

Role of vasculature in atopic dermatitis

Martin Steinhoff, MD, PhD,^{a,b,c} Antje Steinhoff, PhD,^a Bernhard Homey, MD,^d Thomas A. Luger, MD,^{a,c} and Stefan W. Schneider, MD^a Münster and Düsseldorf, Germany

Atopic dermatitis (AD) lesions are characterized by differences in the activation state of endothelial cells and vascular smooth muscle cells and the release of inflammatory mediators by and toward the vasculature. The vascular system, including endothelial cells and smooth muscle cells, is ultimately involved in clinical symptoms of AD, such as erythema, edema, leukocyte recruitment, and white dermographism. Various mediators and bidirectional neurovascular interactions regulate the inflammatory response during AD. T cell–endothelial cell interactions are a crucial component to establish acute AD. Various immune cells, including monocytes and mast cells, communicate with the endothelium by releasing inflammatory mediators, thereby stimulating inflammatory mediator release from activated endothelial cells. The process of adhesion, tethering, and transmigration of infiltrating cells is a highly regulated and an active communication process between endothelial cells and leukocytes. Endothelial cells play a pivotal role in the pathophysiology of AD and represent future targets for the treatment of AD. (*J Allergy Clin Immunol* 2006;118:190-7.)

Key words: Atopy, inflammation, endothelium, leukocyte, therapy

NEUROVASCULAR INTERACTIONS IN ATOPIC DERMATITIS

The skin of patients with atopic dermatitis (AD) is characterized by atypical vasoconstrictive responses to trigger factors, such as mechanical (white dermographism) or chemical (eg, acetylcholine) stimuli. These patients show a pronounced vasoconstriction after exposure to

Abbreviations used

AD:	Atopic dermatitis
CAM:	Cell adhesion molecule
CLA:	Cutaneous lymphocyte antigen
ICAM:	Intercellular adhesion molecule
NO:	Nitric oxide
PAR ₂ :	Proteinase-activated receptor 2
PG:	Prostaglandin
sPLA[2]-IIF:	Soluble phospholipase A-IIF
VCAM:	Vascular cell adhesion molecule

cold and a lower temperature of the body appendices. The underlying pathophysiologic mechanisms of these phenomena are still poorly understood. The role of the β -adrenergic receptor system in the pathophysiology of vascular events during AD is still controversial.¹

In AD the T_H1-T_H2 paradigm has been central to interpreting quantitative differences in cytokine expression in response to environmental stimuli or stress.^{2,3} In addition, other mechanisms (eg, oxidative stress pathways, glucocorticoid resistance, nerve–mast cell interactions, and intestinal dysbiosis) and a broader range of mediators (eg, chemokines, amines, oxidative products, proteases, and neuropeptides) produced by cells communicating with the dermal vasculature might be involved, delineating the true complexity of the mechanisms linking stress to AD (Fig 1).^{4,5} Thus the vascular endothelium comprises a central place for the regulation of acute and chronic inflammatory responses during AD.

The dermal vasculature is highly innervated. Neuropeptide-positive nerve fibers are prominently increased in lesions of AD⁴ and modulate itching, as well as inflammation (eg, by stimulating mediator release from mast cells [IL-4, TNF- α , histamine, and tryptase]). Neurotrophins, such as nerve growth factor or brain-derived neurotrophic factor, adapt the function of mast cells and eosinophils as effector cells in AD.^{6,7} Therefore a dysregulated interaction between the skin vasculature and sensory nerves links pathogenic events during AD (Table I).

In addition to their neurotrophic effects, neurotrophins can be also regarded as inflammatory cytokines. In particular, they exert a networking effect on neurons, skin structural cells (keratinocytes and fibroblasts), and invading immune cells, which simultaneously operate as a source, as well as a target, for neurotrophins during inflammation. Neurotrophins have also been proved to exert angiogenic and microvascular remodeling activity during

From ^athe Department of Dermatology, ^bIZKF Münster, and ^cthe Ludwig Boltzmann Institute for Cell Biology and Immunobiology of the Skin, University Hospital Münster, and ^dthe Department of Dermatology, Heinrich Heine University, Düsseldorf.

Supported by grants from the Deutsche Forschungsgemeinschaft (STE 1014/2-1), IZKF Münster (STE2/076/06), and SFB 293 (A14) (to M.S.). Also supported by “Innovative Medizinische Forschung” IMF Münster and grant support from SFB 492 TPA13 (to S.W.S.).

