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The impact of TH17 cells on transplant rejection and the induction of tolerance

Sebastiaan Heidt, **David San Segundo**, and **Kathryn J. Wood**
Transplant Research Immunology Group, Nuffield Department of Surgery, University of Oxford, Oxford, UK

Abstract

Purpose of review—This review aims to provide an overview of the latest evidence for the involvement of Th17 cells in the rejection of solid organ allografts. It will also consider the implications of the relationship between the differentiation pathways of Th17 and regulatory T cells (Tregs), as well as their plasticity in the context of transplantation tolerance.

Recent findings—In the absence of the Th1 lineage *in vivo*, Th17 cells are capable of rejecting cardiac allografts, showing the capacity of Th17 cells to cause allograft rejection, at least in experimental models. Th17 cells are relatively unsusceptible to suppression by Tregs, although this may be context dependent. Furthermore, addition of inflammatory signals to a Treg inducing environment leads to Th17 development and established Tregs can be converted to Th17 cells under inflammatory conditions.

Summary—The capacity of Th17 cells to cause allograft rejection is becoming increasingly clear. However, the role and contribution of Th17 cells in allograft rejection in the presence of the full orchestra of T helper cells remains elusive. The apparent resistance of Th17 to be suppressed by Tregs may pose a hurdle for effective immunosuppression and tolerance inducing protocols. Furthermore, the close developmental pathways of Th17 and Tregs and the ability of Tregs to convert into Th17 cells in the presence of inflammatory signals may impede the establishment of specific unresponsiveness to donor alloantigens in vivo.

Keywords

IL-17; Tregs; rejection; plasticity

Introduction

Subsets of T helper cells that develop following repeated antigen stimulation have classically been characterised by their profile of cytokine production into either Th1 or Th2 cells. Th1 cells mainly produce IFN-γ and are involved in cell-mediated inflammatory responses and B cell class switching to complement fixing IgG antibodies, whereas Th2 cells are potent producers of IL-4, IL-5, and IL-13, and are associated with IgE class switching and recruitment of eosinophils. Recently, a novel subset of T helper cells, called

Corresponding author: Kathryn J. Wood, Nuffield Department of Surgery, University of Oxford, Level 6, John Radcliffe Hospital, Oxford, OX3 9DU, kathryn.wood@nds.ox.ac.uk.

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Th17, has been characterised by the production of IL-17 [1,2]. In addition, Th17 cells have the ability to produce IL-17F, IL-21 and IL-22 [3]. Th17 cells are important for the clearance of a variety of pathogens [4], and it has been postulated that the primary function of Th17 cells is to clear pathogens that are not adequately handled by Th1 or Th2 cells [5]. Apart from their protective functions, Th17 cells have been associated with numerous autoimmune and inflammatory diseases [4].

The developmental conditions and transcription factors of the Th17 lineage have also been elucidated, although some controversy still exists. Differentiation of naïve T cells into Th17 cells is driven by TGF-β together with IL-6, or TGF-β with IL-21, whereas IL-23 serves as a stabilizing factor for the commitment to the Th17 lineage [6-11]. In addition, the involvement of IL-1β in the development of Th17 cells has been shown in both human and mouse studies [12,13]. Downstream of IL-6, IL-21, and IL-23, signal transducer and activator of transcription 3 (STAT3) is activated by phosphorylation [14-16]. The transcription factor retinoid-related orphan receptor γt (RORγt) is downstream of STAT3 and has been implicated as the key transcription factor for the Th17 subset [17].

This review summarizes the data that have been published on the role of Th17 in organ transplantation recently. Furthermore, the possible impact of the differentiation relationship and plasticity of Th17 and Treg on transplantation tolerance will be discussed.

Th17 cells and allograft rejection

Early work showing a prolongation of graft survival due to blockade of IL-17 in a mouse cardiac allograft model has led to the notion that IL-17 may be involved in the rejection of allografts [18,19]. Since then, the Th17 subset has been defined and by inference has been suggested to be the cell type responsible for IL-17 dependent graft rejection. Indeed, novel data in a variety of model systems suggest the involvement of Th17 cells in the rejection of solid organ allografts. Th17 cells have been shown to reside within the allogeneic T cell compartment in both mouse and human. When $CD4^+$ T cells were cultured with MHC class II mismatched bone marrow dendritic cells, a fraction of the cells proliferated and produced IL-17, suggesting that alloreactive T cells can have a Th17 phenotype [20]. Even more so, by quantification of the alloreactive memory $CD4^+$ T cell repertoire in normal human blood, it was shown that high percentages of alloreactive cells produced IL-17 [21*].

