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BRIEF REVIEWS

IL-17 and Therapeutic Kynurenines in Pathogenic Inflammation to Fungi[1]

Luigina Romani,[2] Teresa Zelante, Antonella De Luca, Francesca Fallarino, and Paolo Puccetti[2]

Largely viewed as proinflammatory, innate responses combine with adaptive immunity to generate the most effective form of antifungal resistance, and T cells exercise feedback control over diverse effects of inflammation on infection. Some degree of inflammation is required for protection, particularly in mucosal tissues, during the transitional response occurring between the rapid innate and slower adaptive response. However, progressive inflammation worsens disease and ultimately prevents pathogen eradication. IDO, tryptophan catabolites ("kynurenines"), and regulatory T cells help to tame overzealous and exaggerated inflammatory responses. In this context, IL-23 and the Th17 pathway, which down-regulate tryptophan catabolism, may instead favor pathology and serve to accommodate the seemingly paradoxical association of chronic inflammation with fungal persistence. Recent data support a view in which IL-23/IL-17 antagonistic strategies, including the administration of synthetic kynurenines, could represent a new means of harnessing progressive or potentially harmful inflammation. The Journal of Immunology, 2008, 180: 5157–5162.

Despite the fact that human beings are constantly exposed to fungi, fungal diseases, although disparate in nature, are relatively rare. A stable pathogen-host interaction is common for pathogens with inherently low virulence, such as the majority of medically relevant fungi. Host-pathogen interactions have ultimately evolved strategies that benefit both parties. Thus a high degree of coexistence occurs between fungi and their mammalian hosts that deviates into overt disease only under specific conditions, including deficits in cellular immunity (1).

Similarly important is the contribution of fungi to the plasticity of the immune system. The ability of fungi to reversibly switch from one form to another accounts for an expanded repertoire of cross-regulatory and overlapping responses in vertebrates. In addition, particularly with commensals, elaborate modalities of immune evasion and prolonged stimulation of the host's immune system contribute toward shaping inflammatory and immune mechanisms (2, 3). Continued integration of proinflammatory and anti-inflammatory stimuli is mandatory for the proper control of infection and T cell homeostasis. IDO and tryptophan catabolites contribute to this delicate balance in experimental candidiasis and aspergillosis by providing the host with immune mechanisms adequate for protection without necessarily eliminating fungal pathogens or causing an unacceptable level of tissue damage (2, 3).

In this article we review evidence supporting opposing roles for IDO-dependent immune regulation—including the generation of regulatory T (Treg)[3] cells (4, 5)—and the IL-23/Th17 axis in controlling inflammation to specific fungi. Although we mostly deal with candidiasis and aspergillosis, the pivotal and sequential roles of the various populations of Treg cells that we discuss here may not be an exception but the rule because most fungal—but also nonfungal and chronic—infections proceed through various stages and therefore require various layers of regulation (6–8).

Inflammation: friend or foe, or something uneasily in between?

Many of the diseases that afflict mankind are thought to result from dysfunctional innate and/or adaptive immune responses (9). The inflammatory response, initiated by cells of the innate immune system, is followed by adaptive immunity, which responds to and at the same time regulates signals emanating from the innate system. Unresolved infection and inflammation are major epigenetic and environmental factors that contribute to chronic diseases and autoimmunity and, in specific settings, to an increased risk of cancer. Another important feature of the innate system is its ability to induce sterile inflammation, that is, a reaction triggered by endogenous TLR ligands (10).

Table I. *Cellular sources of IL-23/IL-17 in response to* Candida *or* Aspergillus[a]

Cytokine	Cell Type	Stimulus	Reference
IL-23	Dendritic cells	*Candida/Aspergillus*	13, 34, 35
	Neutrophils	*Candida/Aspergillus*	Our unpublished observations
IL-17	Vγ1$^+$ $\gamma\delta$ TCR cells	*Aspergillus*	22
	CD4$^+$Th17	*Candida/Aspergillus*	34
	Neutrophils	*Candida/Aspergillus*	Our unpublished observations

[a] Cytokines were determined using cells stimulated in vitro with fungi or Vγ1$^+$ $\gamma\delta$ T cells from the lungs of infected mice.

