



Parasites and autoimmunity: The case of fungi

Luigina Romani*

Microbiology Section, Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Via del Giochetto, 06122 Perugia, Italy

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ABSTRACT

Infectious agents can induce autoimmune diseases in several experimental settings, some of which have clinical counterparts. A variety of mechanisms have been invoked to explain these observations, including molecular mimicry and an increase in the immunogenicity of autoantigens caused by inflammation in the target organ. Paradoxically, infectious agents can also suppress allergic and autoimmune disorders. A central question is to determine whether immune dysregulation precedes, if not promotes, infection or alternatively, but not mutually exclusive, the extent to which microbial exposure/colonization contributes to the burst of pathogenic autoimmunity. Here we discussed recent evidence with fungi that help to accommodate microbes, either commensals or ubiquitous, within the immune homeostasis and its dysregulation.

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1. Infections and autoimmunity

Infections are major players in the environmental factors which modulate the development of autoimmune diseases, both on positive and negative ways [1]. The underlying mechanisms are multiple and complex, probably different according to pathogens [2–4]. Mimicry of host antigens by infectious agents may induce cross-reactive autoimmune

responses to epitopes within host proteins which, in susceptible individuals, may tip the balance of immunological response versus tolerance toward response and subsequently lead to autoimmune disease. Chronic diseases, such as inflammatory bowel diseases and rheumatoid arthritis, are characterized by a robust immune response resulting in unresolved inflammation [5]. Despite clear evidence that vaccination with mimetic microbial antigens has the potential to activate autoreactive T cells, crucial evidence for triggering of autoimmunity by mimetic sequences in natural pathogens remains lacking, although they may provoke a prolonged inflammatory response when occurring on a susceptible immunological background. Considering that activation rather than the

* Tel./fax: +39 039 075 5853411.
E-mail address: lromani@unipg.it.

presence of autoreactive T cells and antigen spreading are the hallmarks of autoimmune disease, the creation of an environment resulting in failure of tolerance and regulatory mechanisms, rather than emergence of novel microbial antigenic determinants, may well be at the root of autoimmunity. Because microbial degradation products, and even bacterial DNA, are present at sites of autoimmunity, this has led to the speculation that the continuous seeding of bacterial products from the gut may eventually favour, on a permissive genetic background, onset of inflammatory autoimmunity. As the vast majority of infections pertain to our resident microbiota, focus has been given toward understanding the mechanisms underlying transition from healthy carrier state to infectious syndromes, including autoimmune diseases [4].

More surprisingly, infections may also protect from autoimmune diseases [6]. Western countries are being confronted with a disturbing increase in the incidence of most immune disorders, including autoimmune and allergic diseases, inflammatory bowel diseases, and some lymphocyte malignancies. Epidemiological and clinical data support the hygiene hypothesis according to which the decrease of infections observed over the last three decades is the main cause of the incessant increase in immune disorders. The hypothesis does not exclude an etiological role for specific pathogens in a given immune disorder as might notably be the case in inflammatory bowel diseases. With regard to the mechanisms of protection, antigenic competition, immune regulation, innate and adaptive mechanisms have been considered. Infectious agents stimulate a large variety of regulatory cells (Th2, CD25⁺, Tr1, NKT) whose effects extend to other specificities than those which triggered their differentiation (bystander suppression). Infectious agents may also intervene through components which are not recognized as antigens but bind to specific receptors on cells of the immune system. Major attention has been drawn to Toll receptors [7].

2. Fungal infections and diseases as examples of immune-related pathology

Patients with phagocytic, cellular, combined and other primary immunodeficiencies (PID)—such as, severe combined immunodeficiency, chronic mucocutaneous candidiasis (CMC), APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy), hyper-IgE syndrome, myeloperoxidase deficiency, leukocyte adhesion deficiency, DiGeorge syndrome, XI-EDA-ID (defects of NEMO), Wiskott–Aldrich syndrome and common variable immunodeficiency [8,9]—exhibit increased susceptibility to fungal infections. Clinically, severe fungal infections also occur in patients with immune reconstitution syndrome an entity characterized by local and systemic reactions that have both beneficial and deleterious effects on infection [10]. These patients may experience intractable fungal infections despite the occurrence of pathogen-specific immunity.