Disclosure of potential conflict of interest: B. Homey has received grant support from the German Research Foundation and the German Cancer Foundation. The rest of the authors have declared that they have no conflict of interest.

Received for publication March 16, 2006; revised April 16, 2006; accepted for publication April 18, 2006.

Available online June 8, 2006.

Reprint requests: Martin Steinhoff, MD, PhD, Department of Dermatology, University of Münster, Von-Esmarch-Str. 58, D-48149 Münster, Germany. E-mail: martin_steinhoff@web.de.

0091-6749/\$32.00

© 2006 American Academy of Allergy, Asthma and Immunology
doi:10.1016/j.jaci.2006.04.025

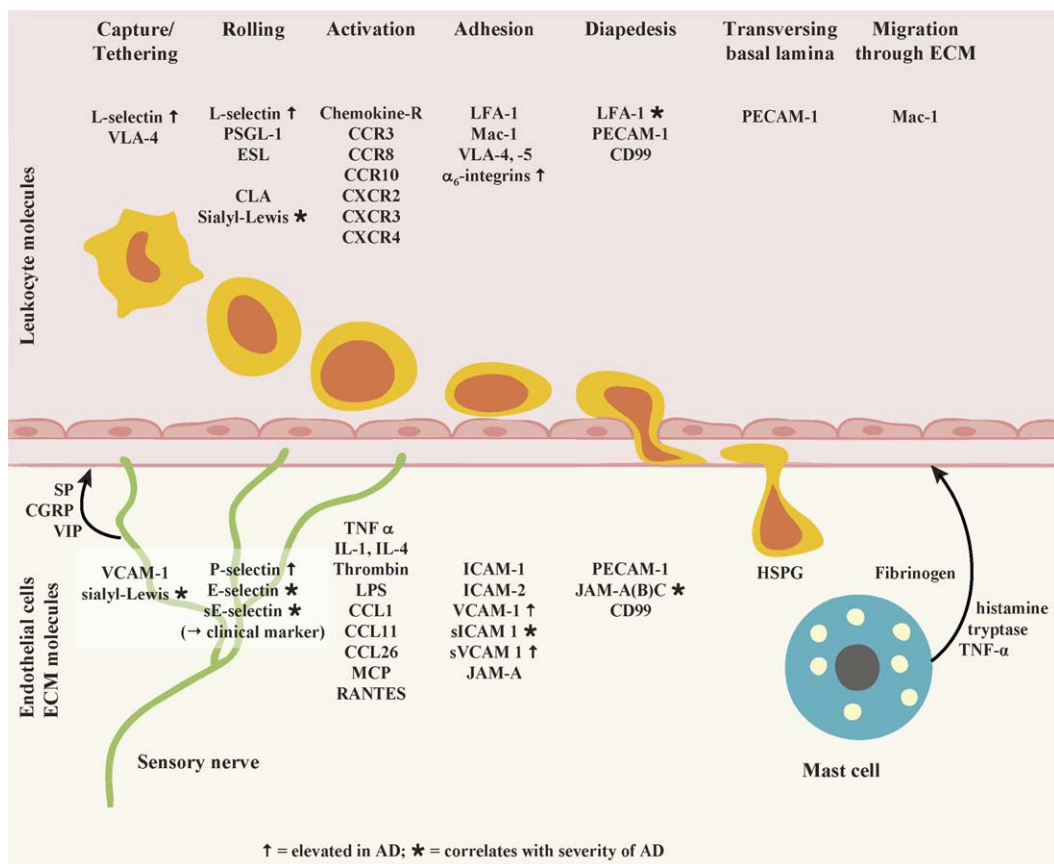


FIG 1. Sequential steps of leukocyte extravasation and the various tethering and adhesion molecules, chemokines, and receptors involved. *ESL*, E-selectin ligand; *HSPG*, heparan sulfate proteoglycan; *LFA*, leukocyte function-associated antigen; *CCR2*, *CCL2/MCP-1/3* receptor; *CCR5*, *CCL1/-5/RANTES* receptor; *CXCR3*, *CXCL9/10/11* receptor; *CXCR4*, *SDF-1/CXCL12* receptor; *PECAM-1*, platelet/endothelial cell-adhesion molecule 1; *JAM*, junctional adhesion molecules; *PSGL*, P-selectin glycoprotein ligand; *s-Le-X*, sialyl-Lewis-X carbohydrate antigen; *VLA*, very late antigen (modified from Steinhoff et al⁴ and Radeke et al⁵).

allergic airway inflammation.⁸ Thus an innovative future perspective in research could be to investigate the angiogenic effects of neurotrophins in AD.