Fungi can exploit or subvert a host's inflammatory response (11) and thus affect carriage (12–14) and pathogenicity. A hyperinflammatory response does, in fact, enhance virulence in *Saccharomyces cerevisiae* (15) and *Aspergillus nidulans* (16) infections. In the normal skin, the fungus *Malassezia* down-regulates inflammation via TGF-β1 and IL-10 and establishes itself as a commensal (17). In contrast, in atopic dermatitis and psoriasis the skin barrier acts to enhance the release of allergens and molecules involved in hyperproliferation, cell migration, and disease exacerbation (18). Therefore, proper manipulation of the inflammatory response could offer strategies to control or prevent exacerbations in those diseases (3).

Candidiasis and aspergillosis as examples of immune-related pathology

Bidirectional influences between infection and immune-related pathology have been known to exist in chronic mucocutaneous candidiasis (CMC), a primary immune deficiency presenting as an inability to clear *Candida albicans* yeasts, which persist in recurring lesions of the skin, nails, and mucous membranes (18, 19). Although occasionally associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (a condition of dysfunctional T cell activity), CMC encompasses a variety of clinical entities, the pathogenesis of which is largely unclear. CMC patients often develop endocrine and inflammatory disorders, suggesting deregulation of the inflammatory and immune responses (19). A generalized and sustained inflammatory reaction also predicts poor prognosis in patients with *Candida* spp. bloodstream infection (20). Most prominently, in patients with chronic granulomatous disease (CGD) a hyperinflammatory phenotype and a defective fungal (typically *Aspergillus fumigatus*) clearance have long been known to benefit each other (21).

Bipolar nature of inflammation in CGD and immune reconstitution syndrome (IRS)

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. 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* (22). 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.

Clinically, severe fungal infections occur in patients with IRS, an entity characterized by local and systemic reactions that have both beneficial and deleterious effects on infection (23, 24). Intriguingly, IRS responses are also found in immunocompetent individuals and after rapid resolution of immunosuppression, indicating that inflammatory responses can result in quiescent or latent infections manifesting as opportunistic mycoses. Thus, although host immunity is crucial in eradicating infection, immunological recovery can also be detrimental and may contribute toward worsening disease in opportunistic (25, 26) and nonopportunistic (27) infections.

IL-23 and IL-17 in local pathology by Candida and Aspergillus

The mechanisms that link innate immunity, inflammation, and chronic infection are now beginning to be unraveled. Important components in this network are cytokines produced by activated innate immune cells, which stimulate adaptive responses that mediate inflammation (28). Soluble mediators produced by fungi also recruit and activate inflammatory cells, further increasing inflammation. In general, the heterodimeric cytokine IL-12 (p40/p35), by initiating and maintaining Th1 responses, has long been thought to account for overreacting immune and autoimmune disorders (29). This likely holds true of specific fungal pathology, where immunoregulation is essential in modulating inflammation and potentially uncontrolled Th1 or Th2 reactivity (1, 2, 30). However, two additional cytokines, IL-23 (p40/p19) and IL-17A, have recently been credited with a similar, if not greater, offending potential.

IL-17A has a nonredundant role in neutrophil recruitment (31), and IL-23 regulates polymorphonuclear neutrophil (PMN) homeostasis (32). However, the activity of IL-23 and IL-17A affects both the innate and adaptive response to fungi. In experimental models of mucosal candidiasis and pulmonary aspergillosis, IL-23 and IL-17A are rapidly produced at sites of infections (33, 34), particularly under conditions of increased TLR signaling (35). Inflammatory dendritic cells (DCs) are a major source of IL-23 in response to *Candida* and *Aspergillus* in vitro (Table I and Refs. 13, 34, and 35). However, PMNs, and particularly those from IL-12 p35-deficient mice, appear to produce IL-23 when stimulated with *Candida* or *Aspergillus* in vitro. PMNs also produce IL-17A in response to either organism in vitro. In vivo, however, the Vγ1$^+$ subset of TCR $\gamma\delta$ T cells is a major source of IL-17A in the lungs of conventional and CGD mice with invasive pulmonary aspergillosis (Ref. 22 and Table I). Therefore, although their cellular sources may depend on sites of infection, the production of IL-23 and IL-17A is augmented in the condition of IL-12 p35 deficiency, and this worsens local disease (34).

