

Rostrum

Indoleamine 2,3-dioxygenase-expressing antigen-presenting cells and peripheral T-cell tolerance: Another piece to the atopic puzzle?

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There is growing evidence that dendritic cells, the major antigen-presenting cells and T-cell activators, have a broad effect on peripheral T-cell tolerance and regulation of immunity. Very recently, a new feature of regulatory antigen-presenting cells was observed. Certain dendritic cells, monocytes, and macrophages express the enzyme indoleamine 2,3-dioxygenase, and thus because of enhanced degradation of the essential amino acid tryptophan, they modulate T-cell activity in specific local tissue environments. In this review we discuss the various and apparently disparate effects of indoleamine 2,3-dioxygenase induction in cells of the immune system. We place current knowledge about this mechanism in the context of atopy. We introduce the hypothesis that tryptophan degradation might add to the ability to control and downregulate allergen-specific T-cell responses in atopic individuals. (*J Allergy Clin Immunol* 2003;112:854-60.)

Key words: Tryptophan degradation, T-cell suppression, FcεRI, immunoregulation, antigen-presenting cells

Tryptophan is an essential amino acid, and it is the rarest of the 20 amino acids found in proteins. Tryptophan is involved in 2 distinct biochemical pathways: (1) tryptophan 5-hydroxylase converts tryptophan into serotonin, an important neurotransmitter, and (2) tryptophan is catabolized through the kynurenine pathway to form adenosine dinucleotides as end products and neurotoxic intermediates, such as kynurenic acid and quinolinic acid (Fig 1).¹ The transformation of tryptophan to kynurenine in the latter pathway is performed by 2 different enzymes. In hepatic cells this is accomplished by tryptophan pyrrolase, and in other cells, mainly macrophages, monocytes, and dendritic cells (DCs), this is accomplished by the enzyme

Abbreviations used

AEDS: Atopic eczema/dermatitis syndrome
APC: Antigen-presenting cell
CTLA-4: Cytolytic T lymphocyte-associated antigen 4
DC: Dendritic cell
IDO: Indoleamine 2,3-dioxygenase
1-MT: 1-Methyl-tryptophan

indoleamine 2,3-dioxygenase (IDO). In contrast to tryptophan pyrrolase, the activation of IDO is linked to immune responses because IFN- γ is a strong stimulator of IDO.² Interestingly, in monocyte-derived macrophages, LPS has been shown to induce IDO as effectively as IFN- γ by means of an IFN- γ -independent pathway (Fig 2, A).³ Induction of IDO in vitro or in vivo leads to rapid depletion of intracellular tryptophan and excretion of its catabolites into the medium or microenvironment.^{4,5} Fig 3 summarizes various pathologic conditions influenced by IDO activity. It is noticeable that IDO⁺ DCs have been detected preferentially and in advance of tumor cells in metastatic lymph nodes, suggesting efficient tumor immune escape strategies through local tryptophan depletion.⁶ Tryptophan depletion also plays a role in antimicrobial defense mechanisms of intracellular pathogens, such as *Toxoplasma* and *Chlamydia* species.^{7,8} During pregnancy, IDO was described as crucial for establishing immune tolerance.⁹ In addition, the expression of IDO by certain macrophages, defined DCs, and monocytes suggests its role in immunoregulatory mechanisms.¹⁰ We detected IDO activation in monocytes from atopic individuals by cross-linking of the high-affinity receptor for IgE (FcεRI) on the cell surface.¹² This finding might indicate a role for IDO expression in the regulation of atopic diseases.

TRYPTOPHAN CATABOLISM: A NEW PARADIGM FOR T-CELL SUPPRESSION?

