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Forkhead transcription factors in chronic inflammation

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Abstract

Forkhead (Fox) transcription factors have been increasingly recognized to play key roles in immune homeostasis, especially Foxp3 for its role in the development and function of regulatory T cells, and Foxo family members for their regulatory role in T and B lymphocytes as well as other leukocytes. Although these transcription factors positively regulate the expression of multiple target genes, a unique functional attribute of these genes is the maintenance of leukocyte homeostasis, such as the preservation of the naïve or quiescent T cell state and prevention of autoimmunity. As a result, many chronic inflammatory processes appear to reflect a relative loss of activity of one of these transcription factors, raising the possibility that therapeutic approaches which confer gain-of-function Fox activity may be beneficial. On the other hand, however, some of the Fox family members also appear to promote and/or maintain chronic inflammation by preserving inflammatory leukocyte survival and/or otherwise promoting the expression of inflammatory target genes, at least in some cell types such as neutrophils. Therefore, although the role of Fox in inflammatory disorders remains complex and incompletely understood, the continued study of these factors provides new insight into the initiation, maintenance, and propagation of inflammation.

Keywords

Autoimmunity; Transcription Factors; Forkhead; Neutrophils; Lymphocytes

Introduction

The forkhead (Fox) family comprises a large and diverse group of transcription factors that share a “winged helix” DNA binding domain, consisting of three alpha helices flanked by two “wings” of beta strands and loops, and play critical roles in multiple biological processes, including development, metabolism, aging and cancer (reviewed in Tran et al. 2003; Carlsson and Mahlapuu 2002). Several Fox family members have received increasingly growing attention in immunology due to their now well-recognized importance in the regulation of immune homeostasis (reviewed in Jonsson and Peng 2005). Interestingly, however, whereas traditional models for transcription factors in immunity have involved the positive regulation of pro-inflammatory or pro-proliferative target genes (e.g., Peng 2008b), many Fox genes control anti-inflammatory or anti-proliferative programs in cells, in an intrinsic or extrinsic manner. This review summarizes such current data, focusing upon potential implications for the pathogenesis of chronic inflammatory diseases, such as autoimmunity and allergy. For details regarding the specific mechanisms of some of these family members, the reader is

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directed to one of several recent reviews (e.g., Peng 2008a; Bacchetta et al. 2007; Jonsson and Peng 2005).

Foxp3 in the maintenance of chronic inflammation

Foxp3 (scurfin, sf, JM2) remains the currently most well-studied immunological Fox family member, largely because of its characteristic presence and function in the natural suppressor/regulatory (nTreg) subset of CD4+ T cells, which are produced in the thymus and are essential for the maintenance of immunological tolerance (Sakaguchi et al. 2008). Foxp3-deficient mice develop a fatal systemic autoimmune and allergic syndrome (Brunkow et al. 2001), and Foxp3 mutant humans develop multiple organ-specific autoimmune diseases such as type 1 diabetes, allergy and inflammatory bowel disease (Wildin et al. 2001; Bennett et al. 2001), all attributed to the lack of this Treg cell subset otherwise required to suppress the activity of autoaggressive leukocytes. The acquisition of an nTreg phenotype appears to require high and persistent expression of Foxp3 to stabilize and amplify a Treg genetic program, which consists of regulatory target genes such as CTLA-4, CD25, IL-10, TGF-β and IL-35 (Gavin et al. 2007; Nomura and Sakaguchi 2007; Campbell and Ziegler 2007). Loss of even partial expression of Foxp3, therefore, might play a significant factor in the initiation or maintenance of chronic inflammatory states by resulting in the loss of Treg numbers and/or function.