Bidirectional influences between infection and immune-related pathology have been known to exist in CMC, a PID presenting as an inability to clear *Candida albicans* yeasts, which persist in recurring lesions of the skin, nails, and mucous membranes [11,12]. CMC patients often develop endocrine and inflammatory disorders, which suggests deregulation of the inflammatory and immune responses [12]. Although antifungal drugs are effective in clearing the infections, treatments that

restore cellular immunity have also produced long term remissions in CMC [11], this last finding highlighting the contribution of a dysregulated adaptive immunity to disease. The recent observation that therapy with corticosteroids is associated with a prompt resolution of symptoms and of inflammatory response in chronic disseminated candidiasis—a chronic infection typically occurring during neutrophil recovery in patients with acute leukemia and requiring protracted antifungal therapy—supports the pathophysiological hypothesis that chronic candidiasis may belong to the spectrum of fungus-related immune reconstitution inflammatory syndrome [13]. This condition is crucially exemplified by recent findings in CGD mice, in which an intrinsic, genetically determined failure to control inflammation to sterile fungal components determines the animals' inability to resolve an actual infection with *Aspergillus fumigatus* [14]. A main implication of these findings is that, at least in specific clinical settings, it is an exaggerated inflammatory response that likely compromises a patient's ability to eradicate infection, and not an "intrinsic" susceptibility to infection that determines a state of chronic or intractable disease [15]. The above observations highlight a truly bipolar nature of the inflammatory process in infection, at least by specific fungi, such as *Candida* or *Aspergillus* spp. Early inflammation prevents or limits infection, but an uncontrolled response may eventually oppose disease eradication [15,16].

A central question is to determine whether immune dysregulation precedes, if not promotes, infection or alternatively, but not mutually exclusive, whether fungal exposure/colonization contributes to the burst of pathogenic autoimmunity and allergy.

3. Fungi and autoimmunity: the Th17 connection

Although cellular components of the *Candida* may act as a trigger for autoimmune disease in experimental arthritis [17,18], no causal association of *Candida* with human autoimmune diseases is known. In contrast, there is evidence that fungal sensitization may contribute to autoreactivity against self-antigens due to shared epitopes with homologous fungal allergens [19]. Recent evidence have shed new lights on the reciprocal influence between fungi, such as *Candida* and *Aspergillus*, and peripheral immune homeostasis and its dysregulation [17,18].

The inflammatory response to fungi may serve to limit infection but an overzealous or heightened inflammatory response may contribute not only to chronic diseases and autoimmunity but also to fungal virulence. Inflammation is mediated by proinflammatory cytokines; recently, a novel subset of T-helper (Th) cells (Th17) was identified that plays a crucial role in inflammation and autoimmune disease. Inflammatory cytokines, including IL-17, are implicated in the progression of localized chronic infections as well as in serious systemic pathologies, such as diabetes, chronic obstructive pulmonary disease, and cardiovascular disease [5,20]. Therapeutics that antagonize inflammatory cytokines ameliorate inflammation and may have implications in local and systemic diseases in which inflammation and autoimmunity predominate [21].

IL-12, by initiating and maintaining Th1 responses, was thought to be responsible for overreacting immune and autoimmune disorders. This was also the case in fungal