Immunologic tolerance to a nonpathogenic protein challenge and self-antigens prevents harmful immune responses that would otherwise lead to constant activation of the immune system and autoimmunity. The first

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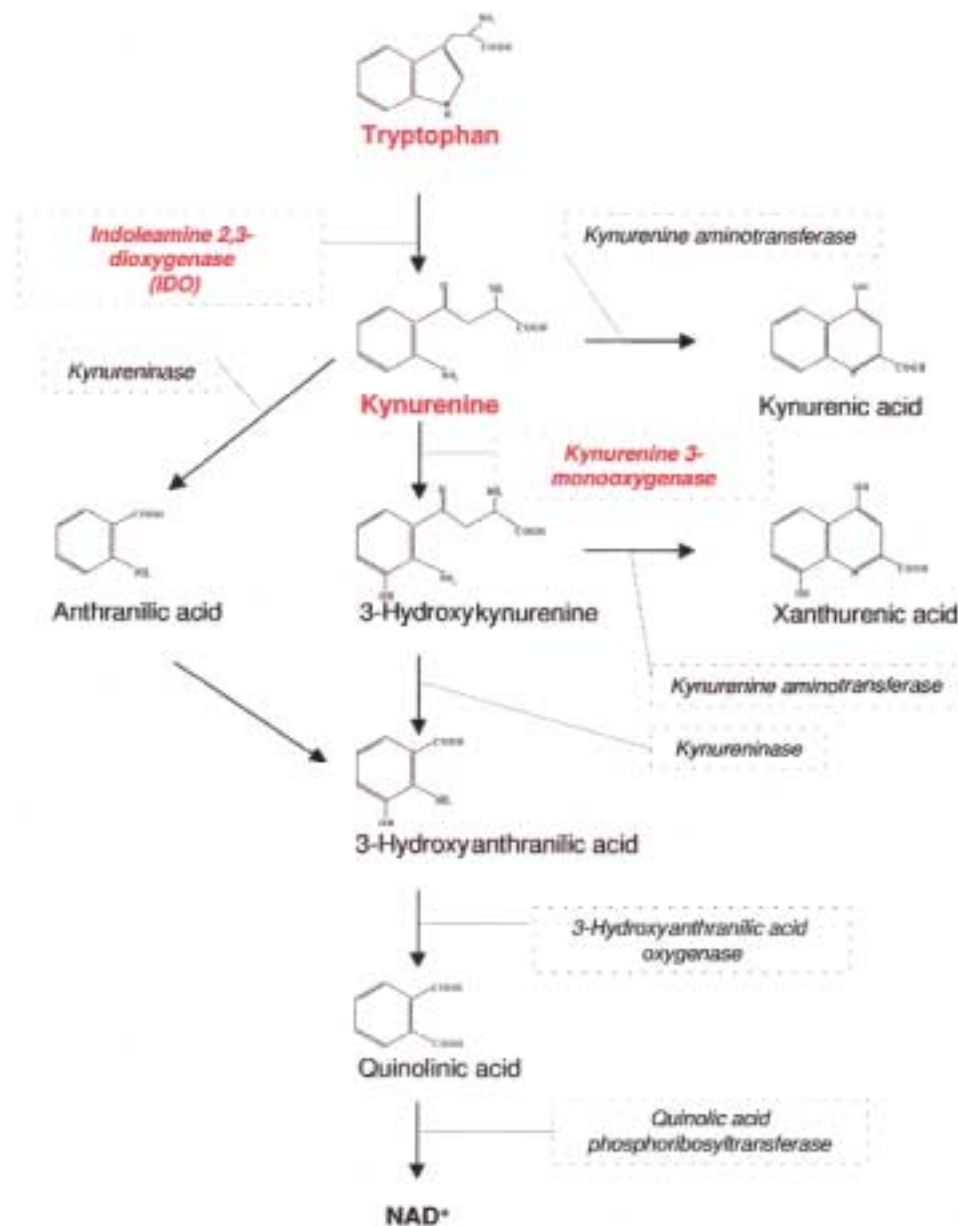