IRS-like pathology in experimental systemic mycoses

Observations in acute disseminated candidiasis corroborate the findings in the mucosal model and highlight a regulatory role for IL-23 and IL-17A in the innate response to a generalized
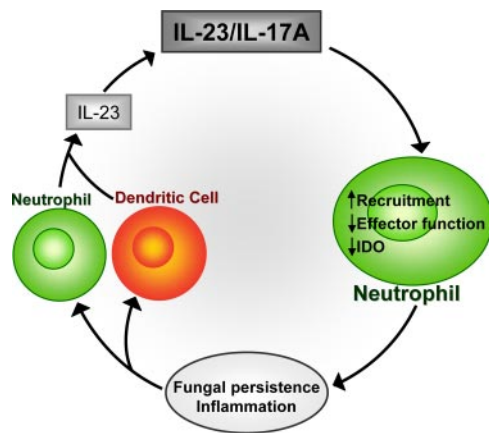
FIGURE 1. The IL-23/IL-17 axis favors pathogen survival and chronic inflammation in fungal infections. Although IL-17A contributes to neutrophil mobilization in disseminated candidiasis (33) and IL-23 regulates neutrophil homeostasis (32), both IL-23 and IL-17A, which are rapidly produced at sites of infections (33, 34), impair antifungal effector activities of neutrophils and activate their inflammatory program (i.e., release of metalloproteinases and oxidants) by opposing IFN-γ-dependent activation of IDO, which limits fungal inflammation (2, 3). Fungal persistence in this setting may further stimulate IL-23 production by both neutrophils and DCs, thus perpetuating inflammation and further stimulating IL-17A production. Thus, failure to down-regulate microbe-induced expression of IL-23/IL-17 could be an important link between infection and chronic inflammation.

infection. Both cytokines are produced to significant extents and, again, particularly under conditions of IL-12 p35 deficiency. Interestingly, not only is IL-23 absent in p19- or p40-deficient mice, but levels of IL-17A are also significantly reduced in those mice in contrast to their p35-deficient counterparts. This confirms that the production of IL-17A in innate immunity is positively controlled by IL-23 in a T cell-independent fashion (36).

Unlike mice deficient in both IL-12 and IL-23 (p40-deficient mice), which do rapidly clear infection with minimum pathology (34), survival is severely impaired in the absence of IL-12 (in p35-deficient mice), and this unfavorable outcome is associated with pyogranulomatous lesions and extensive fungal growth. In contrast, a mild mononuclear inflammation with reduced pathogen burden characterizes the improved survival seen in the absence of IL-23 (in p19-deficient mice).

Neutralization of IL-17 or IL-23 greatly reduces fungal burden and corrects inflammation in wild-type and more so in p35-deficient mice (34, 35). Both cytokines enhance the inflammatory potential of PMNs, which is instead restrained by IDO once the enzyme is activated by proinflammatory cyto-

kines and IFN-γ (37, 38). This suggests that although neutrophils ought to be present to control systemic infection and may become activated in an autocrine fashion, optimal protection requires a staged response involving a timely restriction of PMN inflammatory potential. Fungal persistence might otherwise occur and further stimulate IL-23 production by both DCs and PMNs, thus perpetuating inflammation and maintaining IL-17 production in a vicious circle (Fig. 1). Eventually, failure to down-regulate microbe-induced expression of IL-17 could be one major link connecting infection with chronic inflammation (22, 39).