Some studies in both autoimmune and allergic diseases have in fact suggested that disease activity may be inversely related with Treg number, functionality, or both. For instance, in type 1 diabetes, autoimmune polyglandular syndrome II, multiple sclerosis and perhaps also asthma and allergy, nTreg appear to be similar in number to healthy control subjects but may exhibit reduced suppressive activity (Battaglia et al. 2006; Brusko et al. 2005; Putnam et al. 2005; Lindley et al. 2005; Shi et al. 2004a; Kriegel et al. 2004; Viglietta et al. 2004; Bellinghausen et al. 2003; Lee et al. 2007; Shi et al. 2004b; Karlsson et al. 2004; Putheti et al. 2004). On the other hand, several other inflammatory diseases appear to exhibit normal number and function of nTregs, including ulcerative colitis, thyroiditis, and sarcoidosis (Yu et al. 2007; Marazuela et al. 2006; Miyara et al. 2006). In rheumatoid arthritis, nTreg in the synovial fluid actually appears to be higher in number than the peripheral blood, suggesting the presence of a negative feedback system at the site of inflammation (Mottonen et al. 2005; van Amelsfort et al. 2004), consistent with a Treg model in which cytokines highly present at inflammatory sites inhibit Treg activity, as has been suggested for IL-21, TNF-α, and IL-17 (Stockinger and Veldhoen 2007; van Amelsfort et al. 2007; Peluso et al. 2007). Thus, altered nTreg homeostasis may indeed be responsible, at least in part, for chronic inflammation in these diseases.

No studies to date, however, have demonstrated that significant alterations in Foxp3 expression levels or *FOXP3* polymorphisms account for Treg defects in these diseases. However, since most methods for Treg identification rely upon high, constitutive expression of Foxp3 (e.g., Tang and Bluestone 2008)), this lack of evidence may reflect limitations of current techniques. Conventional T cells may acquire a regulatory T cell phenotype in the periphery, generating induced or adaptive Treg (aTreg), which include at least IL-10 secreting Tr1 and TGF-β-secreting Th3 subsets (Roncarolo et al. 2006; Chen et al. 2003; Weiner 2001), and are associated with only a transient induction of Foxp3 – a phenomenon which has also been observed during the pro-inflammatory activation of conventional T cells (Allan et al. 2007; Walker et al. 2005). Furthermore, both Treg formation and optimal effector T cell (Teff) activation require the cytokine IL-2, suggesting the presence of a complex interplay between the pathways which induce and maintain suppressor versus effector activities (Stockinger 2007; Bettelli et al. 2007; Davidson et al. 2007; Laurence et al. 2007; Wang et al. 2007; Zorn et al. 2006). Therefore, several potentially Foxp3-independent pathways for the generation of aTregs exist, and yet Foxp3 appears to be at least part of an effector T cell (Teff) program; however, its importance in these non-nTreg populations remains largely unclear. Its role in

chronic inflammation therefore may extend beyond simply a fate-inducing or –maintaining gene for nTregs, but also to the homeostasis of aTregs and/or perhaps Teff function.

Foxo family members in chronic inflammation

The three most well-studied Foxo family members include Foxo1 (Fkhr), Foxo3a (Fkhrl1) and Foxo4 (Afx), which are all mammalian homologues of the *Caenorhabditis elegans* longevity gene DAF-16 (reviewed in Peng 2008a). Their transcriptional activity is generally regulated by phosphorylation-dependent nuclear export, initiated upon cellular exposure to stimuli such as mitogens via the phosphoinositide 3-kinase (PI3K)-protein kinase B (PKB, Akt) pathway. In immune cells, Foxo1 in particular plays critical roles in the regulation of several effector functions, such as T cell homing by regulating the expression of L-selectin and other trafficking-related receptors such as Edg, CCR7 and IL-7Rα (Ouyang et al. 2009; Kerdiles et al. 2009; Fabre et al. 2008). In B cells, Foxo1 is required to express IL-7Rα at the pro-B cell stage, to induce recombinase activating gene (Rag)-1 and Rag-2 at the pre-B cell stage, and to mediate homing and class switch recombination in peripheral B cells via expression of L-selectin and activation-induced cytidine deaminase (Dengler et al. 2008; Amin and Schlissel 2008). As such, it is intriguing to speculate that upregulation of Foxo family members might participate in the pathogenesis of multiple inflammatory diseases.