FIG 1. Tryptophan metabolism along the kynurenine pathway in mammalian cells. IDO catalyzes the initial rate-limiting step in the degradation of tryptophan. Immunologically relevant metabolites and enzymes that have been mentioned in the text are shown in red. Several products of the pathway are neuroactive (eg, quinolinic acid). The alternative pathways occurring in brain cells and liver cells are not shown.

evidence of immunoregulatory IDO-producing cells came from a study in which investigators reported that the mouse placenta produced an enzyme that suppressed maternal T-cell proliferation. Application of an IDO inhibitor, 1-methyl-tryptophan, resulted in high rates of fetal abortion. The authors hypothesized that under normal circumstances the maternal-fetal interface creates a zone of low tryptophan in which maternal T-cell activity against fetal alloantigens is suppressed. In human subjects IDO is expressed constitutively in several different cell types from tissues, such as gut, spleen, thymus, and lymph nodes.^{13,14} In these tissues constant tryptophan

degradation and some of its breakdown products have been implicated in the control of cellular gluconeogenesis, free radical scavaging, and serotonin synthesis (a vasoconstrictor), which are useful to defend against potential tissue inflammation.¹⁵ Contemporary research has primarily focused on IDO activation in antigen-presenting cells (APCs). There IDO expression has been evaluated particularly in macrophages and DCs. It is thought that these cells play an important role in mediating immunosuppression in various disorders, such as viral infections and autoimmunity.¹ Although IFN- γ is a major inducer of IDO expression in APCs, antigen-spe-

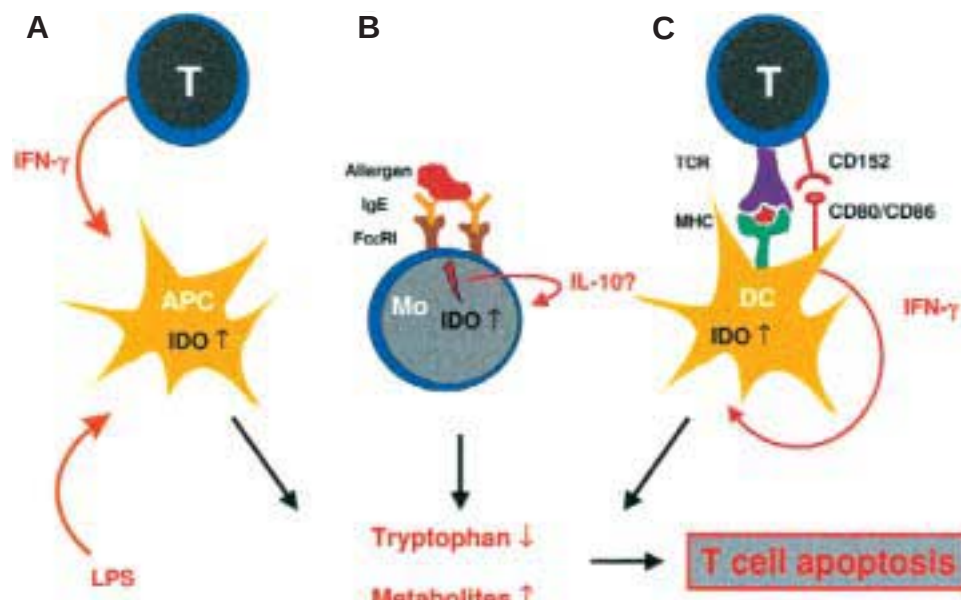


FIG 2. Mechanisms leading to the induction of IDO expression in APCs. **A**, IFN- γ from activated T cells and LPS from bacteria are strong inducers of IDO in APCs. **B**, Stimulation of atopic monocytes by Fc ϵ RI leads to the induction of IDO. In addition, factors such as IL-10 might be involved in downregulating allergic responses. **C**, CTLA-4 (CD152) expressed by T cells and other cell types (eg, placental fibroblasts) acts as ligand for B-7 (CD80 and CD86) accessory molecules on DCs. Signaling through CD80-CD86 causes the induction of IFN- γ in these cells, which leads to autocrine, paracrine, or both IDO induction.