infections where immunoregulation proved to be essential in fine-tuning inflammation and uncontrolled Th1/Th2 antifungal reactivity [22]. Recent evidence have shown that it is the Th17 pathway—and not the uncontrolled Th1 response—that is associated with defective pathogen clearance, failure to resolve inflammation and to initiate protective immune responses. Both IL-17 and IL-23 inhibited the fungicidal activity and subverted the inflammatory program of neutrophils even in the presence of IFN- γ , a finding suggesting that the Th17 effector pathway prevails over the Th1 pathway. As in other infections, the Th1 and Th17 developmental pathways are reciprocally regulated in fungal diseases. Cross-regulation occurs at different levels, including IL-12 (p70) and IL-23 production by dendritic cells [23]. TLR4 appeared to play a major role in controlling the balance between protective and protective immune responses to the fungus through its ability to both promote (via MyD88) and inhibit (via TRIF) Th17 development [24]. This suggests that conditions of high-threat inflammation may represent a local environmental factor that predispose to Th17 activation in candidiasis or aspergillosis. IL-17-producing cells are induced by *C. albicans* or *A. fumigatus*, through innate signaling via Dectin-1/CARD9 [25] and TLR/MyD88 [23] and they are inhibited by negative regulators of TLRs [26] and TRIF [24]. Activation of pathogenic Th17 cells accounts for susceptibility to candidiasis and aspergillosis under conditions of deficient p35 [23], TRIF [24], TIR8/SIGIRR [26], or functional NADPH oxidase expression [14]. In all of these settings, Th17 pathway expression—rather than an unrestrained Th1 response—correlates directly with defective pathogen clearance, and failure to resolve inflammation as well as initiate protective responses to *Candida* and *Aspergillus*. Blockade of IL-17/IL-23 prevented pathogenic inflammatory responses, ameliorated infections and restored protective Th1 antifungal resistance, thus causally linking pathogenic inflammation to Th17 development [16]. The ability of fungi to activate Th17 cells as well as their ability to subvert a host's inflammatory response, which may impact on carriage and pathogenicity (reviewed in Ref. [16]), indicates possible patho-mechanisms through which fungi may contribute to exacerbation of (auto)immune diseases.

4. Fungi and immunoregulation: the role of Tregs

In its ability to inhibit Th1 activation, the Th17-dependent pathway could be responsible for failure to resolve an infection in the face of an ongoing inflammation. However, an intriguing link exists with Tregs, which can be generated by stimulation with TGF- β and IL-27 in the absence of IL-6 [27,28]. Tregs, capable of fine-tuning protective antimicrobial immunity in order to minimize harmful immune pathology, have become an integral component of the immune response to fungi [31]. The capacity of Tregs to inhibit aspects of innate and adaptive antifungal immunity, including functional Th17 antagonism, is required for protective tolerance to fungi [16]. The circumstances in which protective or tissue-damaging T cell responses to fungi are affected by the activity of Tregs are becoming to be elucidated. The relationships range from situations in which the Treg response seems to contribute to immune dysfunction to those that minimize tissue damage caused by immunoinflammatory cell reactions.

Diverse types of Tregs, with disparate and multiple functions, are induced in fungal infections (reviewed in Ref.

[29]). CD4⁺CD25⁺Foxp3⁺ naturally occurring (n)Tregs operating in the respiratory or the gastrointestinal mucosa accounted for the lack of pathology associated with fungal clearance and/or persistence in mice with fungal pneumonia or mucosal candidiasis [30,31]. Fungal growth, inflammatory immunity, and tolerance to *C. albicans* and *A. fumigatus* were all controlled by the coordinate activation of nTregs—limiting early inflammation at the sites of infection—and pathogen-induced (i)Tregs, which regulated the expression of adaptive Th immunity in secondary lymphoid organs. Early in infection, inflammation was controlled by the expansion, activation and local recruitment of nTregs suppressing innate immune activation through the combined actions of IL-10 and cytotoxic T lymphocyte antigen-4 acting on the enzyme indoleamine 2,3-dioxygenase (IDO, see below). Late in infection, the inflammatory immunity was modulated by iTregs, which acted through activation of IDO in dendritic cells and prevented Th17 cell development [31]. Thus, IDO, known to have a central role in the induction of Th1 immunity within a regulatory environment [32], is crucially involved in tolerance to fungi. By dampening Th1 immunity, iTregs producing IL-10 and expressing membrane-bound TGF- β and Foxp3 prevented sterilization of *C. albicans* from the gastrointestinal tract and maintained equilibrium to ensure fungal persistence, minimal tissue damage and immunity to re-infection (Fig. 1). Because Tregs induction is defective in patients with CMC [33], our data would suggest that Tregs are essential for the induction of a state of protective tolerance to *Candida*, in which fungal persistence is maintained in the context of a poorly inflammatory environment. In fungal allergy, IDO-dependent, tolerogenic iTregs inhibited Th2 cells and