However, studies in gene-targeted mice indicate that the role of the Foxo family members in inflammation is more complex, involving both regulatory and effector functions. Despite the findings above, Foxo1 deficiency also leads *in vivo* to spontaneous T cell activation and effector differentiation, as well as the enhanced ability to induce inflammatory bowel disease in a transfer model of (Ouyang et al. 2009). Likewise, Foxo3a deficiency leads to spontaneous lymphoproliferation, T cell hyperactivation, and a Sjögren's-syndrome like inflammation, especially of the salivary glands, in association with hyperactivity of the pro-inflammatory transcription factor NF-κB and related pro-inflammatory target genes such as IL-2 and IFN-γ (Lin et al. 2004a). In the 16/6Id murine model of lupus, the inhibitory peptide hCDR1 ameliorates the disease in association with the induction of Foxo3a (Sela et al. 2006), and disease activity in at least some lupus patients correlates inversely with Foxo1 expression levels (Kuo and Lin 2007). Finally, in a mouse model of multiple sclerosis, the pro-inflammatory chemokine ostopontin appears to promote autoaggressive T cell activity by inhibiting Foxo3a (Hur et al. 2007). Thus, Foxo family members play critical roles in the suppression of T cell activation, at least of naïve autoreactive cells.

Mouse models of neutrophilic inflammation, including acute arthritis and peritonitis, require Foxo3a to suppress pro-apoptotic Fas ligand; without Foxo3a, the pro-inflammatory environment of the synovium elicits an apoptotic response in neutrophils (Jonsson et al. 2005). Analogously, neutrophils in rheumatoid arthritis patients express elevated levels of Foxo3a compared to healthy controls (Turrel-Davin et al. 2009). Rheumatoid arthritis synovium, however, exhibits differential phosphorylation of the Foxo family members among different cell types, such as fibroblast-like synoviocytes and macrophages, with a strong negative correlation between inactivation of FoxO4 in RA synovial tissue and increased serum C-reactive protein levels and a raised erythrocyte sedimentation rate (Ludikhuize et al. 2007). Such findings indicate that Foxo3a may play different functions in T cell versus neutrophil versus other inflammatory cell subsets.

Additional insight regarding the importance of Foxo family members in inflammation can be derived from its emerging role in the CD4 lymphopenia observed in chronic HIV infection. There, activity of Foxo3a appears responsible for the apoptosis of CD4+ T cells and macrophages, probably via the Tat-dependent activation of the Egr1-PTEN and/or PI3K-Akt1 pathways (Cui et al. 2008; Dabrowska et al. 2008). This likely involves specifically central

memory CD4 cells, which in turn may correspond with overall host fate to become an HIV+ elite controller versus an aviremic successfully treated subject (van Grevenynghe et al. 2008b). In one model, HIV-mediated immune suppression and/or leukopenia, perhaps associated with breakdown of the lymph node microenvironment, leads to decreased survival signals to T cells and perhaps B cells, leading to Foxo3a dephosphorylation and activation (reviewed in van Grevenynghe et al. 2008a). In this sense, Foxo3a appears to contribute to the potential for chronic inflammation by perpetuating viral pathology but at the same time, delimits overall inflammation by arresting or killing its host cell(s). Such observations indicate that the pro-versus anti-inflammatory roles of the Foxo family members therefore are highly cell- and context-dependent, but nonetheless mediate critical fate decisions within each specific context.