IL-17 at the intersection of fungal protection with pathology

Although the importance of the IL-17 cytokine family and in particular that of IL-17A and IL-17F has been known for years, it is only recently that IL-17-producing T cells have been recognized as constituting a separate subset of T cells, termed Th17, in which STAT3 as well as retinoic acid receptor-related orphan receptor (ROR)γ and more recently RORα (40) mediate lineage specification. Th17 cells, which produce IL-17A, IL-17F, IL-21, and IL-22, have been linked with the proinflammatory cytokine IL-23, because IL-23-deficient (p19$^{-/-}$) mice contain very few Th17 cells and are protected from autoimmune diseases (29). However, although IL-23 seems to be involved in Th17-mediated antimicrobial protection (41) and in immune pathology as well (42), it is not required for the differentiation of Th17 from naive CD4 T cells in that they lack an IL-23 receptor (43).

As in other infections (31, 44), 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 DCs. IL-23 production by murine DCs occurs in response to high yeast numbers through the MyD88 pathway, which indicates that IL-23 is produced in settings of sustained inflammation. IL-17–producing cells are induced by *C. albicans* or *A. fumigatus* through innate signaling via Dectin-1/CARD9 (45) and TLR/MyD88 (34), and they are inhibited by negative regulators of TLRs (35) and TRIF (13). Activation of pathogenic Th17 cells accounts for susceptibility to candidiasis and aspergillosis under conditions of deficient p35 (34), TRIF (13), TIR8/SIGIRR (35), or functional NADPH oxidase expression (22) (e.g., in CGD mice; Table II). In all of these settings, Th17 pathway expression rather than an unrestrained Th1 response correlates directly with defective pathogen clearance and the failure to resolve inflammation as well as to initiate protective responses to *Candida* and *Aspergillus* (Fig. 2).

Table II. *Pathogenic Th17 cell activation in fungal infections*[a]

Genotype	Infection	Clinical Features	Reference
IL-12 p35 deficiency	Candidiasis/Aspergillosis	Defective clearance/inflammation	34
TRIF deficiency	Candidiasis	Defective clearance/inflammation	13
TIR8/SIGIRR deficiency	Candidiasis/Aspergillosis	Defective clearance/inflammation	35
NADPH oxidase deficiency	Aspergillosis	Defective clearance/inflammation	22

[a] SIGIRR, Single Ig IL-1R-related molecule; TIR8, Toll/IL-1R 8; TRIF, TIR-domain-containing adapter inducing IFN-β.
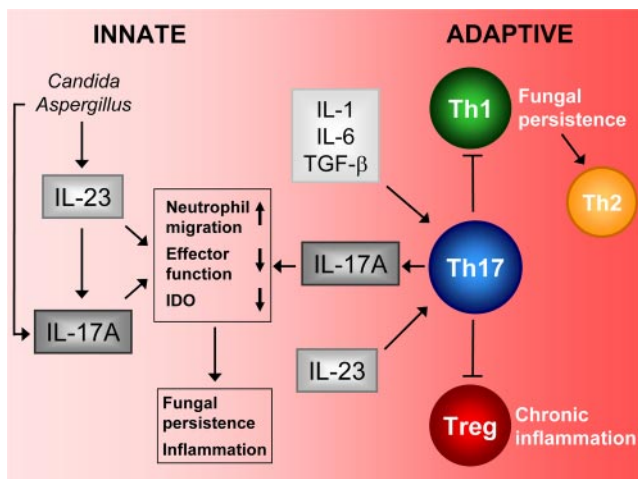
FIGURE 2. The intricacies of cytokine effects that converge on a dual function of IL-17A at the fungal/host interface. Although some degree of inflammation is probably required for IL-17A protective effects at the mucosal level, persistent or exuberant inflammation resulting from dysregulated actions of multiple cytokines, including IL-1, which orchestrates activation of Th17 cells (35), and IL-17A, could ultimately initiate a vicious circle and thus sustain chronic and refractory infection.

The roles of IFN-γ, IL-10, IL-1, IL-6, and TGF-β: an intricate balance

IFN-γ-producing T-bet$^+$ Th1 cells increase and IL-17-producing RORγt$^+$ Th17 cells decrease under conditions of IL-23 genetic deficiency or functional ablation; the opposite pattern is observed in settings of IL-12 genetic deficiency or functional ablation (22, 34). Like Th1 cells, IL-10$^+$ Foxp3$^+$ Treg cells also increase in the absence of IL-23 and decrease in the absence of IL-12 (22, 34). This suggests a common pathway leading to Th1/Treg activation in fungal infections. A recent study of mice with candidiasis in which both Th1 and Th17 cells were activated clearly showed that in the condition of Th1 deficiency Th17 may provide some protection, but when both components are present protection is provided through the Th1 pathway and is opposed by the Th17 pathway (34).

