Indoleamine 2,3-Dioxygenase (IDO)

The Antagonist of Type I Interferon-Driven Skin Inflammation?

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Recent studies have provided evidence that a type I interferon (IFN)-driven immune response might play an important role in the pathogenesis of lichen planus (LP), an inflammatory disorder of the skin of unclear etiology. Plasmacytoid dendritic cells in affected skin from LP have been proposed to produce IFN-α/β locally, which leads to the expression of IFN-inducible chemokines such as IP10/CXCL10 in the epidermis. This chemokine recruits chemokine receptor CXCR3-expressing T-lymphocytes into the skin via CXCR3/IP10 interactions. Indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan and suppresses T-cell proliferation, is induced by IFNs and other inflammatory cytokines. We show that type I IFN-mediated skin disorders, such as LP, strongly express IDO in lesional skin. This expression closely correlates to the expression of the highly specific type I IFN marker MxA. We further demonstrate that the IDO+ cells in LP are large myeloid CD11c+S100+CD68+ dendritic cells. Accordingly, CD11c+ antigen-presenting cells significantly up-regulate IDO gene expression and intracellular IDO protein expression after stimulation with IFN-α in vitro. These findings reveal that both proinflammatory and counterregulatory mechanisms are operative in cutaneous lesions of LP. We propose that the balance of these mechanisms may be involved in the pathogenesis of this disorder. (Am J Pathol 2007, 171:1936–1943; DOI: 10.2353/ajpath.2007.070281)

Interferons (IFNs) are a family of cytokines with anti-proliferative, anti-viral, and immunomodulatory properties. Their action provides a critical link between innate and adaptive immune responses.1 In the skin, plasmacytoid dendritic cells (pDCs), which recognize pathogen-associated molecular patterns via Toll-like receptors, are presumed to be the main source of type I IFNs.2,3 Besides these physiological roles, type I IFNs are also involved in several pathological conditions. In particular, high expression of type I IFNs and IFN-inducible proteins was found in Th1-biased cell-mediated autoimmune skin diseases such as lichen planus (LP), lupus erythematosus (LE), dermatomyositis, and psoriasis.4–8 Recently, we and others provided evidence that the type I IFN-induced recruitment of skin homing lymphocytes via CXCR3/IP10 interaction participates in the skin inflammation in these disorders.9–13 The lesional inflammation is critically important for activating innate and adaptive immunity and is followed closely by the induction of anti-inflammatory mechanisms that protect tissue from collateral damage.

Indoleamine 2,3-dioxygenase (IDO) is an IFN-inducible enzyme that suppresses adaptive T-cell immunity by catabolizing the essential amino acid tryptophan from the cellular microenvironment.14,15 It is believed that T lymphocytes’ deprivation of tryptophan and generation of biologically active metabolites along the tryptophan degradation pathway cause T-cell apoptosis and preclude a T-cell response.16 IFN-α itself is supposed to be a weak inducer of IDO in antigen-presenting cells (APCs) but has an indirect effect on these cells through a yet to be defined 15-kDa protein.16–18 This protein is a product of IFN-α-stimulated APCs and lymphocytes and stimulates both IDO and IFN-γ production. IFN-γ, in turn, is one of the most potent IDO inducers in cells of the immune system such as APCs as well as in local bystander cells such as in epithelial cells, lung cells, fibroblasts, and others.19 IDO expression increases when inflammation is induced by wounding, infection, or tumor growth. In

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fection, IDO activity was first described as a mechanism for stopping the growth of microorganisms that otherwise depend on tryptophan.20 Another study pointed to a role for IDO in tumor escape: expression of IDO by immunogenic tumor cells in mice prevented rejection in preimmunized recipients.21 Furthermore, allergic asthma bronchiale in mice could be abrogated when IDO was induced in lung epithelial cells.22 Taken together, these observations in mice demonstrate that IDO can indeed have an immunoregulatory role. In humans, the role of IDO is less clear. IDO can be induced in many human cell types in vitro by stimulation with IFNs, lipopolysaccharide, tumor-necrosis factor-α (TNF-α), Toll-like receptor ligands, or FcεRI.15, 23–26 In human samples, direct evidence for the concomitant presence of inflammation and IDO is scarce. Therefore, the present study was designed to explore IDO expression in human skin. Our data demonstrate that IDO is highly expressed in lesional skin from patients with LP and other type I IFN-mediated diseases. We hypothesize that IDO may provide a counterplayer of the type I IFN-driven inflammation in the skin.