Galectin-9, a member of the galectin family that has cytotoxic effects on Th1 and Th17 cells, prolonged graft survival in a fully allogeneic mouse cardiac allograft model. Decreased intragraft mRNA levels of both IFN-γ and IL-17 suggested the involvement of both Th1 and Th17 in graft rejection. However, the individual contribution of these cell types to rejection was not investigated [22]. In a mouse model of collagen V (col(V)) induced acute lung rejection, IL-17 mRNA levels in the lung draining lymph node were increased [23*]. Moreover, co-injection of col(V) sensitized lymph node cells with the antigen col(V) lead to a delayed-type hypersensitivity (DTH) reaction, whereas the same protocol under the cover of an IL-17 neutralizing antibody showed an attenuated DTH response, confirming at least a partial role for IL-17 in the rejection process. Additional indirect evidence for the involvement of Th17 in allograft rejection came from a study by Pober and colleagues, who showed a modest neutrophil infiltration upon injection of IL-17 in human skin grafts transplanted onto immunodeficient mice, resulting in mild inflammation [24]. Moreover, transplantation of human artery allografts in humanised mice caused IL-1 driven T cell infiltration coinciding with IL-17 expression. Blockade of IL-17 did not alter total T cell infiltration but reduced graft expression of several chemokines, which likely altered the inflammatory response. IL-17 produced by Th17 cells may therefore be involved in allograft rejection. However, for the interpretation of these data it is

important to remember that multiple cell types can produce IL-17 [5], and therefore it is conceivable that cell types other than Th17 are involved in these inflammatory responses.

Direct evidence on the ability of Th17 cells to cause cardiac allograft rejection came from experiments using mice lacking the Th1 specific transcription factor T-bet. Upon receiving MHC class II mismatched vascularised cardiac allografts, these mice experienced accelerated rejection compared to wild type mice. Histology showed clear signs of vasculopathy, coinciding with an increase of IL-17 expressing lymphocytes and neutrophils. Neutralization of IL-17 resulted in significant prolongation of allograft survival, suggesting that IL-17 was responsible for the rejection [25]. Similarly, $CD8^+$ IL-17 producing cells were associated with costimulator blockade resistant rejection of vascularised cardiac allografts in T-bet knockout mice [26]. Neutralization of either IL-17 or IL-6 negated rejection, confirming the role of IL-17 in this mouse model. From these studies it is apparent that, in the absence of the Th1 pathway of rejection, Th17 cells have the ability to cause allograft rejection. However, from these data it is not clear what the contribution of Th17 cells would be in wild-type recipients. The involvement of Th17 in rejection in the presence of a Th1 response was studied in a model system in which inflammation by TLR signalling was used to elicit allograft rejection. Administration of TLR9 ligand CpG at time of transplantation abrogated costimulator blockade mediated cardiac allograft acceptance in wild type mice by the induction of the inflammatory cytokines IFN-γ and IL-17. Interestingly, when both IL-6 and IL-17 were eliminated, CpG failed to abrogate rejection, indicating an important role for Th17 cells in allograft rejection [27**]. However, a similar study indicates that IFN-γ plays a role in this setting as well, suggesting that Th17 cells have the capacity to cause rejection, but may be redundant [28]. Further evidence that Th17 cells contribute to the rejection process but are not required for the rejection of allografts came from a corneal transplant model. Mice deficient of IL-17 experienced delayed graft rejection compared to wild-type mice, but overall graft survival remained unaffected [29]. Furthermore, the contribution of Th17 cells in clinical transplantation has not yet been widely established. In our preliminary analysis of peripheral blood from renal transplant recipients with acute rejection we can find no evidence for a Th17 signature (San Segundo, Heidt and Wood, unpublished results).

