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Catecholamines Inhibit the Antigen-Presenting Capability of Epidermal Langerhans Cells

Kristina Seiffert,* Junichi Hosoi,* Hidestu Torii,* Hiroaki Ozawa,* WanHong Ding,* Kristina Campton,* John A. Wagner,† and Richard D. Granstein 2*

The sympathetic nervous system modulates immune function at a number of levels. Within the epidermis, APCs (Langerhans cells (LC)) are frequently anatomically associated with peripheral nerves. Furthermore, some neuropeptides have been shown to regulate LC Ag-presenting function. We explored the expression of adrenergic receptors (AR) in murine LC and assessed their functional role on Ag presentation and modulation of cutaneous immune responses. Both purified LC and the LC-like cell lines XS52-1D and XS106 expressed mRNA for the ARs \( \alpha_{1A} \) and \( \beta_2 \). XS106 cells and purified LC also expressed \( \beta_2 \)-AR mRNA. Treatment of murine epidermal cell preparations with epinephrine (EPI) or norepinephrine inhibited Ag presentation in vitro. Furthermore, pretreatment of epidermal cells with EPI or norepinephrine in vitro suppressed the ability of these cells to present Ag for elicitation of delayed-type hypersensitivity in previously immunized mice. This effect was blocked by use of the \( \beta_2 \)-adrenergic antagonist ICI 118,551 but not by the \( \alpha_2 \)-antagonist phentolamine. Local intradermal injection of EPI inhibited the induction of contact hypersensitivity to epicutaneously administered hapten. Surprisingly, injection of EPI at a distant site also suppressed induction of contact hypersensitivity. Thus, catecholamines may have both local and systemic effects. We conclude that specific ARs are expressed on LC and that signaling through these receptors can decrease epidermal immune reactions.

The sympathetic division of the autonomic nervous system-with the spleen, thymus, and lymph nodes (11, 12), where they terminate near or in direct contact with lymphocytes. The presence of adrenergic receptors (AR) on lymphocytes suggests that sympathetic innervation may be important in the modulation of immune responses (3, 13). Although neuronal influences on lymphocytes have been explored, their effects on professional APCs are already begun to be studied.

The skin is an easily accessible immunocompetent organ in which these regulatory mechanisms can be examined. Within the epidermis, Langerhans cells (LC) are dendritic APCs that play a key role in the cutaneous immune system (14). They reside in the suprabasilar portion of the epidermis and have been shown to be capable of presenting haptens, immunogenic peptides, and tumor Ags for T cell-dependent immune responses (15–18). The observation that epidermal LC often lie in apposition with epidermal nerves and that calcitonin gene-related peptide (CGRP), a neuropeptide found in epidermal nerves, can regulate LC Ag-presenting function provides evidence for a regulatory interaction between the nervous system and the immune system within the skin (19).

The sympathetic division of the autonomic nervous system within the skin is supplied by postganglionic fibers of the paravertebral chain ganglia. Sympathetic fibers travel together with sensory nerve fibers to innervate blood vessels, sweat glands, and hair follicles (20). They also appear as single nerve fibers in the dermis and epidermis (21–23). Because the nerve fibers present in the skin release classical neurotransmitters, we examined whether catecholaminergic neurotransmission affects the immunocompetent cells of the skin. We provide evidence for the presence of distinct ARs on murine LCs and show functional effects of adrenergic agents on Ag presentation.

Materials and Methods

Media and cell lines

Complete medium (CM) consists of RPMI 1640 (Cellgro, Herdon, VA) containing 10% FCS (Life Technologies, Gaithersburg, MD), 100 U/ml penicillin, 100 \( \mu \)g/ml streptomycin, 0.1 mM nonessential amino acids, 0.1 mM essential amino acids, 2 mM L-glutamine, 1 mM sodium pyruvate, and 10 mM Hepes buffer (Life Technologies). CM was used in cell culturing unless stated otherwise.

The keyhole limpet hemocyanin (KLH)-specific, I-A\(^d\)-restricted Th1 clone HDK-1 was kindly provided by A. Takashima, Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX. It was maintained in CM containing 5 \( \times \) 10\(^{-7}\) M 2-ME (Sigma-Aldrich, St. Louis, MO) and 200 U/ml recombinant mouse IL-2 (BD PharMingen, San Diego, CA).

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SI509a is an immunogenic spindle cell tumor cell line induced by methylicholanthrene in an A/J mouse (I-A^b, H-2^d). It was kindly provided by Dr. M. I. Greene (University of Pennsylvania, Philadelphia, PA).