Materials and Methods

Donors

Lesional skin biopsies (n = 31) from different inflammatory skin disorders were analyzed. All skin biopsies included were taken for diagnostic purposes in stages of active skin disease before treatment. Patients suffered from chronic discoid lupus erythematosus (CDLE) (n = 9), LP (n = 5), cutaneous herpes simplex infection (HSV)-infection (n = 5), psoriasis vulgaris (n = 5), and atopic dermatitis (AD) (n = 6). Control biopsies were taken from unaffected skin of patients undergoing surgery for skin tumors (n = 5). Informed consent was obtained from all donors. The study was performed according to local ethical guidelines and approved by the local regulatory committee.

Histology and Immunohistology

Serial sections were prepared from formalin-fixed, paraffin-embedded skin biopsies. Standard hematoxylin and eosi stained sections and periodic acid-Schiff reactions were performed for diagnostic purposes. In situ IFN-α/β production was evaluated by immunostaining for MxA (mAb M143, dilution 1:100; a kind gift from Dr. Haller, University of Freiburg, Freiburg, Germany), an IFN-α/β-inducible antiviral intracellular protein well established as a surrogate marker for local IFN-α/β production, as described before.26,27 Mouse anti-human IDO antibody (IgG1 Ab, 1:150; as described previously26,29 labeling was performed on paraffin-embedded tissue sections (4 μm) after heat pretreatment as described in detail elsewhere.27,30 Appropriate isotype-matched controls were included. Visualization was performed using the LSAB2 staining kit (DAKO, Hamburg, Germany) with fast red as chromogen, for sequential double staining combined with the Envision System (DAKO) with the chromogen diaminobenzidine (brown). Results were evaluated on blinded specimens by two experienced dermatopathologists (J.W. and T.T.) independently. IDO+ cells were counted per three representative high-power fields (HPFs, ×200) in a microscope (BH-2 microscope and DF 70 camera; both from Olympus Europe GmbH, Hamburg, Germany), and the mean IDO+ cells per three HPFs was calculated.

The expression of MxA in the epidermis and in the inflammatory infiltrate was scored semi quantitatively (0 = no expression; + = weak expression; ++ = fair expression; +++ = strong expression) within the same three HPFs used for IDO detection, and the mean lesional MxA expression was calculated.

Immunofluorescence Staining

Immunofluorescence double staining was performed using formalin-fixed, paraffin-embedded sections after heat antigen retrieval following standard protocols. The following primary monoclonal antibodies (mAbs) were used: anti-IDO mAb (AHF833, dilution 1:200; Serotec, Düsseldorf, Germany), anti-CD11c mAb (dilution 1:10; Novocastra, Newcastle, UK), anti-CD68 mAb (dilution 1:40, Novocastra), anti-CD1a mAb (undiluted; Immunotech, Marseille, France), anti-S100 mAb (dilution 1:1200, DAKO), anti-CD123 mAb (dilution 1:50; Becton-Dickinson, San Jose, CA), and anti-CD3 mAb (undiluted; Beckman Coulter, Krefeld, Germany). As secondary Ab we used a fluorescein isothiocyanate (FITC)-conjugated donkey anti-sheep-IgG (dilution 1:100, Serotec) to detect the IDO mAb, and to detect the S100 mAb we used a CY3-conjugated goat anti-rabbit-IgG (dilution 1:50; Zymed, München, Germany). For the other primary Abs, we used a CY3-conjugated goat anti-mouse IgG (1:200, Zymed).

Isolation of Peripheral Blood Monocytes and T Cells

All blood samples were obtained after informed consent from healthy volunteers (n = 5) in accordance with the local ethics committee. Monocytes were isolated from peripheral blood with a density gradient protocol using Nycoprep (Nycomed, Oslo, Norway). Briefly, red blood cells were separated from plasma by sedimentation from ethylenediaminetetraacetic acid blood with one-tenth (w/v) 6% dextran 500 in 0.9% NaCl. Plasma was layered over Nycoprep and centrifuged for 20 minutes at 600 × g. After separation, the interphase and upper part of the Nycoprep were collected and washed three times. Monocyte isolation was confirmed by CD14 expression and was >90%.