Regulation of Th17 responses

Transplantation tolerance, the long-lived presence of an allograft without the need of immunosuppression, remains the Holy Grail of transplantation. One of the ways to achieve transplantation tolerance may be by induction or transfer of regulatory T cells (Tregs [30]). Regulatory T cells, both naturally occurring (nTreg), as well as induced (iTreg) are capable of inhibiting a variety of cellular immune responses by cell contact or soluble mediators, respectively. Tregs have been shown to prolong graft survival in various mouse models, although there are limitations to those studies [31]. Since Th17 cells appear to be at least involved in transplant rejection, it is important to determine the ability of Tregs to inhibit Th17 mediated immune responses.

Interestingly, when tested in a proliferation inhibition assay, a Th17 clone proved to be resistant to autologous Treg suppression, whereas Th1 and Th2 clones were susceptible to suppression [32]. In line with these observations, Tregs failed to affect IL-17 production when added to $CD4^+$ memory T cells, whereas IFN-γ production was significantly inhibited [33]. Moreover, Tregs promoted the induction of Th17 cells as shown by an increase in the percentage of $IL\text{-}17^+$ cells. Likewise, in an MHC class II mismatched mixed lymphocyte reaction, polyclonal nTregs were capable of inhibiting the production of IFN-γ, IL-2 and IL-13 by $CD4^+$ cells, but actually enhanced the production of IL-17 [20].

Additionally, the resistance of Th17 to Treg mediated suppression has been shown in various autoimmune models. Interestingly, in many of these models, the relative unresponsiveness of Th17 cells to regulation compared to other T helper subsets has been shown. In a type I diabetes mouse model, polyclonal iTregs reduced the percentage of IFN-γ producing cells as well as their IFN-γ production, but did not affect the Th17 population [34]. Similar findings were made in a passive transfer model of experimental autoimmune encephalomyelitis (EAE), where the administration of effector T cells resulted in the development of a profound population of Tregs. When tested *in vitro*, these Tregs were capable of inhibiting the IFN-γ response of $CD4^+CD25^-$ cells towards antigen, but not the IL-17 response [35]. In a model for autoimmune gastritis, each of the three subsets of T helper cells was capable of inducing disease, allowing comparison of the effect of Tregs on all three subsets. Whereas both Th1 and Th2 responses could be inhibited by the addition of polyclonal Tregs, Th17 responses were unaffected by Treg suppression, suggesting that Th17 cells are relatively resistant to suppression by Tregs [36]. However, in the same setting, more potent antigen specific Tregs were capable of inhibiting Th17 responses [37]. Similarly, in the setting of col(V)-induced acute lung isograft rejection, in which an essential role for Th17 cells has been described, splenocytes from col(V)-tolerant mice were capable of ameliorating lung isograft rejection [23*]. These data indicate that antigen specific Tregs may be capable of suppressing Th17 cells, whereas polyclonal Tregs appear to have no or little effect on Th17 cells.

The apparent lower susceptibility of Th17 cells to be suppressed by Tregs as compared to Th1 and Th2 subsets may pose a serious hurdle to overcome when aiming at establishing transplantation tolerance. However, whether Th17 cells are equally sensitive to regulation as their Th1 and Th2 counterparts in the context of transplantation has yet to be firmly established. Our preliminary data suggest that mesenchymal stem cells are more potent than Treg in their ability to suppress Th17 mediated rejection *in vivo* (Feng, Ding, Bushell and Wood, unpublished data). Nonetheless, it appears that antigen specific Tregs may be potent enough to attenuate Th17 driven immune responses. Whether the same holds true for allogeneic Th17 responses is yet to be determined.

Developmental pathways and plasticity of Th17 and Tregs

Induction of $CD4^+CD25^+Foxp3^+$ Tregs from $CD4^+CD25^-$ cells requires the presence of TGF-β [38]. However, by using Foxp3-GFP reporter mice, it was shown that addition of IL-6 to TGF-β inhibited the generation of $CD4^+CD25^+Foxp3^+$ Tregs. Instead, a profound induction of Th17 cells occurred, suggesting that Tregs and Th17 cells can develop from the same precursors depending on the cytokine environment [6]. TGF-β produced by Tregs with the addition of exogenous IL-6 was sufficient for Th17 development [39]. Likewise, culturing naïve T cells with IL-6 deficient antigen presenting cells (APC) under Treg differentiation conditions resulted in the induction of Tregs and not of Th17 cells, whereas culturing with IL-6 competent APCs abrogated Treg differentiation and induced Th17 cell differentiation [27**]. These findings were confirmed in a study in which increased levels of Th17 cells were observed due to the knockout of STAT5, a transcription factor essential for Tregs to respond to IL-2 [40].