The SI509a cells and the SXXS2-4D subclone of the SXXS2 cell line are LC-like lines derived from neonatal BALB/c epidermis or AJ epidermis, respectively. They were prepared by limiting dilution cloning (24). These cells are dendritic, capable of Ag presentation, and have several phenotypic characteristics of LCs (25, 26). They were a kind gift of A. Takashima. Cytokine assays

IFN-γ production by HDK1 cells was quantified by sandwich ELISA (BD Pharmingen). Purified rat anti-mouse IFN-γ mAb (4 μg/ml) was used as the primary (coating) Ab, with biotinylating rat anti-mouse IFN-γ mAb as the secondary (detection) Ab. Avidin-HRP conjugate was added at a 1/1000 dilution, followed by color development with ABTS substrate solution. The level of colored reaction product was measured spectrophotometrically at 410 nm.

Immunization of mice and elicitation of DTH

Immunity to the SI509a spindle cell carcinoma was induced by s.c. inoculation of 2 × 10^6 SI509a (killed by four freeze-thaw cycles) at weekly intervals into naive syngeneic mice (C57BL/6J) for a total of three immunizations. Delayed-type hypersensitivity (DTH) was elicited 1 wk after the last immunization by injecting a hind footpad with TAA-pulsed eEC incubated with or without adrenergic antagonists. Specifically, 5 × 10^6 CAF1, eEC were incubated at 37°C with 10^6 M EPI or NE for 3 h. In some experiments the β2-blocker ICI 118,551 (30, 31) or the α-blocker phentolamine at 10^-5 M was added as well. Cells were then washed three times with 0.15 M PBS containing 10^-5 M Ca^2+ and 5 × 10^6 cells/ml were pulsed with soluble TAA for 3 h. eEC were washed four times in PBS to remove catecholamines, unbound TAA, and medium, before injection of 7.5 × 10^5 cells in 50 μl PBS into the right hind footpad of each of five CAF1 mice. Control mice received injections of eEC not pulsed with TAA or pulsed with TAA but not treated with EPI or NE. Footpad swelling was assessed at 24 and 48 h with a spring-loaded engineer's micrometer (Mitutoyo, Tokyo, Japan) and compared with the noninjected foot.

PCR analysis

Total RNA was extracted from >98% purified LC as well as the cell lines XS106 and SXXS2-4D using a total RNA extraction kit as per the manufacturer's instructions (RNeasy total RNA Mini kit; Qiagen, Santa Clarita, CA) including an additional DNA degradation step (RNeasy-free DNA set; Qiagen). RT-PCR was performed for catecholamine receptors using a RT-PCR kit (Gene-Ampl RNA PCR kit; PerkinElmer, Norwalk, CT). Briefly, 0.1 μg of RNA was incubated in a reaction mixture containing 5 nM KCl, 10 mM Tris-HCl, 1 mM dNTPs, 2.5 μM oligo(dT), 1/μl RNase inhibitor, and 2.5 U Moloney murine leukemia virus reverse transcriptase per micro liter in 10 μl at room temperature for extension of the primers, for 15 min at 42°C for annealing, and then for 5 min at 90°C to denature the enzyme. Ten microliters of the reverse-transcribed reaction were transferred to a PCR mixture containing primers (Life Technologies) designed using sequences in GenBank. The reaction mixture consisted of 50 nM KCl, 10 nM Tris-HCl, 2 mM MgCl2, 5 μM primers, and 1 U AmpliTaq DNA Polymerase in a total volume of 50 μl.

Presentation of KLH to a responsive T cell clone (HDK1)

EC or pLC were prepared from BALB/c (I-A^b) mice as described above, plated out in 96-well plates at a concentration of 1 × 10^5 cells/well in CM, and exposed to increasing concentrations of EPI or NE (100 pm, 1 nM, 10 nM, or 100 nM) or the inactive (+) or the active (−) isomer of ISO (100 nM) for 3 h at 37°C. After 3 h, KLH (Sigma-Aldrich) was added to a final concentration of 100 μg/ml. After 18 h, cells were gamma irradiated (3000 rads) and washed three times. Soluble TAA was added to 25 μg/ml in 0.15 M PBS into the right hind footpad of each of 10 mice. Control mice received injections of eEC not pulsed with TAA or pulsed with TAA but not treated with EPI or NE. Footpad swelling was assessed at 24 and 48 h with a spring-loaded engineer's micrometer (Mitutoyo, Tokyo, Japan) and compared with the noninjected foot.