Among inflammatory stimuli, IL-6 and other cytokines are known to divert murine Treg generation to Th17 induction in the presence of TGF-β (46). Recent studies, however, have suggested that these two cytokines also drive the differentiation of nonpathogenic Th17 cells that produce IL-10 in the presence of IL-27 and the absence of IL-23, resulting in a bystander regulatory response and the regulation of pathogenic Th17 cell responses (42). In line with previous findings on the protective role of either cytokine in candidiasis and aspergillosis (1), we found that IL-6 plus TGF-β do not drive pathogenic Th17 cells in fungal infections but that IL-1 signaling is essentially required for the activation of pathogenic Th17 cell by IL-6 and TGF-β (Fig. 2 and Ref. 35). Actually, because IL-6 also inhibits IDO (47), which is known to be required for peripheral Treg generation (2, 5), the high susceptibility of *Il6*$^{-/-}$ mice to candidiasis (48) or aspergillosis (49) correlates with increased IL-10 production. Interestingly, in aspergillosis IL-6 deficiency is also associated with high-level production of IL-17 and defective antifungal effector function by phagocytes (49).
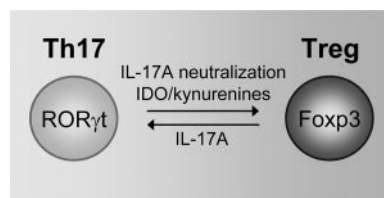

FIGURE 3. Metabolic regulation of Th17/Treg lineage decision; the opposing roles of IL-17 and kynurenines. In its ability to inhibit Th1 activation, the Th17-dependent pathway could be responsible for failure to resolve infection in the face of ongoing inflammation. However, Tregs may actively participate in this process (54). Tryptophan metabolites will induce the Foxp3-encoding gene and suppress that coding for RORγt (4, 5, 13, 22). Thus tryptophan catabolites support the generation of Foxp3$^+$ cells but inhibit RORγt-expressing T cells. This suggests the occurrence of IFN-γ/IDO-dependent pathways resulting in coordinate activation of Th1 and Treg cells.

Metabolic regulation of Th17/Treg cell lineage decision: the contribution of kynurenines

Recent data suggest that the functions of transcription factors, cytokines, and their receptors in T cell "decision making" need further analysis to clarify the intricacies of Th1/Treg/Th17 cell development (50–52). In addition, more flexibility may exist in cytokine production than one would predict from the terminal differentiation model of Th1 vs Th2, and these considerations cannot help but have important implications for the pathogenesis of fungal infection and disease (53).

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 that can be generated by stimulation with TGF-β and IL-27 in the absence of IL-6 (54). Tregs, capable of fine-tuning protective antimicrobial immunity to minimize harmful immune pathology, have become an integral component of the immune response to fungi (2). Treg induction is defective in patients with CMC (55). In experimental models of infection, fungal growth, inflammatory immunity, and tolerance to *C. albicans* and *A. fumigatus* are all controlled by the coordinate activation of naturally occurring Tregs, which limit early inflammation at the sites of infection, and pathogen-induced Tregs, which regulate the expression of adaptive Th immunity in secondary lymphoid organs (2, 3).

A major observation from these studies was that, using naive CD4$^+$ cells from naive mice, tryptophan metabolites were capable of inducing the Foxp3-encoding gene transcriptionally and suppressing the gene encoding RORγt (13, 22). Thus, the same tryptophan catabolites can foster DC-supported generation of Foxp3$^+$ cells (4, 5) and mediate, at the same time, the inhibition of RORγt-expressing T cells. Because IFN-γ is a potent IDO activator, this suggests the existence of an IFN-γ/IDO-dependent pathway leading to sequential Th1/Treg cell activation in infection.