The molecular basis for the reciprocal developmental pathways of Tregs and Th17 cells has recently been elucidated. TGF-β induces the expression of both the Treg transcription factor Foxp3, as well as the Th17 specific transcription factor RORγt. In the absence of IL-6, Foxp3 represses RORγt, establishing a Treg phenotype. However, when IL-6 is present, Foxp3 levels are reduced, releasing RORγt from Foxp3 suppression, which leads to a Th17 phenotype [41,42].

Besides the development of Th17 cells from $CD4^+CD25^-Foxp3^-$ cells in the presence of TGF-β production from Tregs supplemented with IL-6, the conversion of Tregs towards Th17 cells themselves occurs under these conditions [39]. The conversion of established $CD4^+CD25^+Foxp3^+$ Tregs towards IL-17 producing cells in addition to their reciprocal developmental pathway has been confirmed to occur *in vitro* under inflammatory conditions [43,44], as well as *in vivo* [13,42]. This conversion of Tregs towards a Th17 phenotype truly affects their function, since Tregs converted *in vivo* by IL-6 production from DC were found to be capable of breaking immune tolerance causing diabetes in a mouse model [45].

Treg conversion towards Th17 cells appears to be gradual. A subset of $Foxp3^+$ Tregs with the ability of producing IL-17, depending on the nature of the stimulus they received was recently described [46*]. By analogy with previous studies, the pro-inflammatory cytokines IL-1 and IL-6 led to the production of IL-17. The presence of Th17 producing $Foxp3^+$ was confirmed in other studies, further establishing the presence of a transitional state in between Tregs and Th17 cells [39,44,47*]. Of note, $Foxp3^+$ Tregs producing IL-17 have some phenotypic and functional dissimilarities with conventional Th17 cells, suggesting that these cells, and their function, may be slightly different [48**].

Given the above, it may not be surprising that CpG induced IL-6 production favoured the development of Th17 cells instead of Tregs, leading to allograft rejection in a murine cardiac transplant model [27]. These data are of interest when one takes into account the production of inflammatory cytokines, including IL-1 and IL-6, due to the impact of ischemia reperfusion injury at the time of transplantation [49]. Indeed, in both vascularised heart iso- and allografts, an early peak of the acute phase cytokines TNF and IL-6 were observed [50], indicating that the mere procedure of transplantation may already skew the immune response away from a tolerant Treg phenotype towards an inflammatory Th17 phenotype.

Discussion

Th17 cells represent a novel subset of T helper cells that can potentially lead or contribute to allograft rejection. However, it is not clear whether the presence of Th17 cells is a prerequisite for allograft rejection, although current data suggest that both Th1 and Th17 cells play a role. Work in autoimmunity suggests that Th17 cells may contribute to the immune response mainly in the context of a Th1-initiated immune response [51]. Alternatively, both subsets may act sequentially with different effector functions, as has also been suggested for autoimmune diseases [52]. In concert with the latter, early involvement of IL-17 in the rejection of kidney allografts has been shown in both murine and human studies, suggesting a role of Th17 cells particularly in the initiation of rejection [53,54].

In the absence of a Th1 response, Th17 cells clearly can give rise to transplant rejection. However, both the Th1 transcription factor T-bet as well as the Th1 cytokine IFN-γ has been shown to inhibit the development of the Th17 lineage [1,2,25,26]. Indeed, there exists a substantial cross-regulation of T helper subsets [55]. Therefore, the question remains whether the contribution of Th17 cells in the presence of a Th1 response is significant. This question needs to be addressed in systems where the Th17 subset is specifically targeted and/or quantified in the presence of both Th1 and Th2 subsets, which is complicated by the fact that Th17 cytokines and cell surface markers are not unique for the Th17 subset [51].

Importantly, when thinking of interfering with rejection by the use of Tregs, it is vital to consider the plasticity of the subset, since the presence of inflammatory cytokines *in vivo* may potentially tip the balance towards a Th17 driven immune response. Targeting these inflammatory signals in concert with the administration or induction of Tregs may be required to achieve Treg mediated transplantation tolerance.