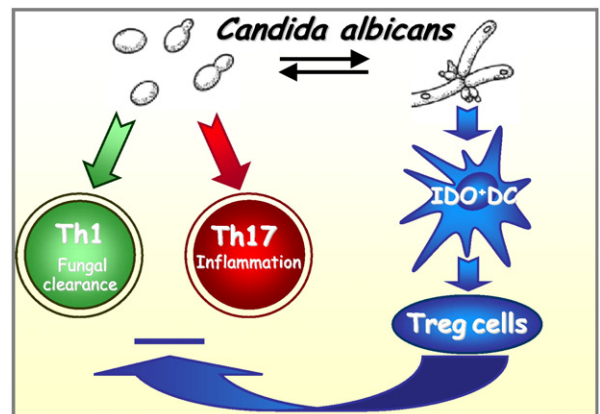


Fig. 1. The benefit of a commensal. The capacity of regulatory T cells (Tregs) to inhibit aspects of innate and adaptive antifungal immunity, including functional Th17 antagonism, is required for protective tolerance to *Candida albicans*. By dampening Th1 immunity, different Tregs subsets prevent sterilization of *C. albicans* from the gastrointestinal tract and maintain equilibrium to ensure fungal persistence, minimal tissue damage and immunity to re-infection. In their ability to inhibit Th17 immunity, microbial Tregs may also represent a mechanism whereby local and peripheral dysregulated immunity is concomitantly prevented. Interestingly, the fact that hyphae, more than yeasts, activate the IDO-dependent tolerogenic program [24], suggests that fungal hyphae, by promoting tolerance, pivotally contribute to commensalism and eventually to immunoevasion. This reinforces the concept of fungal dimorphism as a mechanism of fungal adaptation to mammalian host. DC, dendritic cells; IDO, indoleamine 2,3-dioxygenase.

prevented allergy to the fungus [34,35]. Collectively, these observations suggest that the capacity of Tregs to inhibit aspects of innate and adaptive immunity is pivotal in their regulatory function and further support the concept of “protective tolerance” to fungi, implying that a host’s immune defense may be adequate for protection without necessarily eliminating fungal pathogens or causing an unacceptable level of tissue damage [15,29].

5. IDO at the intersection between immunity and tolerance

IDO has a complex role in immunoregulation in infection, pregnancy, autoimmunity, transplantation, and neoplasia [35,36]. The IDO mechanism has revealed an unexpected potential in the control of inflammation, allergy and Th17-driven inflammation in fungal infections [15,16]. IDO expression is paradoxically up-regulated in patients with allergy or autoimmune inflammation (reviewed in [35]), a finding suggesting the occurrence of a homeostatic mechanism to halt ongoing inflammation. In experimental fungal infections, IDO blockade greatly exacerbated infections, the associated inflammatory pathology and swept away resistance to re-infection, as a result of deregulated innate and adaptive immune responses caused by the impaired activation and functioning of suppressor CD4⁺CD25⁺ Tregs producing IL-10. More recently, while capable of inducing the Foxp3-encoding gene transcriptionally, tryptophan catabolites were also found to suppress the gene encoding retinoid-related orphan receptor gamma t (RORγt), the Th17 lineage specification factor [24]. These data further establish IDO as a truly immunoregulatory mechanism in infection, controlling the balance between Th17

and Treg cell subsets [16]. These observations also suggest that IDO and kynurenines, in their capacity to induce Tregs and inhibit Th17, pivotally contribute to cell lineage decision in fungal infections and highlight the emerging regulatory role of metabolic pathways tolerogenesis and prevention of autoimmune inflammation and allergy [36,37].

6. The host/fungus interaction: an old pathway revisited

The above considerations highlight the “double-edged” sword nature of the host/fungus interaction. If the ability to subvert the inflammatory program through the activation of the IL-23/IL-17 axis may eventually lead to immune dysregulation, the ability to activate Tregs, integral and essential components of protective antifungal immunity, may represent a mechanism whereby dysregulated immunity is prevented (Fig. 2). Preliminary evidence indicate that, through bystander effects and molecular mimicry, Tregs activated in fungal infections could be exploited for the control of inflammation and autoimmunity in experimental models of inflammatory and autoimmune diseases (unpublished observations). Thus, despite our limited understanding of the significance and interplay of infection-driven Tregs with other pathways of immunity and autoimmunity, it is likely that microbial Tregs could be successfully exploited to prevent inflammation and maintain immune homeostasis [38], that is, the exploitation of oral tolerance driven by commensals for the treatment of inflammatory autoimmune diseases [39,40].