In vivo EPI injection, immunization to hapten, and challenge to eliciting C57BL/6J mice received an intradermal injection of 100 μl PBS containing 1 μg EPI on the lower back as described before (32). Successful immunizations were characterized by the appearance of a flattened swelling with defined
lateral margins immediately beneath the epidermis (33). Control animals were injected with PBS. Fifteen minutes later mice were sensitized by application of 5 μl 1% 2,4-dinitrofluorobenzene (DNFB; Sigma-Aldrich) in acetone/oil (4:1) to the injected area with care to avoid spread to the adjacent skin. Control animals were painted with acetone/oil (4:1) alone. Seven days later baseline ear thickness was measured using a spring-loaded micrometer (Mitutoyo) and all mice were challenged by applying 0.2% DNFB in acetone/oil to each side of each ear. Ear thickness was measured after 24 and 48 h. Specific ear swelling was calculated by subtracting the ear thickness before challenge from the 24- and 48-h values for each mouse.

Additional experiments were performed to examine whether the EPI effect was local or systemic. In these experiments 100 μl of PBS containing 1 μg EPI were administered intradermally to the lower right back 15 min before sensitization with DNFB at a distant site (upper left back). Elicitation of contact hypersensitivity (CHS) was performed as described above.

### Data generation and statistical analysis

Statistical differences among groups were determined using Excel software (Microsoft, Redmond, WA) and tested by the two-tailed Student t test for independent samples. Mean values were considered to be significantly different when p ≤ 0.05.

### Results

**AR mRNA is expressed in pLC and LC-like cell lines**

A major impediment to performing receptor studies in LCs lies in the fact that these cells comprise only ~2% of the total EC population. Significant efforts must be taken to obtain highly purified populations. However, such techniques result in isolation of relatively few cells, making it difficult to examine protein expression or to perform Northern analysis. Thus, the more sensitive method, RT-PCR, was used to examine AR expression in these experiments. Epidermal LCs were enriched to >98% by enzymatic digestion and separation with A-I-A^{4}-targeted magnetic beads. This purified LC population expressed mRNA for the ARs β_{1}, β_{2}, and α_{1A} (Fig. 1). The PCR products were of the expected size, and sequence specificity of expressed bands was confirmed by restriction enzyme cleavage at the expected sites (data not shown). The mRNAs for β_{3}, α_{1B}, α_{1D}, and α_{2} were not detected in the purified LCs. Due to the fact that 98% pure LC may still be contaminated by other EC types (predominantly keratinocytes), we also investigated AR expression in the LC-like clones XS52-4D and XS106. The use of these cells avoids the problems of possible contaminating cells. We were able to confirm the expression of β_{1}, β_{2}, and α_{1A}AR in XS106 cells as well as the expression of β_{2} and α_{1A}AR in XS52-4D cells (Fig. 1B). Because β_{1}-AR was expressed by XS106, but not by XS52-4D cells, it is possible that β_{1}-AR is expressed by a subpopulation of LCs. To test whether functional ARs were produced and to test the consequences of engaging these receptors with their ligands, we examined the effect of adrenergic agents on Ag presentation both in vivo and in vitro.

**EPI and NE inhibit Ag presentation by murine EC and LC**

We examined the ability of both EPI and NE to affect KLH-specific EC Ag presentation to the T cell clone HDK1 in vitro. HDK1 cells respond to presentation of KLH by I-A^{d}-targeted accessory cells by secretion of IFN-γ. EPI significantly reduced the ability of ECs to stimulate IFN-γ production in HDK1 cells in a dose-dependent manner (Fig. 2A). In two separate experiments, (+)-ISO, the structurally similar inactive isomer of the β-adrenergic agonist (-)-ISO, had no effect on the magnitude of T cell IFN-γ production in response to presentation of KLH, while the active isomer decreased it significantly, supporting the specificity of the effect (Fig. 2B). Additionally, treatment with EPI (100 nM) did not affect the viability of ECs or LCs as determined by trypan blue exclusion or FACS analysis after propidium iodide stain (data not shown).