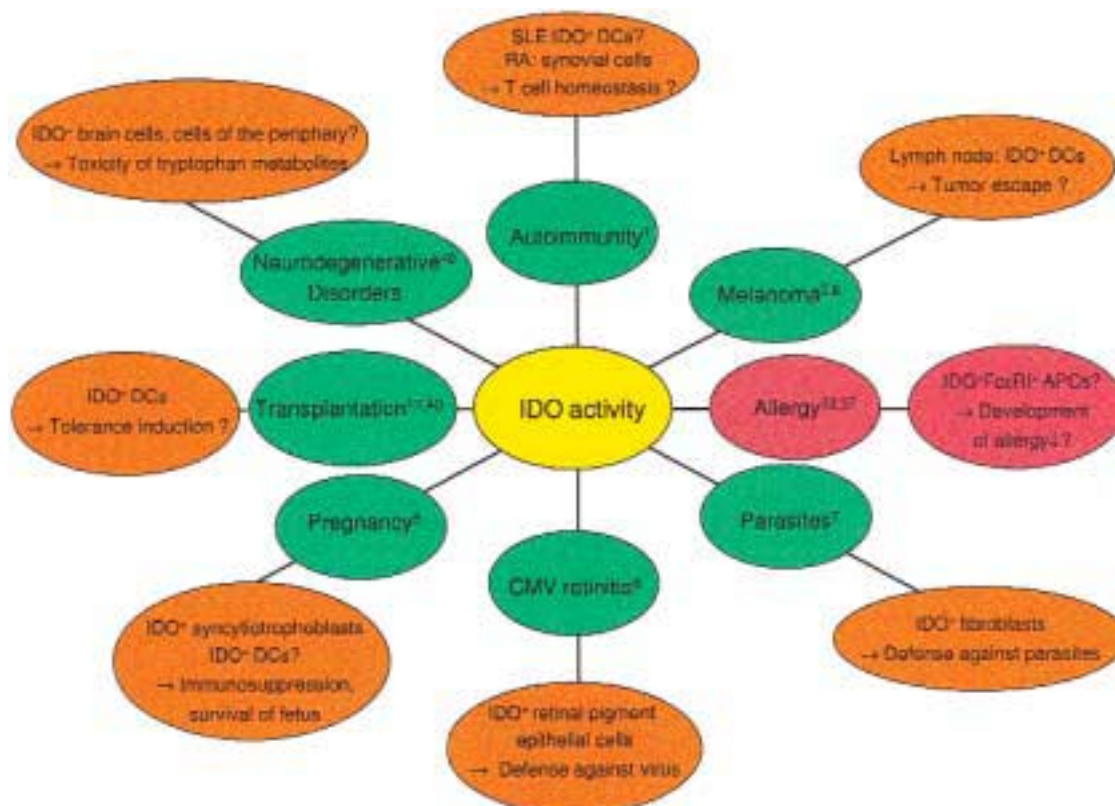


FIG 3. Diseases and corresponding cells in which the tryptophan degradation pathway is involved. The scheme first introduces the condition in which IDO activity was observed. It discloses the cells that have been described to be IDO⁺ in regard to the pathophysiologic condition. Question marks are placed where the correlation is hypothetical.