Other Fox family members

Increasing data with other Fox family members suggest potentially analogous roles in immunoregulation. Foxj1 (HNF4, FKHL13) and Foxd1 (BF-2, FREAC4, Hfh10, Hfhbf2), for instance, have been implicated in the homeostasis and suppression of naïve T cell activation, since mice with lymphoid deficiencies in either gene exhibit spontaneous, multiorgan, systemic inflammation associated with T cell hyperactivity and increased activity of NF-κB and or NFAT and their target genes such as IL-2, IFN-γ and IL-4 (Lin et al. 2004b; Lin and Peng 2006), and Foxj1 deficiency further results in spontaneous and accentuated B cell activation and spontaneous autoantibody production (Lin et al. 2005). In addition, overexpression of Foxj1 ameliorates inflammation in the MRL/lpr lupus model (Srivatsan and Peng 2005), and polymorphisms in FOXJ1 have been implicated in susceptibility to lupus and possibly rheumatoid arthritis (Li et al. 2007). Indeed, in lymphocytes, Foxd1, Foxj1 and Foxo appear to participate in a regulatory network that maintains naïve lymphocyte quiescence and prevents spontaneous autoimmunity (Lin and Peng 2006). As a result, a growing number of Fox genes may turn out to play critical roles in the homeostasis of immune cells, and therefore be subject to dysregulation in chronic inflammatory diseases.

Conclusions and Future Prospects

These accumulating studies demonstrate highly varied roles for the forkhead transcription factors in the regulation of immunity and therefore likely also highly varied roles in chronic inflammatory diseases. Whereas Foxp3 may primarily play an “extrinsic” role in the regulation of inflammation by supporting the development of and maintaining the activity of Treg cells, potential “intrinsic” roles in the modulation of inflammatory genes, even in Teff cells, seem theoretically possible as supported by circumstantial expression data. Indeed, Foxo family members, especially Foxo1 and Foxo3a, appear to play key roles in the development, homing, and/or differentiation of lymphocytes, yet at the same time are required for the maintenance of T cell quiescence. Similar findings have emerged for two other Fox genes, Foxj1 and Foxd1, which also regulate the quiescence of mature T and/or B cells. These concepts are further supported by findings in human autoimmune diseases such as lupus and rheumatoid arthritis, where genetic polymorphisms and/or variations in expression of Fox genes appear to correlate with disease susceptibility and/or activity.

Although intriguing, such diverse pathways and mechanisms of activity suggest that the deliberate therapeutic manipulation of Fox genes may prove difficult in the clinical treatment of inflammatory diseases. For instance, inhibition of Foxo3 activity might be highly desirable for inflammatory arthritis (Jonsson et al. 2005), but may bear the risk of lymphoproliferative disease (Lin et al. 2004a). On the other hand, such risk-benefit issues are familiar to clinicians experienced with immunosuppressive therapies, such as with the TNF-α antagonists which are effective in inflammatory arthritis yet may convey an increased risk for lymphoma (e.g.,

Geborek et al. 2005); and at the same time, it may be possible to direct immunomodulation at specific cell types, such as has been accomplished for photodynamic therapy with antibody conjugates (e.g., van Dongen et al. 2004). Therefore, future studies will hopefully further elucidate the many context-specific roles of the Fox genes in inflammation, enabling further insight into the pathogenesis of and hopefully also future avenues for therapeutic intervention upon chronic inflammatory diseases.

Abbreviations

Fox	forkhead
PI3K	phosphoinositide 3-kinase
PKB	protein kinase B
RAG	recombinase activating gene
aTreg	adaptive regulatory T cell
nTreg	natural regulatory T cell
Teff	effector T cell
Treg	regulatory T cell

References

Allan SE, Crome SQ, Crellin NK, Passerini L, Steiner TS, Bacchetta R, Roncarolo MG, Levings MK. Activation-induced FOXP3 in human T effector cells does not suppress proliferation or cytokine production. Int Immunol 2007;19:345–354. [PubMed: 17329235]

Amin RH, Schlissel MS. Foxo1 directly regulates the transcription of recombination-activating genes during B cell development. Nat Immunol 2008;9:613–622. [PubMed: 18469817]

Bacchetta R, Gambineri E, Roncarolo MG. Role of regulatory T cells and FOXP3 in human diseases. J Allergy Clin Immunol 2007;120:227–235. [PubMed: 17666212]

Battaglia M, Stabilini A, Migliavacca B, Horejs-Hoeck J, Kaupper T, Roncarolo MG. Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and type 1 diabetic patients. J Immunol 2006;177:8338–8347. [PubMed: 17142730]