![FIGURE 1. Murine LC express mRNA for ARs. Murine LCs were enriched to >98% purity and poly(A)^{+} RNA was extracted. Poly(A)^{+} RNA was also extracted from the LC-like cell lines XS106 and XS52-4D and from murine brain tissue, as a positive control. RT-PCR was performed using primers designed from sequences in GenBank (see Materials and Methods). Purified LC expressed mRNA of the expected size for the ARs β_{1} (441 bp), β_{2} (600 bp), and α_{1A} (119 bp). The LC-like cell line XS106 expressed mRNA for β_{1}, β_{2}, and α_{1A}AR as well. XS52-4D expressed mRNA for β_{2} and α_{1A}AR, but not for β_{1}-AR. Expression of mRNA for β_{2}-AR (B), α_{1A}AR (C), and α_{1D}AR (D) was not found in LCs or the LC-like cell lines. Receptor expression was verified with three separate RNA isolations.](http://www.jimmunol.org/content/161/9/6130/F1)

Ag-dependent T cell activation depends mostly on the function of certain APCs, but other cells may also elaborate factors that either directly affect the lymphocyte or act indirectly on APCs. Indeed, injury- or irritant-activated keratinocytes have the ability...
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their ability to present KLH to HDK1 cells was signi-
cantly re-
(H-2d ) mice using enzymatic digestion and magnetic separ-
ation failed to effectively present Ag (data not shown). Thus, LCs express functional ARs and agonist binding to these receptors inhibits Ag presentation.

EPI and NE inhibit T cell cytokine production in response to Ag presentation. Murine ECs were preincubated with EPI, NE (A), or ISO (B) at concentrations from 10^{-9} to 10^{-7} M and later pulsed with KLH. Upon coculture with HDK1 cells, Th1 cytokine production in response to KLH presentation by epidermal LC was assessed and compared with puls-
ing with KLH alone. Seventy-two-hour IFN-γ production in conditioned supernatants was measured by ELISA (mean ± SEM; *, p < 0.05 for EC plus KLH vs EPI 10^{-9} M and iso (active isomers) 10^{-7} M; **, p < 0.01 for EC plus KLH vs EPI 10^{-8} M, NE 10^{-8} M, and NE 10^{-7} M). A representative experiment from six individual experiments, including two with additional NE treatments, is shown.

FIGURE 2. EPI and NE inhibit T cell cytokine production in response to Ag presentation. Murine ECs were preincubated with EPI, NE (A), or ISO (B) at concentrations from 10^{-9} to 10^{-7} M and later pulsed with KLH. Upon coculture with HDK1 cells, Th1 cytokine production in response to KLH presentation by epidermal LC was assessed and compared with puls-
ing with KLH alone. Seventy-two-hour IFN-γ production in conditioned supernatants was measured by ELISA (mean ± SEM; *, p < 0.05 for EC plus KLH vs EPI 10^{-9} M and iso (active isomers) 10^{-7} M; **, p < 0.01 for EC plus KLH vs EPI 10^{-8} M, NE 10^{-8} M, and NE 10^{-7} M). A representative experiment from six individual experiments, including two with additional NE treatments, is shown.

TAA in vitro, were used to elicit a DTH response in vivo in tumor-immune mice (35). Subsequently, mice were immunized by s.c. injection of S1509a tumor fragments. Mice treated in this fashion have been shown to be immune to subsequent tumor challenge (36). These mice were challenged 7 days after the third immuniza-

FIGURE 3. EPI directly inhibits Ag presentation by purified LCs. LCs were enriched to >98% purity by enzymatic digestion and magnetic separ-

Intradermal injection of EPI inhibits the induction of CHS to epicutaneously administered hapten

Next, we tested the ability of EPI to modify the sensitization phase of immune reactions in vivo by studying CHS, a prototype of T cell-mediated immunity. This reaction is characterized by inflammation and edema at the site of challenge and there is a positive correlation between the intensity of the immune reaction and the increase in pinna thickness (as reviewed by Dhabhar and McEwen in Ref. 37). CAF1 mice that were injected intradermally with EPI before application of the contact sensitizer DNFB at the injected site showed a reduced response upon DNFB challenge 7 days later (Fig. 5A) compared with mice that were injected with vehicle only. Rapid exit from the site of injection or degradation of cat-

In additional experiments, we tested the specificity of the cate-

EPI and NE suppress eEC presentation of TAA for elicitation of DTH

To define the effects of EPI on Ag presentation in the elicitation phase of an immune response, a mixed in vitro/in vivo system was used. First, eEC, exposed to EPI or NE and pulsed with soluble
(--)-ISO was administered at 1 µg per mouse no effect was seen. Three experiments were performed at a dose of 10 µg per mouse. Significant inhibition was induced in one experiment. In a second experiment, inhibition was observed but did not reach statistical significance, while the third experiment failed to show inhibition. No inhibition was seen with the inactive isomer at 1 and 10 mg per mouse. We conclude that (--)-ISO probably has an effect on the induction of CHS but is less potent than EPI.