Conclusion

It is becoming clear that Th17 cells can cause or at least contribute to allograft rejection in certain settings. However, in the complex immune response towards an allograft, involving a multitude of cell types, the role of Th17 cells is yet to be defined. It is important to establish what role Th17 cells play in the rejection of allografts since Th17 cells appear to be relatively resistant to regulation. Moreover, the fact that organ transplantation initially creates an inflammatory environment in which Tregs potentially can convert into Th17 cells should be taken into consideration when thinking about Treg therapy.

Recent work suggests a potential role of Th17 cells in organ transplantation, however, much research needs to be done to understand the impact of this cell type in the heterogeneity of an alloimmune response.

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References

1. Harrington LE, Hatton RD, Mangan PR, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol. 2005; 6:1123–1132. [PubMed: 16200070]
2. Park H, Li Z, Yang XO, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol. 2005; 6:1133–1141. [PubMed: 16200068]
3. Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity. 2008; 28:454–467. [PubMed: 18400188]
4. Crome SQ, Wang AY, Levings MK. Translational Mini-Review Series on Th17 Cells: Function and regulation of human T helper 17 cells in health and disease. Clin Exp Immunol. 2009
5. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. Annu Rev Immunol. 2009; 27:485–517. [PubMed: 19132915]
6. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006; 441:235–238. [PubMed: 16648838]
7. Mangan PR, Harrington LE, O'Quinn DB, et al. Transforming growth factor-beta induces development of the T(H)17 lineage. Nature. 2006; 441:231–234. [PubMed: 16648837]
8. Veldhoen M, Hocking RJ, Atkins CJ, et al. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity. 2006; 24:179–189. [PubMed: 16473830]
9. Zhou L, Ivanov II, Spolski R, et al. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nat Immunol. 2007; 8:967–974. [PubMed: 17581537]
10. Korn T, Bettelli E, Gao W, et al. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature. 2007; 448:484–487. [PubMed: 17581588]
11. Nurieva R, Yang XO, Martinez G, et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature. 2007; 448:480–483. [PubMed: 17581589]
12. Manel N, Unutmaz D, Littman DR. The differentiation of human T(H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgammat. Nat Immunol. 2008; 9:641–649. [PubMed: 18454151]
13. Chung Y, Chang SH, Martinez GJ, et al. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. Immunity. 2009; 30:576–587. [PubMed: 19362022]
14. Yang XO, Panopoulos AD, Nurieva R, et al. STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. J Biol Chem. 2007; 282:9358–9363. [PubMed: 17277312]