Bellinghausen I, Klostermann B, Knop J, Saloga J. Human CD4+CD25+ T cells derived from the majority of atopic donors are able to suppress TH1 and TH2 cytokine production. J Allergy Clin Immunol 2003;111:862–868. [PubMed: 12704370]

Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001;27:20–21. [PubMed: 11137993]

Bettelli E, Oukka M, Kuchroo VK. T(H)-17 cells in the circle of immunity and autoimmunity. Nat Immunol 2007;8:345–350. [PubMed: 17375096]

Brunkow ME, Jeffery EW, Hjerrild KA, Paeper B, Clark LB, Yasayko SA, Wilkinson JE, Galas D, Ziegler SF, Ramsdell F. Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat Genet 2001;27:68–73. [PubMed: 11138001]

Brusko TM, Wasserfall CH, Clare-Salzler MJ, Schatz DA, Atkinson MA. Functional defects and the influence of age on the frequency of CD4+ CD25+ T-cells in type 1 diabetes. Diabetes 2005;54:1407–1414. [PubMed: 15855327]

Campbell DJ, Ziegler SF. FOXP3 modifies the phenotypic and functional properties of regulatory T cells. Nat Rev Immunol 2007;7:305–310. [PubMed: 17380159]

Carlsson P, Mahlapuu M. Forkhead transcription factors: key players in development and metabolism. Dev Biol 2002;250:1–23. [PubMed: 12297093]

Chen W, Jin W, Hardegen N, Lei KJ, Li L, Marinos N, McGrady G, Wahl SM. Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. J Exp Med 2003;198:1875–1886. [PubMed: 14676299]

Cui M, Huang Y, Zhao Y, Zheng J. Transcription factor FOXO3a mediates apoptosis in HIV-1-infected macrophages. J Immunol 2008;180:898–906. [PubMed: 18178829]

Dabrowska A, Kim N, Aldovini A. Tat-induced FOXO3a is a key mediator of apoptosis in HIV-1-infected human CD4+ T lymphocytes. J Immunol 2008;181:8460–8477. [PubMed: 19050264]

Davidson TS, DiPaolo RJ, Andersson J, Shevach EM. Cutting Edge: IL-2 is essential for TGF-beta-mediated induction of Foxp3+ T regulatory cells. J Immunol 2007;178:4022–4026. [PubMed: 17371955]

Dengler HS, Baracho GV, Omori SA, Bruckner S, Arden KC, Castrillon DH, DePinho RA, Rickert RC. Distinct functions for the transcription factor Foxo1 at various stages of B cell differentiation. Nat Immunol 2008;9:1388–1398. [PubMed: 18978794]

Fabre S, Carrette F, Chen J, Lang V, Semichon M, Denoyelle C, Lazar V, Cagnard N, Dubart-Kupperschmitt A, Mangeney M, Fruman DA, Bismuth G. FOXO1 regulates L-Selectin and a network of human T cell homing molecules downstream of phosphatidylinositol 3-kinase. J Immunol 2008;181:2980–2989. [PubMed: 18713968]

Gavin MA, Rasmussen JP, Fontenot JD, Vasta V, Manganiello VC, Beavo JA, Rudensky AY. Foxp3-dependent programme of regulatory T-cell differentiation. Nature 2007;445:771–775. [PubMed: 17220874]

Geborek P, Bladstrom A, Turesson C, Gulfe A, Petersson IF, Saxne T, Olsson H, Jacobsson LT. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis 2005;64:699–703. [PubMed: 15695534]

Hur EM, Youssef S, Haws ME, Zhang SY, Sobel RA, Steinman L. Osteopontin-induced relapse and progression of autoimmune brain disease through enhanced survival of activated T cells. Nat Immunol 2007;8:74–83. [PubMed: 17143274]

Jonsson H, Allen P, Peng SL. Inflammatory arthritis requires Foxo3a to prevent Fas ligand-induced neutrophil apoptosis. Nat Med 2005;11:666–671. [PubMed: 15895074]