Because there are functional ARs on LCs, EPI and NE can be expected to act locally, but these agents may also have a systemic effect. To determine whether EPI acts only locally or also systemically, we determined the effect of administering EPI at a distant site. Mice received intradermal injections of EPI on the lower right back. Control animals received injections of PBS at the same site. Fifteen minutes later mice were sensitized with DNFB on the upper left back. Administration of EPI at a distant site inhibited CHS equivalently to local administration (Fig. 5B). Thus, catecholamines may act both locally and systemically to affect Ag presentation in the sensitization phase of CHS.

Discussion

The present study demonstrates that epidermal LC express ARs and that these receptors are functional in Ag presentation, and, thus, most probably are involved in regulating cutaneous immune functions such as DTH and CHS.

To date AR are subdivided into nine types termed β1, β2, β3, α1A, α1B, α1D, α2A, α2B, and α2C (38). In human and murine skin, β2-AR seems to be the most abundant adrenoceptor (23, 39, 40), although α-ARs are present as well (41, 42). Among the AR-expressing cell populations within the skin are keratinocytes, melanocytes, fibroblasts, and mast cells (43–45). Specifically, human keratinocytes as well as the nontumorogenic keratinocyte cell line HaCat have been shown to express β2-AR and β1-AR by autoradiographic mapping and radioligand binding experiments (46,
47), and β-agonists (predominantly β2) and α1-agonists stimulate adenylate cyclase activity and cAMP production in vitro (48). We have examined in this work the expression of ARs by LC and we have also investigated the LC-like clones XS52-4D and XS106 to confirm our results in a system without the possibility of contamination by other cells. We found mRNA for the ARs β2-AR and α1A-AR to be expressed not only on murine LCs but also in LC cell lines. Expression by XS52-4D and XS106 cells verifies the finding with fresh LC and makes it very unlikely that the results with LC are due to contamination with another cell type. Because increasing concentrations of catecholamines directly reduce the Ag-presenting capability of murine ECs in vitro in comparable inhibitory potencies, LCs also express functional ARs. The inhibitory concentrations in our assay correspond to levels catecholamines can reach locally, in the immediate vicinity of a synapse or close to a sympathetic varicosity during stressful events (50–500 nM) (49, 50). Physiologically, however, EPI and NE could be derived from other sources. Epidermal keratinocytes and melanocytes are capable of producing catecholamines (51) and EPI of adrenomedullary origin may reach skin cells as a hormone. Thus, the true physiological roles of ARs on LC and their function in states of sympathetic arousal remain to be elucidated.

Our work indicates that catecholamines affect both phases of the immune response, sensitization, and elicitation, in which APC such as LC play a crucial role (52). Repression of Ag presentation in a β2-AR-mediated way provides a mechanism that may contribute to the effects of stress on cutaneous immune functions such as DTH and CHS. Indeed, it has been shown that immobilization stress in mice inhibits elicitation of DTH when the adrenal axis is intact (53). Likewise, CHS reactions in mice have been reported to be suppressed by psychological and social stress induced by immobilization and overcrowding, respectively (54, 55). Interestingly, in regard to CHS, a recent study by Flint et al. (56) demonstrated that acute restraint before sensitization diminished CHS, whereas restraint administered before challenge enhanced CHS.

While demonstrating that intradermal EPI injections reduce the sensitization phase of CHS, we cannot exclude the possibility that local vasoconstriction, undoubtedly induced by EPI, contributes to the immune reduction, perhaps by interfering with immune cell trafficking. If vasoconstriction alone is sufficient to impair the development of CHS, this effect should be seen with other vasoconstricting substances as well. However, preliminary experiments provide evidence that intradermal injection of PYY does not reduce CHS reactions in the same model (data not shown) despite being an equipotent vasoconstrictor in certain organs (57–59). Thus, it seems unlikely that vasoconstriction alone explains the observed effect.