15. Harris TJ, Grosso JF, Yen HR, et al. Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. J Immunol. 2007; 179:4313–4317. [PubMed: 17878325]
16. Wei L, Laurence A, Elias KM, O'Shea JJ. IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner. J Biol Chem. 2007; 282:34605–34610. [PubMed: 17884812]
17. Ivanov II, McKenzie BS, Zhou L, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell. 2006; 126:1121–1133. [PubMed: 16990136]
18. Antonysamy MA, Fanslow WC, Fu F, et al. Evidence for a role of IL-17 in organ allograft rejection: IL-17 promotes the functional differentiation of dendritic cell progenitors. J Immunol. 1999; 162:577–584. [PubMed: 9886435]
19. Tang JL, Subbotin VM, Antonysamy MA, et al. Interleukin-17 antagonism inhibits acute but not chronic vascular rejection. Transplantation. 2001; 72:348–350. [PubMed: 11477368]
20. Benghiat FS, Craciun L, De Wilde V, et al. IL-17 production elicited by allo-major histocompatibility complex class II recognition depends on CD25posCD4pos T cells. Transplantation. 2008; 85:943–949. [PubMed: 18408572]
21. Litjens NH, van de Wetering J, van Besouw NM, Betjes MG. The human alloreactive CD4+ T-cell repertoire is biased to a Th17 response and the frequency is inversely related to the number of HLA class II mismatches. Blood. 2009; 114:3947–3955. [PubMed: 19713464] * This study shows that a profound proportion of human alloreactive T cells are capable of producing IL-17
22. He W, Fang Z, Wang F, et al. Galectin-9 significantly prolongs the survival of fully mismatched cardiac allografts in mice. Transplantation. 2009; 88:782–790. [PubMed: 19920777]
23. Braun RK, Molitor-Dart M, Wigfield C, et al. Transfer of tolerance to collagen type V suppresses T-helper-cell-17 lymphocyte-mediated acute lung transplant rejection. Transplantation. 2009; 88:1341–1348. [PubMed: 20029330] * This study shows that antigen specific Tregs cells can ameliorate IL-17-mediated acute rejection of lung transplants
24. Rao DA, Eid RE, Qin L, et al. Interleukin (IL)-1 promotes allogeneic T cell intimal infiltration and IL-17 production in a model of human artery rejection. J Exp Med. 2008; 205:3145–3158. [PubMed: 19075290]
25. Yuan X, Paez-Cortez J, Schmitt-Knosalla I, et al. A novel role of CD4 Th17 cells in mediating cardiac allograft rejection and vasculopathy. J Exp Med. 2008; 205:3133–3144. [PubMed: 19047438]
26. Burrell BE, Csencsits K, Lu G, et al. CD8+ Th17 mediate costimulation blockade-resistant allograft rejection in T-bet-deficient mice. J Immunol. 2008; 181:3906–3914. [PubMed: 18768845]
27. Chen L, Ahmed E, Wang T, et al. TLR signals promote IL-6/IL-17-dependent transplant rejection. J Immunol. 2009; 182:6217–6225. [PubMed: 19414775] ** This study shows that proinflammatory signals *in vivo* skew Treg differentiation towards a Th17 phenotype, preventing allograft acceptence.
28. Porrett PM, Yuan X, LaRosa DF, et al. Mechanisms underlying blockade of allograft acceptance by TLR ligands. J Immunol. 2008; 181:1692–1699. [PubMed: 18641305]
29. Chen H, Wang W, Xie H, et al. A pathogenic role of IL-17 at the early stage of corneal allograft rejection. Transpl Immunol. 2009; 21:155–161. [PubMed: 19358887]
30. Wood KJ, Sakaguchi S. Regulatory T cells in transplantation tolerance. Nat Rev Immunol. 2003; 3:199–210. [PubMed: 12658268]
31. Long E, Wood KJ. Regulatory T cells in transplantation: transferring mouse studies to the clinic. Transplantation. 2009; 88:1050–1056. [PubMed: 19898199]
32. Annunziato F, Cosmi L, Santarlasci V, et al. Phenotypic and functional features of human Th17 cells. J Exp Med. 2007; 204:1849–1861. [PubMed: 17635957]
33. Evans HG, Suddason T, Jackson I, et al. Optimal induction of T helper 17 cells in humans requires T cell receptor ligation in the context of Toll-like receptor-activated monocytes. Proc Natl Acad Sci U S A. 2007; 104:17034–17039. [PubMed: 17942669]