cific T-cell downregulation by tryptophan degradation, its metabolites, or both is more complex (Fig 3, C). Additional regulatory interactions between APCs and activated T cells could lead to tolerogenic signaling in subsets of APCs. In particular, the inhibitory receptor cytolytic T lymphocyte-associated antigen 4 (CTLA-4) on activated T cells does not act exclusively as a negative regulator of T-cell activation when binding to its counterligands B7-1 and B7-2 on DCs.¹⁶ Instead, when CTLA-4 binds to these receptors, both cell types become activated. This leads to changes in the functional state not only of the T cell but also of the DC. Specifically, in a murine model in which pancreatic islet allograft survival has been studied, recognition of CTLA-4 on T cells by B7 expressed on APCs leads to reverse signals. These signals elicit the production of IFN- γ by the DCs, which results in regulation of IDO in an autocrine or paracrine fashion.¹⁷ This mechanism allows B7 accessory molecules to operate as more than simply forward regulators of immunity by supporting T-cell activation and proliferation. Instead, it broadens their regulatory function by modulating tolerogenic effects of certain inhibitory T-cell receptors. Bidirectional signaling by coreceptor molecules on APCs and T cells might also apply to CD40 expressed on APCs and CD40 ligand expressed on activated T cells.¹⁸ Although initially identified for its activation properties, CD40 is also able to enhance, in concert with IFN- γ , tryptophan depletion through induction of IDO in monocyte-derived macrophages. The net effect of this is inhibition of T cells undergoing activation.¹⁰

Several *in vitro* studies have identified specific tryptophan catabolites in the kynurenine metabolic pathway that act specifically as potent apoptotic agents for activated T cells.¹⁹ In particular, L-kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and picolinic acid seem to exert inhibitory functions on T cells. An additive effect of several metabolites resulting in decreased T-cell proliferation has been demonstrated *in vitro*.²⁰ Very low levels of kynurenine in the serum might be sufficient to exert a similar effect on T cells *in vivo*. In the absence of tryptophan, these metabolites seem to act more potently to promote T-cell apoptosis than in its presence. The biochemical cascade for tryptophan degradation might exert its function 2-fold. Certain catabolites could act synergistically to downregulate T-cell activation and indirectly by enhancing their downregulatory potential on T cells by lowering tryptophan levels at specific sites of the immune system.

REGULATION OF IDO FUNCTION BY CYTOKINES

IFN- γ seems to be a major effector cytokine for the induction of IDO.²¹ IFN- γ -induced IDO is differentially regulated not only in certain cell types but also by other cytokines. Recently, monocyte-derived DCs that constitutively express IDO have been identified. Phenotypically, these DCs are characterized by the coexpression of CD123 (the IL-3 receptor α chain) and CCR6 on their cell

surface.⁶ CD123 is also found on plasmacytoid DCs, called DC2s, but to a much higher level (10- to 100-fold higher) than on IDO⁺ monocyte-derived DCs.²² DC2s, in contrast to IDO⁺ DCs or IDO⁺ DC1s, are thought to be of lymphoid origin and are characterized by a unique surface phenotype: CD4⁺CD3⁺IL3R α ⁺HLA-DR⁺. Functionally, plasmacytoid DCs produce large amounts of type I IFN (IFN- α and IFN- β) during viral infection. IDO⁺ DCs are of myeloid origin because they express myeloid markers (CD11c and CD11b), whereas DC2s are CD11c⁻. Myeloid DCs differentiate from CD34⁺ hematopoietic progenitor cells or from myeloid blood precursors, such as monocytes, *in vitro*. On maturation, IFN- γ completely downregulates the enzymatic activity of IDO in CD123⁺CCR6⁺CD11c⁺ DC1s. However, in the presence of the regulatory cytokines IL-10 or TGF- β during maturation, this downregulation is reversed and leads to sustained expression of functional IDO. Similarly, in a model for the control of intracellular parasites in fibroblasts, IL-10 does not seem to negatively regulate IFN- γ -induced IDO activity.²³ Although reports have been controversial about the function of IL-10 in tryptophan catabolism,²⁴ recent data suggest that IL-10 and IFN- γ act synergistically in the kynurenine pathway. In contrast to IL-10, IL-4 has been consistently reported as a negative regulator of IFN- γ -induced IDO not only in the abovementioned fibroblast model but also in cells of the monocyte-macrophage lineage.²⁵ The roles of other cytokines for the induction of IDO, such as IFN- α , IFN- β , TNF- α , or IL-1 have not been completely investigated, but they seem to potentiate the effect of IFN- γ in the induction of IDO.²⁶ In conclusion, IFN- γ -induced expression of IDO activity seems to rely on regulatory instructions from the environment that contribute to the balance between immunogenic and tolerogenic APC subsets.