T cells were isolated from heparin blood with a density gradient protocol using Lymphoprep (Nycomed). After the blood was diluted 1:1 with phosphate-buffered saline (PBS), suspended cells were overlayed on prior undiluted blood volume of Lymphoprep. Peripheral blood mononuclear cells were isolated as interface cells after density gradient centrifugation (30 minutes at 2000 × g at room temperature). T cells were then purified from peripheral blood mononuclear cells using a nylon wool column.
In Vitro Stimulation of Monocytes and T Cells

Isolated peripheral blood monocytes and T cells (each 1 x 10^6/ml RPMI 1640) were stimulated for 24 hours with 1000 U/ml IFN-α (recombinant interferon alpha-2b, INTRON A; Essex Pharma, Munich, Germany) and 100 U/ml IFN-γ (R&D Systems, Wiesbaden-Nordenstadt, Germany), respectively. Unstimulated controls were included. The cells were washed twice before staining. Stimulations were done with five different donors.

Immunostaining of Peripheral Blood Monocytes and T Cells

Peripheral blood monocytes or T cells from healthy donors (n = 5) were stained by using a 96-well round-bottom plate (10^5 cells/well). Monocytes and T cells were washed three times with PBS and incubated for 15 minutes with 7-amino-actinomycin D to exclude dead cells from analysis. Intracellular staining with anti-IDO Ab was done as follows: after fixation and permeabilization with 4% formaldehyde and saponine buffer, respectively, cells were stained with anti-IDO mAb (2.5 μg/ml) for 20 minutes, followed by FITC-labeled F(ab')2 of goat-anti-mouse Ab (GaM/FITC) from Jackson ImmunoResearch Laboratories (West Grove, PA). After washing with saponine buffer and PBS/BSA/Na-Azid, the extracellular staining for monocytes was performed with anti-CD14 mAb (mouse IgG2b, Becton-Dickinson) and anti-CD11c mAb. T cells were stained with anti-CD3 mAb. Analysis of cells was performed with a FACS Canto cytometer (Becton-Dickinson, Heidelberg, Germany). Monocytes and T cells were gated on forward and sideward scatter.

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)

Total RNA was extracted from monocytes using Trizol (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. Reverse transcription was done with 1 μg of total RNA. The resulting cDNA was amplified by PCR usingIDO sense (5'-CTTCCTGGTCTCTCATTTG-3') and antisense (3'-GAAAGTCTCAGTGGCTG-5') primers. Amplification was performed on a Perkin-Elmer GeneAmp PCR system 9600 thermocycler (Applied Biosystems, Weiterstadt, Germany). β-Actin was used to normalize specific PCR amplifications. The PCR cycle number for the detection of IDO was 26. PCR fragments were separated on 1% agarose gels, visualized using ethidium bromide staining and analyzed by digital image analysis using the WinCam system (Cybertech, Berlin, Germany).

Statistical Analysis

Computer-based statistical analyses were performed using SPSS software (version 12; SPSS, Chicago, IL). The nonparametrical Mann Whitney U-test was used to compare the expression of IDO and MxA in different skin disorder subsets and healthy controls. Correlation analysis was done by Spearman’s ρ. Probabilities <0.05* were considered to be significant, P values <0.01** as highly significant.

Results

IDO Is Strongly Expressed in Lesions of Type I IFN-Mediated Skin Disorders

Earlier studies provided evidence that type I IFNs participate in the pathogenesis of several Th1-based inflammatory skin disorders such as LP, LE, and psoriasis.9,13,31,32 We analyzed the concomitant expression of the highly specific type I IFN marker MxA and the enzyme IDO in adjacent tissue sections from several skin disorders. A strong (+++) MxA expression was found in all donor samples from inflammatory lesions of LP, CDLE, and HSV infection (Figure 1a). Psoriatic skin samples fairly (+) expressed MxA whereas in AD MxA expres-
Expression ranged from very low to weak (+). In healthy control biopsies, MxA expression was nearly absent. MxA expression was seen in the epidermis as well as in the inflammatory dermal infiltrate. Figure 1, b–g, depicts representative findings on MxA expression in the different diseases.