Jonsson H, Peng SL. Forkhead transcription factors in immunology. Cell Mol Life Sci 2005;62:397–409. [PubMed: 15719167]

Karlsson MR, Rugtveit J, Brandtzaeg P. Allergen-responsive CD4+CD25+ regulatory T cells in children who have outgrown cow's milk allergy. J Exp Med 2004;199:1679–1688. [PubMed: 15197226]

Kerdiles YM, Beisner DR, Tinoco R, Dejean AS, Castrillon DH, DePinho RA, Hedrick SM. Foxo1 links homing and survival of naive T cells by regulating L-selectin, CCR7 and interleukin 7 receptor. Nat Immunol 2009;10:176–184. [PubMed: 19136962]

Kriegel MA, Lohmann T, Gabler C, Blank N, Kalden JR, Lorenz HM. Defective suppressor function of human CD4+ CD25+ regulatory T cells in autoimmune polyglandular syndrome type II. J Exp Med 2004;199:1285–1291. [PubMed: 15117972]

Kuo CC, Lin SC. Altered FOXO1 transcript levels in peripheral blood mononuclear cells of systemic lupus erythematosus and rheumatoid arthritis patients. Mol Med 2007;13:561–566. [PubMed: 17873969]

Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, Blank RB, Meylan F, Siegel R, Hennighausen L, Shevach EM, O'shea JJ. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity 2007;26:371–381. [PubMed: 17363300]

Lee JH, Yu HH, Wang LC, Yang YH, Lin YT, Chiang BL. The levels of CD4+CD25+ regulatory T cells in paediatric patients with allergic rhinitis and bronchial asthma. Clin Exp Immunol 2007;148:53–63. [PubMed: 17349011]

Li CS, Zhang Q, Lim MK, Sheen DH, Shim SC, Kim JY, Lee SS, Yun KJ, Moon HB, Chung HT, Chae SC. Association of FOXJ1 polymorphisms with systemic lupus erythematosus and rheumatoid arthritis in Korean population. Exp Mol Med 2007;39:805–811. [PubMed: 18160851]

Lin L, Brody SL, Peng SL. Restraint of B cell activation by Foxj1-mediated antagonism of NF-kappa B and IL-6. J Immunol 2005;175:951–958. [PubMed: 16002694]

Lin L, Hron JD, Peng SL. Regulation of NF-kappaB, Th activation, and autoinflammation by the forkhead transcription factor Foxo3a. Immunity 2004a;21:203–213. [PubMed: 15308101]

Lin L, Peng SL. Coordination of NF-kappaB and NFAT antagonism by the forkhead transcription factor Foxd1. J Immunol 2006;176:4793–4803. [PubMed: 16585573]

Lin L, Spoor MS, Gerth AJ, Brody SL, Peng SL. Modulation of Th1 activation and inflammation by the NF-kappaB repressor Foxj1. Science 2004b;303:1017–1020. [PubMed: 14963332]

Lindley S, Dayan CM, Bishop A, Roep BO, Peakman M, Tree TI. Defective suppressor function in CD4 (+)CD25(+) T-cells from patients with type 1 diabetes. Diabetes 2005;54:92–99. [PubMed: 15616015]

Ludikhuize J, de LD, Groot D, Smeets TJ, Vinkenoog M, Sanders ME, Tas SW, Tak PP, Reedquist KA. Inhibition of forkhead box class O family member transcription factors in rheumatoid synovial tissue. Arthritis Rheum 2007;56:2180–2191. [PubMed: 17599731]

Marazuela M, Garcia-Lopez MA, Figueroa-Vega N, de la FH, varado-Sanchez B, Monsivais-Urenda A, Sanchez-Madrid F, Gonzalez-Amaro R. Regulatory T cells in human autoimmune thyroid disease. J Clin Endocrinol Metab 2006;91:3639–3646. [PubMed: 16804051]