POTENTIAL REGULATORY FUNCTION OF IDO-EXPRESSING Fc ϵ RI⁺ APCs IN ATOPIC DISORDERS

Fc ϵ RI is a key molecule for IgE-mediated allergic reactions.^{27,28} Fc ϵ RI has been shown to be constitutively expressed on effector cells of anaphylaxis (eg, mast cells and basophils). Fc ϵ RI expression on APCs, however, allows the differentiation of individuals with an extrinsic or intrinsic type of atopy. The strongest Fc ϵ RI expression on monocytes or blood DCs has been shown to be linked to the extrinsic type of atopic individuals.^{29,30,31} These individuals display increased allergen-specific IgE in the blood, whereas within individuals of the intrinsic type, specific IgE cannot be detected. Most interestingly, in the extrinsic type of atopic individuals, Fc ϵ RI on blood monocytes can be highly expressed in both patients with atopic symptoms, such as allergic rhinitis, bronchial asthma, or the atopic eczema/dermatitis syndrome (AEDS), and in individuals who are clinically healthy but with a family history of atopic diseases.

In nonatopic individuals nonpathogenic allergens delivered through intact mucosa surfaces do not evoke

inflammatory immune responses but instead induce antigen-specific T-cell hyporesponsiveness. The cellular mechanisms that lead to T-cell downregulation after an allergen encounter, as well as the types of APCs involved in these processes, are poorly understood. Recently, new insights into the development of tolerance toward inhaled allergens have been gained from the murine model. In these experiments mature IL-10-producing pulmonary DCs were shown to be mediators of allergen-specific T-cell tolerance and were protective against asthma.³² Because the very initial event in IgE-mediated allergy reactions is the binding of allergen to specific IgE on FcεRI, followed by the release of well-defined immunostimulatory and immunomodulatory signals, this early step might represent a critical immunoregulatory mechanism that determines the pathophysiology of FcεRI-mediated reactions.

While searching for genes differentially expressed after FcεRI cross-linking on monocytes by suppression subtractive hybridization, we identified the downstream enzyme kynurenine 3-monooxygenase, which converts kynurenine into 3-hydroxykynurenine and quinolinic acid, to be overexpressed in FcεRI⁺ monocytes from atopic individuals.¹² Kynurenine is the first stable metabolite in the tryptophan degradation pathway and results from the degradation of tryptophan by IDO. In addition, transcripts for IDO are overexpressed after ligation of FcεRI on monocytes. Kinetic studies of kynurenine 3-monooxygenase expression revealed that the number of transcripts for this gene increased for a period of at least 24 hours after cross-linking of FcεRI on monocytes.³³ Accordingly, functionally active IDO can be detected about 6 to 8 hours after FcεRI ligation. Importantly, by inducing this enzyme, FcεRI⁺ monocytes acquire the ability to suppress T-cell proliferation. Selective blockade of IDO functional activity by 1-methyl-tryptophan reverses the T-cell suppressive effect. It is likely that tryptophan metabolites and low tryptophan levels account for the T-cell downregulation after FcεRI ligation because cDNA of a downstream enzyme, kynurenine 3-monooxygenase, was identified in a cDNA bank from FcεRI cross-linked monocytes.

