large degree of flexibility of cytokine production [3].

In this issue of Transplant International, Wang *et al.* [4] report that retinoic acid (RA), a metabolite of the nutrient vitamin A, in a TGF-β dependent manner promotes the differentiation of T cells to iTreg and at the same time inhibits the differentiation to the pro-inflammatory Th17 subset. Importantly, the authors prove that these iTregs do have suppressive properties *in vivo*. Using a heterotopic mouse heart transplant model RA plus TGF-β treatment significantly prolonged graft survival, which was associated with increased intragraft numbers of FoxP3 positive cells and absence of Th17 cells. RA, the vitamin A metabolite, drives the TGF-β dependent peripheral generation of suppressive iTregs while abrogating the differentiation of Th17 cells, and not of Th1 cells [5,6] (Fig. 1). Vitamin A must be adsorbed by the intestine, a site where also TGF-β is abundantly produced, from the diet. RA enhances TGF-β signalling, which results in increased FoxP3 expression even in the presence of IL-6 or IL-21. RA also inhibits the expression of IL-6Rα, the transcription factor interferon regulatory factor 4 and IL-23R and thus inhibits Th17 development [7]. These findings suggest that RA regulates the balance between pro- and anti-inflammatory immunity. It is therefore tempting to postulate that RA has a beneficial effect on graft survival after organ transplantation. The study by Wang *et al.* [4] indeed showed that RA plus TGF-β has this positive effect on graft survival. This finding was associated with increased numbers of FoxP3+ in the transplanted heart and their spleen derived iTregs were as suppressive as natural Tregs, supporting the hypothesis for an active role of FoxP3+ iTregs in this transplant model. Given the proved physiological

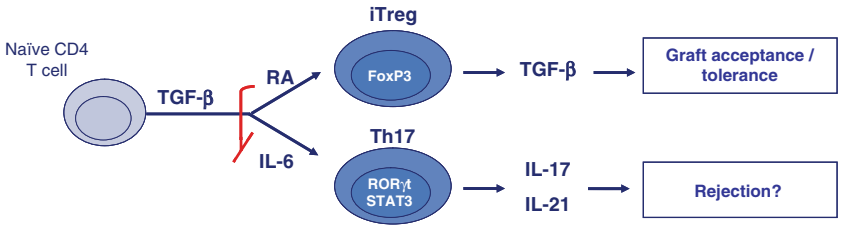

Figure 1 Scheme of induced regulatory T cells (iTreg) by TGF-β and retinoic acid (RA). After activation naïve peripheral CD4 T cells differentiate in the presence of IL-6 and TGF-β into T helper 17 (Th17) cells but when the vitamin A metabolite RA is present these antigen activated T cells differentiate into FoxP3+ iTregs. RA is able to inhibit the TGF-β/IL-6 driven induction of pro-inflammatory Th17 cells that secrete IL-17 and IL-21 and at the same time promote the TGF-β dependent differentiation of anti-inflammatory FoxP3+ iTregs [5,6].

role of FoxP3+ Treg in immune regulation in animal models of graft acceptance and the ability of the vitamin A metabolite RA, to drive the differentiation of antigen exposed T cells into FoxP3+ iTreg are suggestive for a role of RA in the transplantation clinic. It may provide us a simple tool to control anti-donor activity in patients. However, the function of FoxP3+ Tregs in the protection of anti-donor responses in transplant patients is not that clear as in animal models of graft acceptance. In patients FoxP3+ Treg that are present at the graft site are involved in damage control rather than prevent acute cellular rejection [8–10]. Furthermore, the involvement of Th17 cells in alloreactivity in transplant patients has only been marginally demonstrated and requires confirmation [11]. The findings by Wang show that RA mediated effects might be important in transplant patients. However, the complexity of the human immune system, which in transplant patients also is influenced by the given immunosuppressive medication, may make it difficult to identify RA as a key mediator of TGF-β dependent induction of FoxP3+ iTregs. Therefore, a first step to unravel the potential role of RA in the development of FoxP3+ iTregs should be *ex vivo* experiments analysing whether RA plus TGF-β drive the induction of FoxP3+ iTregs in the absence and presence of immunosuppressive drugs of alloantigen activated naïve patient CD4+ T cells. Immunosuppressive drugs like calcineurin inhibitors and mTOR agents influence the production and of TGF-β and interfere TGF-β signalling pathways and thus may have an effect on the induction of FoxP3+ iTregs. Such an approach may help define the importance of vitamin A metabolites in the control of alloreactivity in the clinical transplant setting.

The concept that a vitamin A enriched diet stimulates the development of FoxP3+ iTregs is a new and attractive approach to manipulate the immune system *in vivo*. This may skew the pro- versus anti-inflammatory balance towards the anti-inflammatory FoxP3+ iTregs. RA controlled alloreactivity could be helpful in the prevention of rejection and in the anti-donor response at later stages of immune reactivity in transplant patients.

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