34. Van YH, Lee WH, Ortiz S, et al. All-trans retinoic acid inhibits type 1 diabetes by T regulatory (Treg)-dependent suppression of interferon-gamma-producing T-cells without affecting Th17 cells. Diabetes. 2009; 58:146–155. [PubMed: 18984738]
35. O'Connor RA, Malpass KH, Anderton SM. The inflamed central nervous system drives the activation and rapid proliferation of Foxp3+ regulatory T cells. J Immunol. 2007; 179:958–966. [PubMed: 17617587]
36. Stummvoll GH, DiPaolo RJ, Huter EN, et al. Th1, Th2, and Th17 effector T cell-induced autoimmune gastritis differs in pathological pattern and in susceptibility to suppression by regulatory T cells. J Immunol. 2008; 181:1908–1916. [PubMed: 18641328]
37. Huter EN, Stummvoll GH, DiPaolo RJ, et al. Cutting edge: antigen-specific TGF beta-induced Tregs suppress Th17-mediated autoimmune disease. J Immunol. 2008; 181:8209–8213. [PubMed: 19050237]
38. Zheng SG, Wang JH, Koss MN, et al. CD4+ and CD8+ regulatory T cells generated ex vivo with IL-2 and TGF-beta suppress a stimulatory graft-versus-host disease with a lupus-like syndrome. J Immunol. 2004; 172:1531–1539. [PubMed: 14734731]
39. Xu L, Kitani A, Fuss I, Strober W. Cutting edge: regulatory T cells induce CD4+CD25−Foxp3− T cells or are self-induced to become Th17 cells in the absence of exogenous TGF-beta. J Immunol. 2007; 178:6725–6729. [PubMed: 17513718]
40. Laurence A, Tato CM, Davidson TS, et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity. 2007; 26:371–381. [PubMed: 17363300]
41. Ichiyama K, Yoshida H, Wakabayashi Y, et al. Foxp3 inhibits RORgammat-mediated IL-17A mRNA transcription through direct interaction with RORgammat. J Biol Chem. 2008; 283:17003–17008. [PubMed: 18434325]
42. Yang XO, Nurieva R, Martinez GJ, et al. Molecular antagonism and plasticity of regulatory and inflammatory T cell programs. Immunity. 2008; 29:44–56. [PubMed: 18585065]
43. Zheng SG, Wang J, Horwitz DA. Cutting edge: Foxp3+CD4+CD25+ regulatory T cells induced by IL-2 and TGF-beta are resistant to Th17 conversion by IL-6. J Immunol. 2008; 180:7112–7116. [PubMed: 18490709]
44. Koenen HJ, Smeets RL, Vink PM, et al. Human CD25highFoxp3pos regulatory T cells differentiate into IL-17-producing cells. Blood. 2008; 112:2340–2352. [PubMed: 18617638]
45. Radhakrishnan S, Cabrera R, Schenk EL, et al. Reprogrammed FoxP3+ T regulatory cells become IL-17+ antigen-specific autoimmune effectors in vitro and in vivo. J Immunol. 2008; 181:3137–3147. [PubMed: 18713984]
46. Beriou G, Costantino CM, Ashley CW, et al. IL-17-producing human peripheral regulatory T cells retain suppressive function. Blood. 2009; 113:4240–4249. [PubMed: 19171879] * This study shows the capacity of Tregs to produce IL-17 under inflammatory conditions.
47. Voo KS, Wang YH, Santori FR, et al. Identification of IL-17-producing FOXP3+ regulatory T cells in humans. Proc Natl Acad Sci U S A. 2009; 106:4793–4798. [PubMed: 19273860] * This study shows the capacity of Tregs to produce IL-17 under inflammatory conditions.
48. Ayyoub M, Deknuydt F, Raimbaud I, et al. Human memory FOXP3+ Tregs secrete IL-17 ex vivo and constitutively express the T(H)17 lineage-specific transcription factor RORgamma t. Proc Natl Acad Sci U S A. 2009; 106:8635–8640. [PubMed: 19439651] ** This study shows that Il-17 producing Tregs and conventional Th17 cells are not identical with respect to cell surface markers and cytokine production profiles.
49. Ascon M, Ascon DB, Liu M, et al. Renal ischemia-reperfusion leads to long term infiltration of activated and effector-memory T lymphocytes. Kidney Int. 2009; 75:526–535. [PubMed: 19092796]
50. Ishii D, Schenk AD, Baba S, Fairchild RL. Role of TNFalpha in Early Chemokine Production and Leukocyte Infiltration into Heart Allografts. Am J Transplant. 2009
51. Koenders MI, van den Berg WB. Translational Mini-Review Series on Th17 Cells: Are T helper 17 cells really pathogenic in autoimmunity? Clin Exp Immunol. 2009
52. Bettelli E, Korn T, Oukka M, Kuchroo VK. Induction and effector functions of T(H)17 cells. Nature. 2008; 453:1051–1057. [PubMed: 18563156]

53. Loong CC, Hsieh HG, Lui WY, et al. Evidence for the early involvement of interleukin 17 in human and experimental renal allograft rejection. J Pathol. 2002; 197:322–332. [PubMed: 12115878]

54. Hsieh HG, Loong CC, Lui WY, et al. IL-17 expression as a possible predictive parameter for subclinical renal allograft rejection. Transpl Int. 2001; 14:287–298. [PubMed: 11692212]

55. Chen Y, Wood KJ. Interleukin-23 and TH17 cells in transplantation immunity: does 23+17 equal rejection? Transplantation. 2007; 84:1071–1074. [PubMed: 17998858]

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