Miyara M, Amoura Z, Parizot C, Badoual C, Dorgham K, Trad S, Kambouchner M, Valeyre D, Chapelon-Abric C, Debre P, Piette JC, Gorochov G. The immune paradox of sarcoidosis and regulatory T cells. J Exp Med 2006;203:359–370. [PubMed: 16432251]

Mottonen M, Heikkinen J, Mustonen L, Isomaki P, Luukkainen R, Lassila O. CD4+ CD25+ T cells with the phenotypic and functional characteristics of regulatory T cells are enriched in the synovial fluid of patients with rheumatoid arthritis. Clin Exp Immunol 2005;140:360–367. [PubMed: 15807863]

Nomura T, Sakaguchi S. Foxp3 and Aire in thymus-generated Treg cells: a link in self-tolerance. Nat Immunol 2007;8:333–334. [PubMed: 17375092]

Ouyang W, Beckett O, Flavell RA, Li MO. An essential role of the Forkhead-box transcription factor Foxo1 in control of T cell homeostasis and tolerance. Immunity 2009;30:358–371. [PubMed: 19285438]

Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, Pallone F, Monteleone G. IL-21 counteracts the regulatory T cell-mediated suppression of human CD4+ T lymphocytes. J Immunol 2007;178:732–739. [PubMed: 17202333]

Peng SL. Foxo in the immune system. Oncogene 2008a;27:2337–2344. [PubMed: 18391975]

Peng SL. Transcription factors in autoimmune diseases. Front Biosci 2008b;13:4218–4240. [PubMed: 18508507]

Putheti P, Pettersson A, Soderstrom M, Link H, Huang YM. Circulating CD4+CD25+ T regulatory cells are not altered in multiple sclerosis and unaffected by disease-modulating drugs. J Clin Immunol 2004;24:155–161. [PubMed: 15024182]

Putnam AL, Vendrame F, Dotta F, Gottlieb PA. CD4+CD25high regulatory T cells in human autoimmune diabetes. J Autoimmun 2005;24:55–62. [PubMed: 15725577]

Roncarolo MG, Gregori S, Battaglia M, Bacchetta R, Fleischhauer K, Levings MK. Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. Immunol Rev 2006;212:28–50. [PubMed: 16903904]

Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell 2008;133:775–787. [PubMed: 18510923]

Sela U, Dayan M, Hershkoviz R, Cahalon L, Lider O, Mozes E. The negative regulators Foxj1 and Foxo3a are up-regulated by a peptide that inhibits systemic lupus erythematosus-associated T cell responses. Eur J Immunol 2006;36:2971–2980. [PubMed: 17051618]

Shi HZ, Li S, Xie ZF, Qin XJ, Qin X, Zhong XN. Regulatory CD4+CD25+ T lymphocytes in peripheral blood from patients with atopic asthma. Clin Immunol 2004a;113:172–178. [PubMed: 15451474]

Shi HZ, Li S, Xie ZF, Qin XJ, Qin X, Zhong XN. Regulatory CD4+CD25+ T lymphocytes in peripheral blood from patients with atopic asthma. Clin Immunol 2004b;113:172–178. [PubMed: 15451474]

Srivatsan S, Peng SL. Cutting edge: Foxj1 protects against autoimmunity and inhibits thymocyte egress. J Immunol 2005;175:7805–7809. [PubMed: 16339515]

Stockinger B. Good for Goose, but not for Gander: IL-2 interferes with Th17 differentiation. Immunity 2007;26:278–279. [PubMed: 17376391]

Stockinger B, Veldhoen M. Differentiation and function of Th17 T cells. Curr Opin Immunol 2007;19:281–286. [PubMed: 17433650]

Tang Q, Bluestone JA. The Foxp3+ regulatory T cell: a jack of all trades, master of regulation. Nat Immunol 2008;9:239–244. [PubMed: 18285775]

Tran H, Brunet A, Griffith EC, Greenberg ME. The many forks in FOXO's road. Sci STKE 2003 2003:RE5.