To investigate whether the local production of IFN-α/β is able to induce IDO in the skin, we quantitatively evaluated the number of IDO+ cells in adjacent tissue sections from the various disorders by immunohistochemistry (Figure 2a). Interestingly, the highest numbers of IDO+ cells were seen in LP and HSV skin lesions, followed by tissue from CDLE. In psoriasis, moderate IDO+ cells were seen whereas in AD only few cells expressed IDO. Normal control tissue was virtually negative for IDO. Remarkably, IDO+ cells were exclusively seen within the dermal inflammatory infiltrate and not in the epidermis (Figure 2, b–g). In contrast to human placenta, for example, where endothelial cells do express IDO,33 stromal elements were negative for IDO in all our investigated samples (see enlarged pictures of Figure 2, b–g).

Subsequently, we performed statistical investigations to strengthen our hypothesis of an influence of the type I IFN system on the lesional IDO expression. For this, MxA expression and IDO+ cells of each sample were investigated and correlated to the entire samples independently of the specific diseases (Figure 3). MxA expression was not always in every single specimen but in significantly more specimens was associated with a fair to high IDO expression. The association of the lesional IDO production with the expression of the type I IFN marker MxA was analyzed using computer-based methods to calculate Spearman’s ρ. These analyses revealed a direct, highly significant correlation between the expression of IDO and MxA (ρ = 0.53, P < 0.01) in the investigated specimens, which supports our hypothesis.

Myeloid CD11c+ S100+ CD68− DCs Are the IDO-Expressing Cells in Lesions from LP and Psoriasis

To characterize further the nature of IDO+ cells, we performed double-staining immunofluorescence using the IDO mAb in combination with multiple markers (Figure 4). Staining with a specific Ab to the myeloid marker CD11c revealed that virtually all IDO+ cells were of myeloid origin. In addition, IDO+ cells were also strongly positive for S100, a specific marker for DCs. As expected from these stainings, IDO+ cells were negative for the macrophage marker CD68 and were clearly larger than CD68+ macrophages. Remarkably, epidermal CD1a+ DCs (ie, Langerhans cells) did not express IDO. Unexpectedly, CD123+ pDCs were negative for IDO although present in significant amounts in lesions from LP. Further, the nu-
IDO is expressed by large myeloid CD11c⁺ S100⁺ CD68⁺ DCs. Immunofluorescence double staining for IDO, CD11c, S100, CD68, CD1a, CD123, and CD3 was performed in five skin samples taken from patients with LP (a) and psoriasis (b) (only CD11c/IDO and S100/IDO stainings are shown) to investigate the origin of IDO⁺ cells in the dermis. Photographs of the single stainings for IDO, CD11c, S100, CD68, CD1a, CD123, and CD3 are shown as well as the overlay of IDO (green) with the individual markers (red). Double-positive cells are yellow (arrows).
merous CD3+ T cells were clearly negative for IDO. Here, the presence of large veiled cells just adjacent to the numerous small round T cells can be nicely seen. In summary, large myeloid CD11c+ S100+ CD68+ DCs, and not CD123+ pDCs, are the IDO-expressing cells in LP and psoriasis.

IFN-α and IFN-γ Induce IDO in Peripheral Blood Monocytes but Not in T Cells

To establish further that CD11c+ APCs induce IDO expression in response to type I IFNs, we tested the IDO gene transcription and expression in isolated monocytes. Figure 5a demonstrates that unstimulated CD11c+ monocytes isolated from healthy individuals do not show IDO gene transcription as shown by RT-PCR using IDO-specific primers. In contrast, a strong RT-PCR signal for IDO was detected after treatment of monocytes with IFN-α. To confirm the induction of IDO protein by type I IFNs and also by IFN-γ, we analyzed the intracellular expression of the IDO protein in human APCs after stimulation with IFN-α and IFN-γ in vitro. Monocytes from five different healthy donors were isolated from peripheral blood and stimulated with 1000 U/ml IFN-α or 100 U/ml IFN-γ as described in Materials and Methods. Although unstimulated control monocytes did not show significant IDO protein expression, IFN-α- and IFN-γ-stimulated CD14+ CD11c+ monocytes displayed a significant expression of the intracellular protein IDO (Figure 5b). In contrast, freshly isolated CD3+ T cells did not express IDO after in vitro stimulation with IFN-α and IFN-γ, consistent with our in vivo data.