IDO production after FcεRI cross-linking might be part of a mechanism to suppress unwanted T-cell responses. Allergic inflammation, in particular in AEDS, might be self-limiting or alternate with periods of relapse and remission.³⁴ Here IDO might exert its immunoregulatory function by regaining (retaining) immune homeostasis. Kinetics of functional enzyme expression after FcεRI cross-linking supports this concept because they increase in the late phase of the response (ie, after approximately 8-24 hours). On the other hand, this delay in time could imply that there are additional mediators evoked through FcεRI, which act immediately and in advance to regulate IDO expression. In this context, the abovementioned cytokine IL-10 might be of importance. IL-10 is known to be immediately secreted after FcεRI stimulation on monocytes.³⁵ To further outline this model, the induction of IL-10 (to possibly potentiate sta-

ble IDO expression) and IDO in monocytes might characterize a subset of atopic individuals who successfully cope with an initial allergic challenge (Fig 3, B). IDO and the release of kynurenines might modulate the composition of peripheral T cells, possibly conferring T_R cells to defined atopic individuals.³⁶

Together, these data presume that IDO might be part of a central mode to establish tolerance, homeostasis, or both after a challenge by allergen.

The expression of IDO is differentially regulated in atopic versus nonatopic monocytes.³⁷ An increase of about 4½ times in induction of the gene encoding IDO after IFN-γ exposure in atopic versus nonatopic monocytes has been demonstrated. At present, we favor potential polymorphisms in the regulatory region of the gene encoding IDO or alterations in cytokine expression with cell stimulation, which could account for these observations.^{38,39}

The fact that IDO induction is more pronounced in atopic than in nonatopic individuals might imply that induction of IDO is part of a response mechanism in an altered immune homeostasis.⁴⁰ In atopic subjects sensitization toward allergens need not, per se, be a function associated with IDO. Rather, genetically inherited response mechanisms might influence reaction patterns, such as IgE production, which, in addition, might be related to a symptomatic or asymptomatic phenotype.^{41,42} IDO might be involved in the (down)regulation or tolerance induction of T cells in atopic individuals in whom atopy-related dysregulations (eg, IgE production) take place. By contrast, local IDO induction at contact sites of the immune system with the environment (eg, in the airway epithelium) might be an attractive hypothesis of a naturally occurring tolerance induction mechanism also in nonatopic subjects. Fig 2 summarizes the current knowledge about the molecular mechanism of IDO induction.

Histologically, AEDS is characterized by increased numbers of Langerhans cells, inflammatory dendritic epidermal cells, macrophages, basophils, eosinophils, T_H2 cells, and dermal DCs.^{43,44}

In this review we provide the first evidence that IDO⁺ cells are present in atopic inflammatory skin (Fig 4). These cells are limited in number but stain clearly positive for IDO. IDO⁺ cells are located at the upper front of the infiltrate near the dermal-epidermal junction, suggesting recruitment of these cells by the atopic skin. Further investigations will be necessary to determine the exact nature and function of these IDO⁺ cells.

CONCLUSION

Regulation of T-cell survival through tryptophan depletion and increase of proapoptotic metabolites seems to operate in many physiologic and pathophysiologic conditions. Most of these tolerogenic activities might aim at the maintenance of T-cell homeostasis and self-tolerance. There is strong evidence that IDO activation within the infiltrate of AEDS contributes to the regulation of atopic inflammation. The exact knowledge of how