Turrel-Davin F, Tournadre A, Pachot A, Arnaud B, Cazalis MA, Mougin B, Miossec P. FoxO3a involved in neutrophil and T cell survival is overexpressed in rheumatoid blood and synovial tissue. Ann Rheum Dis. 200910.1136/ard.2009.109991

van Amelsfort JM, Jacobs KM, Bijlsma JW, Lafeber FP, Taams LS. CD4(+)CD25(+) regulatory T cells in rheumatoid arthritis: differences in the presence, phenotype, and function between peripheral blood and synovial fluid. Arthritis Rheum 2004;50:2775–2785. [PubMed: 15457445]

van Amelsfort JM, van Roon JA, Noordegraaf M, Jacobs KM, Bijlsma JW, Lafeber FP, Taams LS. Proinflammatory mediator-induced reversal of CD4+, CD25+ regulatory T cell-mediated suppression in rheumatoid arthritis. Arthritis Rheum 2007;56:732–742. [PubMed: 17328044]

van Dongen GA, Visser GW, Vrouenraets MB. Photosensitizer-antibody conjugates for detection and therapy of cancer. Adv Drug Deliv Rev 2004;56:31–52. [PubMed: 14706444]

van Grevenynghe J, Halwani R, Chomont N, Ancuta P, Peretz Y, Tanel A, Procopio FA, shi Y, Said EA, Haddad EK, Sekaly RP. Lymph node architecture collapse and consequent modulation of FOXO3a pathway on memory T- and B-cells during HIV infection. Semin Immunol 2008a;20:196–203. [PubMed: 18757210]

van Grevenynghe J, Procopio FA, He Z, Chomont N, Riou C, Zhang Y, Gimmig S, Boucher G, Wilkinson P, shi Y, Yassine-Diab B, Said EA, Trautmann L, El FM, Balderas RS, Boulassel MR, Routy JP, Haddad EK, Sekaly RP. Transcription factor FOXO3a controls the persistence of memory CD4(+) T cells during HIV infection. Nat Med 2008b;14:266–274. [PubMed: 18311149]

Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA. Loss of functional suppression by CD4+CD25+ regulatory T cells in patients with multiple sclerosis. J Exp Med 2004;199:971–979. [PubMed: 15067033]

Walker MR, Carson BD, Nepom GT, Ziegler SF, Buckner JH. De novo generation of antigen-specific CD4+CD25+ regulatory T cells from human CD4+ Proc Natl Acad Sci U S A 2005;102:4103–4108. [PubMed: 15753318]

Wang J, Ioan-Facsinay A, van d V, Huizinga TW, Toes RE. Transient expression of FOXP3 in human activated nonregulatory CD4+ T cells. Eur J Immunol 2007;37:129–138. [PubMed: 17154262]

Weiner HL. Induction and mechanism of action of transforming growth factor-beta-secreting Th3 regulatory cells. Immunol Rev 2001;182:207–214. [PubMed: 11722636]

Wildin RS, Ramsdell F, Peake J, Faravelli F, Casanova JL, Buist N, Levy-Lahad E, Mazzella M, Goulet O, Perroni L, Bricarelli FD, Byrne G, McEuen M, Proll S, Appleby M, Brunkow ME. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat Genet 2001;27:18–20. [PubMed: 11137992]

Yu QT, Saruta M, Avanesyan A, Fleshner PR, Banham AH, Papadakis KA. Expression and functional characterization of FOXP3+ CD4+ regulatory T cells in ulcerative colitis. Inflamm Bowel Dis 2007;13:191–199. [PubMed: 17206665]

Zorn E, Nelson EA, Mohseni M, Porcheray F, Kim H, Litsa D, Bellucci R, Raderschall E, Canning C, Soiffer RJ, Frank DA, Ritz J. IL-2 regulates FOXP3 expression in human CD4+CD25+ regulatory T cells through a STAT-dependent mechanism and induces the expansion of these cells in vivo. Blood 2006;108:1571–1579. [PubMed: 16645171]