Discussion

In the present study we provide evidence for a significant expression of the IDO protein in skin disorders associ...
ated with type I IFN. The strongest production of IDO was seen in LP, followed by HSV-infected tissue, and CDLE lesions. In all these diseases, IDO+ cells can be found exclusively in the dermal inflammatory infiltrate and not in the epidermis. This is remarkable because the pathology of AD, psoriasis, or HSV infection also involves the epidermis and epidermal MxA expression is strong. There might be two reasons for this. Recently, our group demonstrated that human keratinocytes do not respond with IDO protein activity on stimulation with IFNs and are thus negative for this protein despite the presence of inflammatory stimuli. In contrast, highly enriched human epidermal LCs were found able to respond with IDO protein activity on stimulation with IFN-γ in vitro. Therefore, it is possible that IFNs, eg, in the course of LP inflammation, act to induce IDO in some APC populations but not in the others, or the level of IFNs reached in the epidermal lesions are too low to induce IDO in LCs.

We further demonstrate that in lesions from LP and psoriasis, large myeloid CD11c+tS100+CD68+ DCs, and not pDCs, are the dermal IDO-expressing cells. Further, our analyses revealed a strong in vitro induction of IDO in CD14+CD11c+ monocytes after stimulation with IFN-α and IFN-γ. These findings suggest a new function of myeloid DCs in autoimmune skin diseases. In addition to their important role for the induction of specific immunity, these DCs seem to have tolerizing properties as a consequence of IDO expression.

Type I IFNs are crucially involved in the recruitment of inflammatory CXCR3+ lymphocytes in LP, probably as a result of IFNxα/β-dependent up-regulation of the chemokine IP10/CXCL10 in the skin. In accordance with this, we have recently demonstrated a large plasma cytoid DCs (pDCs) in LP skin lesions, which are a major source of lesional type I IFN production in LP. We show here that type I and II IFNs are able to induce IDO in CD11c+ APCS in vitro. It is very likely that, also in inflammatory skin from LP, IFN-α from pDCs induces IFN-γ from T cells, both of which promote the function of bystander myeloid DCs to strongly express IDO. Moreover, it has been recently reported, that in mice, IDO itself is required for the production of IFN-α after ligation of B7 molecules on CD19+ DCs. These results suggest a bi-directional feedback loop on IDO induction through IFN-α, which is most likely sustained by IFN-γ.

Recent work has demonstrated a highly complex role for IDO in immunoregulation in infection, pregnancy, autoimmunity, transplantation, allergy, and neoplasia. Because IDO induction represents a ubiquitous and highly conserved inflammatory immune response pattern, the tolerogenic outcome of it may be good or bad for the host, depending on the disease. For example in cancer, IDO expression in APCs or the tumor cells themselves is one possible mechanism by which the immune system might be able to acquire tolerance toward tumor antigens. Moreover, in viral infections including HIV, there is a lot of local and systemic IDO activity. This IDO activity has been suggested to be responsible for cachexia, dementia, diarrhea, and possibly immunosuppression in these patients.

In contrast, apoptosis of potentially autoreactive lymphocytes by IDO-expressing DCs, activated by IFN-α and IFN-γ, might represent a crucial means of maintaining peripheral tolerance during inflammation. These IDO-expressing DCs might thus add to discriminate between self and nonself during active autoimmune disease. It has been suggested, that type I IFNs are key factors when tolerance is lost and autoactivity appears. Although IFN type I is often associated or paralleled with the severity of the autoimmune disease, there are the first examples for the concomitant induction of IDO in these diseases such as in systemic lupus erythematosus. IFN-α was shown to be a necessary upstream inducer of IDO in some mouse pDC subsets after engagement of specific molecules on these cells. These data suggest that, in most conditions involving pDCs, IFN-α will have an obligatory and immediate role in IDO induction. Further, in nonobese diabetic mice, it was found that an impaired tryptophan catabolism is causative to the defective tolerance. Thus, in autoimmune diseases, IDO induction seems to be part of an integrated response for preventing excessive local inflammation and preventing further autoimmune damage. Accordingly, the close association and concomitant expression of IDO and inflammatory stimuli such as type I IFNs that were seen here in lesional skin of LP suggests that IDO expression can be seen as a counterregulatory mechanism directed at dampening the inflammation.

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