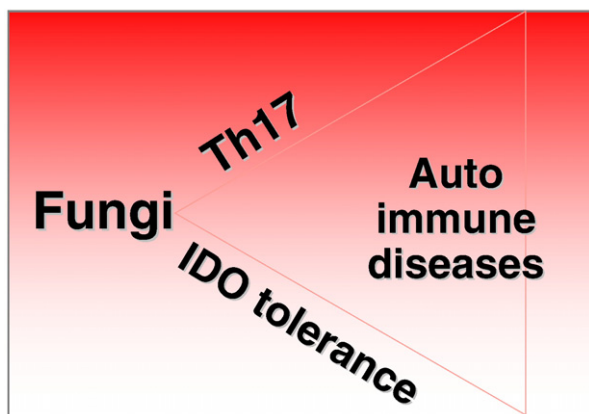


Fig. 2. The “double-edged” sword nature of the host/fungus interaction. The ability of fungi to subvert the inflammatory program through the activation of the IL-23/IL-17 axis may eventually lead to immune dysregulation, autoimmunity and exacerbation of the infection. A central question is to determine whether immune dysregulation precedes, if not promotes, infection or alternatively, but not mutually exclusive, whether fungal exposure/colonization contributes to the burst of pathogenic autoimmunity and allergy. In contrast, the ability to activate Tregs by means of IDO may represent a mechanism to prevent dysregulated immunity, tissue damage and chronic infection. Although largely speculative, the exploitation of microbial Tregs for the control of inflammation, autoimmunity and allergy is an attractive working hypothesis. IDO, indoleamine 2,3-dioxygenase.

Take-home messages

- Chronic diseases, such as inflammatory bowel diseases and rheumatoid arthritis, are characterized by a robust immune response resulting in unresolved inflammation. Inflammation is mediated by proinflammatory cytokines; recently, a novel subset of T-helper (Th) cells was identified that plays a crucial role in inflammation and autoimmune disease. This population secretes several proinflammatory cytokines, including the novel cytokine interleukin (IL)-17, and, hence, has been termed “Th17.”
- Infectious agents can induce autoimmune diseases in several experimental settings, some of which have clinical counterparts. Paradoxically, infectious agents can also suppress allergic and autoimmune disorders.
- A central question is to determine whether immune dysregulation precedes, if not promotes, infection or alternatively, but not mutually exclusive, the extent to which microbial exposure/colonization contributes to the burst of pathogenic autoimmunity.
- Recent evidence with fungi may help to accommodate microbes, either commensals or ubiquitous, within the immune homeostasis and its dysregulation.
- If the ability of fungi to subvert the inflammatory program through the activation of the IL-23/IL-17 axis may eventually lead to immune dysregulation, their ability to activate regulatory T cells (Tregs) may represent a mechanism whereby dysregulated immunity is prevented.
- It is conceivable that microbial Tregs could be exploited for the control of inflammation in allergic and autoimmune diseases.