These data further establish IDO as a true immunoregulatory mechanism in infection, controlling the balance between Th17 and Treg cell subsets (Fig. 3 and Refs 2 and 3). 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 in immunity and tolerance (56–58).

Exogenous kynurenines restrain pathogenic Th17 cell inflammation

Current evidence suggests that Th17 cells, which produce IL-17A preferentially, are involved in the regulation of pulmonary inflammation at multiple levels, in part through the induction of other cytokines and chemokines but also through mucin secretion. In contrast, exaggerated production of IL-17A and IL-17F may contribute to the expression of airway inflammation and pulmonary hyperreactivity. Another source of IL-17A that is likely to be significant is the γδ T cell population. γδ T cells are enriched at mucosal and epithelial surfaces such as the gut, lung, and skin and express a limited TCR Ag-binding repertoire. The role of γδ T cells at these sites is uncertain, but studies have shown that IL-17A production from γδ T cells is important in controlling mouse *Mycobacterium tuberculosis* lung infection (59) as well as mouse i.p. *Escherichia coli* infection (60). These observations may help to explain the finding that pathology in IL-17RA-deficient mice occurs within a few days, before mature effector T cell responses are likely involved, as observed in *Klebsiella pneumoniae* infection (61). Therefore, IL-17A from γδ T cells may be important for initiating an immediate and early neutrophil response to mucosal infections. Furthermore, IL-17A may be a mechanism by which γδ T cells provide defense responses until adaptive immune cells are recruited. γδ T cells are rapidly but transiently expanded in fungal pneumonia and down-regulate infection-induced Th1-mediated inflammation (62).

Both IL-17A and IL-17F may contribute to the expression of airway inflammation and pulmonary hyperreactivity; free soluble IL-17A is increased in asthma (31), and allergic cellular and humoral responses are suppressed in IL-17-deficient mice (63). These findings indicate that the Th17 pathway may also be involved in fungal-associated allergic lung diseases (5, 30). Interestingly, recent insights regarding the development of allergic diseases have also suggested a role for "inflammatory T cells" or Th17 cells producing IL-17 as a link between T cell inflammation and granulocytic influx as observed in allergic airway (64) and dermal (65) inflammation.

Conclusion and perspective

Inflammation regulated by different pathways is important for defense against a variety of mucosal pathogens, but recent evidence indicates a detrimental side to the inflammatory action of an unopposed IL-23/IL-17 pathway that is, under physiological conditions, restrained by IDO through a mechanism leading to the sequential generation of regulatory and anti-inflammatory Vγ4+ γδ (22) and CD25+ αβ (66, 67) T cells. This is exemplified by a series of studies that may represent ground-breaking observations in our understanding of the intricacies of inflammation and chronic infection (2, 3, 5). The main message is that, contrary to established dogma and at least in specific settings, it is an exaggerated inflammatory response that compromises a host's ability to eradicate infection. In addition, it now appears clear that the intersection of γδ cells (present in all vertebrates) with tryptophan catabolism (conserved through the past 600 million years of evolution) might represent a milestone in the evolution of the immune system, combining the innate and acquired immune systems in the proper control of infection. Finally, the data in the CGD experimental model reveal a new mechanism through which the absence of reactive oxygen species, otherwise associated with neutrophil-dependent oxidative stress, causes a distinct form of pathogenic inflammation

and potential immune pathology via unrestrained γδ T cell activity and IL-17 overproduction (22, 68).

In the experimental model of CGD, IL-17 neutralization increased fungal clearance, ameliorated inflammatory pathology, and restored protective Th1 antifungal resistance (22). Perhaps more importantly, complete cure and reversal of the hyperinflammatory CGD phenotype were achieved by the administration of supplemental L-kynurenine, an early amino acid catabolite of L-tryptophan in the IDO-dependent pathway (22). These data expand on previous data of effective treatment of experimental neuroinflammation with a synthetic tryptophan catabolite (69) and suggest common mechanisms of action for new potential drugs that target cytokine signaling and transcription factors to treat pathogenic and allergic inflammation (30, 70, 71).

Disclosures
The authors have no financial conflict of interest.

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