In addition to our findings that injection of EPI at the site of hapten sensitization inhibits CHS reactions, it is able to do so even when injected a considerable distance away. This effect may be either systemic or due to diffusion into the surrounding tissues. Indeed, it has been shown that noradrenergic varicosities can release their catecholamines at considerable distances from the effector tissues (12), permitting them to diffuse through the surrounding region more easily than neuropeptides and, thus, to reach even remote targets (20). This might explain why other neuropeptides such as substance P and CGRP promote CHS induction only by a local effect (60, 61), although CGRP, when used in similar assays, has been shown to result in comparable degrees of inhibition (19, 61). Nevertheless, it is also possible that the catecholamines are taken up systemically and affect immune cell trafficking and other related functions. Indeed, in a recent study, Maestroni (62) found NE to be both a chemoattractant and a chemokinetic factor for immature DC and showed that immature DC participate in cell mobilization and migration to regional lymph nodes in an α1B-AR-mediated fashion. The reasons why ISO was less potent than EPI in inhibiting CHS are speculative. However, ISO is a pure β-agonist, and our findings do not rule out the possibility that additional α-mediated effects of EPI in vivo may also play a role here. Additional markers of LC maturation in relation to migration, such as their chemokine receptor profile, need to be investigated in future studies. For example, only activated, not resting, LCs express CCR7. Through this receptor, their migration is directed toward stromal cells in T cell zones of lymph nodes and lymphatic endothelial cells in peripheral tissues, such as the dermis, that express the CCR7 ligand secondary lymphoid tissue chemokine (63).

Interactions between the different arms of the immune system must be taken into consideration when examining the in vivo effects of stress on immune function. The varying results of studies examining the effect of stress on immunity in general emphasize the complexity of immune reactions. CHS in particular has been described to be either suppressed (54–56) or enhanced (56, 64) by psychological and social stress in mice. Differences in these studies regarding how long and in which phase of the immune reaction the animals were stressed emphasize the importance of timing and duration of stress. In evaluating these in vivo observations, one has to consider that stress activates several systems, accompanied by a release of glucocorticoids, catecholamines, endogenous opioids, and other pituitary hormones with effects on all kinds of immune cells. In an elaborate feedback system glucocorticoids regulate catecholamine biosynthesis in the adrenal medulla and catecholamines stimulate adrenocorticotropin release from the anterior pituitary. Additionally, signals from the periphery are sent back to the brain where they coordinate behavioral and physiological responses to infection and inflammation (65). Compensatory changes appear with prolonged stress (66), partly due to a feedback regulation of activated immunologic cells themselves (67, 68). Considering these tightly regulated feedback processes that ultimately determine the direction of an immune response, it seems worthwhile to elucidate isolated effects of neurotransmitters on specific immune cell function, as done in the present study. Although the (patho-) physiological roles of EPI and NE are not completely understood, we can infer that catecholamines are a regulatory element in the cutaneous stress response. We provide a cellular mechanism by showing that EPI and NE isolated directly inhibit LC Ag-presenting function.

As to the exact mechanisms mediating the immune-inhibitory effects, it remains possible that catecholamines affect expression of class II and costimulatory molecules on APC (69), the efficiency of Ag processing and presentation, as well as changes in cytokine production and response to cytokines. For example, in studies by Hosoi et al. (54) and Kawaguchi et al. (55), LCs are found to be the stress-affected cell population, with significant decreases in Ia expression as well as a marked alteration in LC morphology (decreased number of dendrites and cell size). In fact, preliminary data from our group provide evidence that prolonged exposure of LC to EPI in vitro down-regulates I-A expression, at least in combination with down-regulation induced by anti-I-A Abs. Furthermore, catecholamines down-regulate proinflammatory cytokines such as TNF-α and elevate anti-inflammatory cytokines such as IL-10 via a β-adrenergic receptor-dependent pathway in immune cells (50, 70–72). Interestingly, preliminary data from our group (73) indicate that EPI and NE up-regulate IL-1β and down-regulate TNF-α expression in the LC-like cell line XSS2. Both cytokines are implemented in E-cadherin expression in fetal murine LC-like dendritic cells and dissociation of fetal murine LC-like dendritic cell aggregates (74). There is considerable evidence that immature
LCs are retained in their epidermal environment by E-cadherin-mediated adhesion to keratinocytes (75). These findings might indicate an involvement of stress hormones in cell adhesion.

Thus, abnormal adrenergic regulation of the immune response at the level of LCs may contribute to skin disorders such as atopic dermatitis (which is associated with anxiety where circulating catecholamines are elevated) or psoriasis (which is known to be exacerbated upon treatment with β-adrenergic antagonists).

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References