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References

- [1] Zaccane P, Burton OT, Cooke A. Interplay of parasite-driven immune responses and autoimmunity. *Trends Parasitol* 2008;24:35–42.
- [2] Bach JF. Infections and autoimmune diseases. *J Autoimmunity* 2005;25:74–80.
- [3] Blank M, Barzilai O, Shoenfeld Y. Molecular mimicry and autoimmunity. *Clin Rev Allergy Immunol* 2007;32:111–8.
- [4] Pordeus V, Szyper-Kravitz M, Levy RA, Vaz NM, Shoenfeld Y. Infections and autoimmunity: a panorama. *Clin Rev Allergy Immunol* 2008;34(3): 283–99.
- [5] Afzali B, Lombardi G, Lechler LI, Lord GM. The role of T helper 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. *Clin Exp Immunol* 2007;148:32–46.
- [6] Bach JF. Protective role of infections and vaccinations on autoimmune diseases. *J Autoimmunity* 2001;16:347–53.
- [7] Bach JF, Bendelac A, Brenner MB, Cantor H, De Libero G, Kronenberg M, et al. The role of innate immunity in autoimmunity. *J Exp Med* 2004;200:1527–31.
- [8] Antachopoulos C, Walsh TJ, Roilides E. Fungal infections in primary immunodeficiencies. *Eur J Pediatr* 2007;166:1099–117.
- [9] Carneiro-Sampaio M, Coutinho A. Immunity to microbes: lessons from primary immunodeficiencies. *Infect Immun* 2007;75:1545–55.
- [10] Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. *Lancet, Infect Dis* 2007;7:395–401.
- [11] Kirkpatrick CH. Chronic mucocutaneous candidiasis. *Pediatr Infect Dis J* 2001;20:197–206.
- [12] Lilic D. New perspectives on the immunology of chronic mucocutaneous candidiasis. *Curr Opin Infect Dis* 2002;15:143–7.
- [13] Legrand F, Lecuit M, Dupont B, Bellaton E, Huerre M, Rohrlach PS, et al. Adjuvant corticosteroid therapy for chronic disseminated candidiasis. *Clin Infect Dis* 2008;46:696–702.
- [14] Romani L, Fallarino F, De Luca A, Montagnoli C, D'Angelo A, Zelante T, et al. Defective tryptophan catabolism underlies inflammation in mouse chronic granulomatous disease. *Nature* 2008;451:211–5.
- [15] Romani L, Puccetti P. Controlling pathogenic inflammation to fungi. *Expert Rev Anti Infect Ther* 2007;5:1007–17.
- [16] Romani L, Zelante T, De Luca A, Fallarino F, Puccetti P. IL-17 and therapeutic kynurenes in pathogenic inflammation to fungi. *J Immunol* 2008;180:5157–62.
- [17] Hida S, Nagi-Miura N, Adachi Y, Ohno N. Beta-glucan derived from zymosan acts as an adjuvant for collagen-induced arthritis. *Microbiol Immunol* 2006;50:453–61.
- [18] Yoshitomi H, Sakaguchi N, Kobayashi K, Brown GD, Tagami T, Sakihama T, et al. A role for fungal (beta)-glucans and their receptor Dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice. *J Exp Med* 2005;201:949–60.
- [19] Cramer R, Faith A, Hemmann S, Jaussi R, Ismail C, Menz G, et al. Humoral and cell-mediated autoimmunity in allergy to *Aspergillus fumigatus*. *J Exp Med* 1996;184:265–70.
- [20] Dong C. TH17 cells in development: an updated view of their molecular identity and genetic programming. *Nat Rev, Immunol* 2008;8:337–48.
- [21] Penberthy WT. Pharmacological targeting of IDO-mediated tolerance for treating autoimmune disease. *Curr Drug Metab* 2007;8:245–66.
- [22] Romani L. Immunity to fungal infections. *Nat Rev, Immunol* 2004;4:1–23.
- [23] Zelante T, De Luca A, Bonifazi P, Montagnoli C, Bozza S, Moretti S, et al. IL-23 and the Th17 pathway promote inflammation and impair antifungal immune resistance. *Eur J Immunol* 2007;37:2695–706.
- [24] De Luca A, Montagnoli C, Zelante T, Bonifazi P, Bozza S, Moretti S, et al. Functional yet balanced reactivity to *Candida albicans* requires TRIF, MyD88, and IDO-dependent inhibition of *Rorc*. *J Immunol* 2007;179:5999–6008.
- [25] LeibundGut-Landmann S, Gross O, Robinson MJ, Osorio F, Slack EC, Tsoni SV, et al. Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17. *Nat Immunol* 2007;8:630–8.
- [26] Bozza S, Zelante T, Moretti S, Bonifazi P, De Luca A, D C, 'Angelo, et al. Lack of Toll IL-1R 8 exacerbates Th17 cell responses in fungal infection. *J Immunol* 2008;180:4022–31.
- [27] Awasthi A, Carrier Y, Peron JP, Bettelli E, Kamanaka M, Flavell RA, et al. A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells. *Nat Immunol* 2007;8:1380–9.
- [28] Zhou L, Lopes JE, Chong MM, Ivanov II, Min R, Victora GD, et al. TGF-beta-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing RORgamma function. *Nature* 2008;453(7192):236–40.
- [29] Romani L, Puccetti P. Protective tolerance to fungi: the role of IL-10 and tryptophan catabolism. *Trends Microbiol* 2006;14:183–9.
- [30] Montagnoli C, Bacci A, Bozza S, Gaziano R, Mosci P, Sharpe AH, et al. B7/CD28-dependent CD4⁺CD25⁺ regulatory T cells are essential components of the memory protective immunity to *Candida albicans*. *J Immunol* 2002;169:6298–308.
- [31] Montagnoli C, Fallarino F, Gaziano R, Bozza S, Bellocchio S, Zelante T, et al. Immunity and tolerance to *Aspergillus* involve functionally distinct regulatory T cells and tryptophan catabolism. *J Immunol* 2006;176:1712–23.
- [32] Romani L, Bistoni F, Perruccio K, Montagnoli C, Gaziano R, Bozza S, et al. Thymosin a1 activates dendritic cell tryptophan catabolism and establishes a regulatory environment for balance of inflammation and tolerance. *Blood* 2006;108:2265–74.
- [33] Ryan KR, Lawson CA, Lorenzi AR, Arkwright PD, Isaacs JD, Lilic D. CD4⁺CD25⁺ T-regulatory cells are decreased in patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy. *J Allergy Clin Immunol* 2005;116: 1158–9.
- [34] Grohmann U, Volpi C, Fallarino F, Bozza S, Bianchi R, Vacca C, et al. Reverse signaling through GITR ligand enables dexamethasone to activate IDO in allergy. *Nat Med* 2007;13:579–86.
- [35] Grohmann U, Fallarino F, Puccetti P. Tolerance, DCs and tryptophan: much ado about IDO. *Trends Immunol* 2003;24:242–8.
- [36] Puccetti P, Grohmann U. IDO and regulatory T cells: a role for reverse signaling and non-canonical NF- κ B activation. *Nat Rev Immunol* 2007;7: 817–23.
- [37] Popov A, Schultze JL. IDO-expressing regulatory dendritic cells in cancer and chronic infection. *J Mol Med* 2008;86:145–60.
- [38] Cooke A, Ferracioli GF, Hermann M, Romani L, Schulze C, Zampieri S, et al. Induction and protection of autoimmune rheumatic diseases. The role of infections. *Clin Exp Rheumatol* 2008;26:S1–7.
- [39] Noverr MC, Huffnagle GB. Does the microbiota regulate immune responses outside the gut? *Trends Microbiol* 2004;12:562–8.
- [40] Toussiot EA. Oral tolerance in the treatment of rheumatoid arthritis. *Curr Drug Targets Inflamm Allergy* 2002;11:45–52.