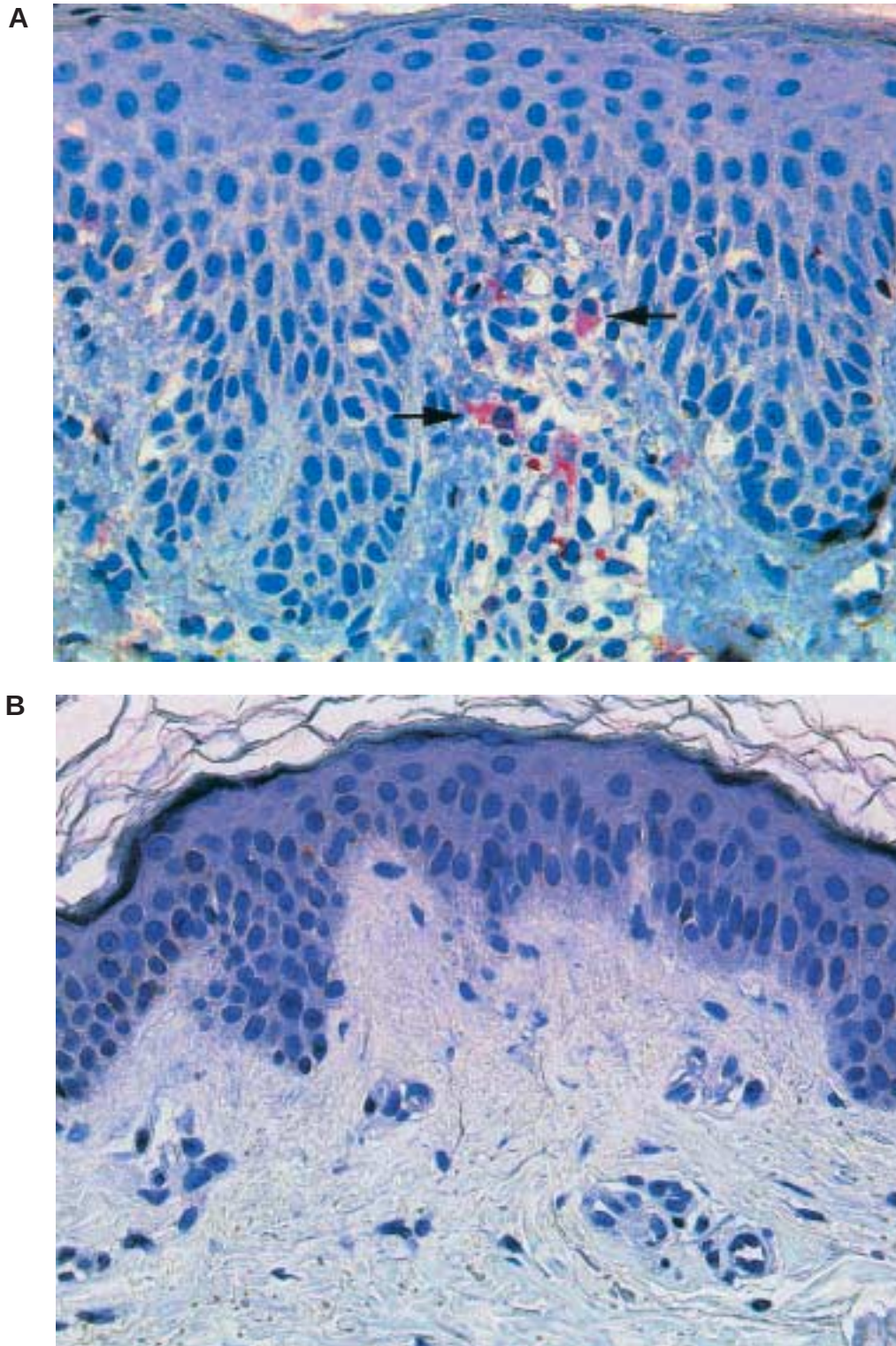


FIG 4. A, Lesional skin biopsy of a 25-year-old woman with subacute AEDS. IDO-expressing cells (→) are scattered within the subepidermal inflammatory infiltrate. Staining was performed with a monoclonal mouse-anti-human IDO antibody (Dr Takikawa, Japan) by using the LSAB2 system (DAKO). The IDO⁺ cells were morphologically monocytic or dendritic in appearance. Typical histologic signs of AEDS, such as acanthosis, spongiosis, and exocytosis of lymphocytes, can be seen (original magnification 40×, paraffin-fixed biopsy specimen). **B,** Control skin tissue. Staining for IDO in normal skin of a healthy 26-year-old woman. IDO⁺ cells are not detectable.

the peripheral kynurenine pathway influences the outcome of the allergic response is of major interest. Compounds of these or selectively treated DCs could be used as therapeutic tools to manipulate the immune system.

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