CD4⁺CD25⁺ regulatory T cells (Treg) in systemic lupus erythematosus (SLE) patients: The possible influence of treatment with corticosteroids

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by loss of tolerance to self-antigens. Regulatory T cells (Treg) are those CD4⁺ T cells that constitutively express high levels of CD25 and exhibit powerful suppressive properties. The aim of this study, Azab NA. et al. (*Clin Immunol* 2008; 127: 151–57) was to quantify Treg cells and the Mean Fluorescence Index (MFI) of Treg in the peripheral blood of patients with SLE and to correlate these findings with their disease activity scores and drug therapy. The study included 24 SLE patients with various disease activity scores (SLEDAI) and 24 healthy age and sex matched controls. Flow cytometry was used to examine the frequency of CD4⁺CD25⁺ T cells and the MFI of CD4⁺CD25⁺ high T cells (Treg). CD4⁺CD25⁺ T cells % and MFI of Treg cells were higher in SLE patients than controls ($p = 0.62$ and $= 0.037$ respectively) and both CD4⁺CD25⁺ T cell % and the MFI of CD4⁺CD25⁺ high T cells showed highly significant correlation with SLEDAI scores (both with a $p < 0.001$) and were higher in patients taking glucocorticoids than those not on glucocorticoids ($p = 0.023$, 0.048 respectively). It was concluded that the increase in Treg cells in SLE patients may be due to corticosteroid treatment.