Furthermore, patients with AD have exaggerated vasodilator responses to emotional stress, with consequent pruritus and scratching. Of note, during vasodilatation, the threshold for itching is decreased, its duration is prolonged, and the frequency of nighttime scratching movements is dramatically enhanced, suggesting an interaction of nerves and vasculature in the pathophysiology of AD.

THE ROLE OF VASCULAR ENDOTHELIUM DURING AD

Cell adhesion between the endothelium and inflammatory cells is an important early step during AD (Fig 1).

ADHESION MOLECULES

Several observations are in favor of an important role of selectins and cell adhesion molecules (CAMs) in AD

(Table II). For example, soluble E-selectin and soluble intercellular adhesion molecule (ICAM) 1 levels are enhanced in children with AD. Moreover, the levels of soluble E-selectin were significantly increased in patients with severe AD over those seen in patients with mild AD. A positive correlation with individual clinical activity was also found for changes in soluble E-selectin and soluble vascular cell adhesion molecule (VCAM) 1 levels. Soluble E-selectin levels were correlated with serum IgE levels and the number of eosinophils. Soluble VCAM-1 levels correlated with the number of monocytes. The expression of VCAM-1 was significantly enhanced in patients with erythrodermic AD compared with those with nonerythrodermic AD lesions.⁹ An increased expression of L-selectin can be detected in the CD4⁺ T cells of patients with AD. In this context TNF-α and IL-4 seem to be pivotal for endothelial-lymphocyte interactions.

INTEGRINS

Leukocyte extravasation depends on the expression and activation of a subset of integrins (Fig 1). For example,

TABLE I. Mediators in AD

Family of mediators	Mediator	Receptor	Effects
Cytokines	IL-1	IL-1R	ICAM-1 ↑; E-selectin ↑ ≥microvascularization, endothelial cells
	IL-4	IL-4R	IL-4 ⁺ mast cells correlate with allergic wheal reaction
	IL-6	IL-6R, which is activated in autocrine manner	Induces CCL17 and CCL22
	IL-8	CXCR2 on EC surface	General early proinflammatory mediator and not restricted to AD
	IL-13	IL-13R	Activation of neutrophils
	IL-17	IL-17R	Anti-inflammatory effects by decreasing inflammatory cytokines in endothelial cells
	IL-31	IL-31RA and OSMR	Induces CCL17 and CCL22
	TNF-α	TNF-α R	Induces IL-1 secretion and upregulation of CAMs
Chemokines	CCL11	CCR 3 on EC surface	CLA ⁺ T cells from patients with AD are able to produce higher levels of IL-31 in comparison with skin of patients with psoriasis and healthy skin
	CCL13	CCR3 on EC surface	General endogenous pyrogen or cachectin
	CCL17	CCR4	Causes NF-κB activation as a transcription factor ≥ involvement in inflammation and regulation of CAMs
	CCL18		Strong inducer of endothelial cell activation
	CCL21	CCR7	Accumulation of eosinophils
	CCL22	CCR4	Attracts monocytes, lymphocytes, basophils and eosinophils but not neutrophils
	CCL27	CCR10 on EC surface	Recruitment of memory T cells to sites of skin inflammation
PGs and leukotrienes	PGE ₁ , PGE ₂	PGE-R PGE ₂ -R	Cooperation of CCL21 and CCL17: mediation of leukocyte arrest and diapedesis; lymphocytes get to site of inflammation during AD
	sPLA(2)-IIF		Induced by IL-4 and IL-13
	Leukotriene E ₄	Leukotriene receptor	Attracts lymphocytes
Nitric oxide	NO		Expressed by activated endothelial cells ≥ T-cell migration
			Closely related to the T _H 2 cytokine response
Histamines	Histamine	H1R	Induced by IL-4 and IL-13
			See CCL17
Proteases	Trypsin	PAR ₂	Attracts and plays a role in mediating homing of lymphocytes
			Vasodilatation

OSMR, Oncostatin M receptor; NF-κB, nuclear factor κB; EC, endothelial cell; H1R, histamine 1 receptor; CGRP, calcitonin gene-related peptide.

TABLE II. Cell adhesion molecules in AD

CAM		Tissue distribution	Ligand	Effects
Selectins	L-selectin	Leukocytes	Sialyl-Lewis of CD34 and GlyCAM-1 on venules	Shed from CD4 ⁺ T cells of patients with AD
	P-selectin	Alpha-granules of platelets and stored in endothelial cells (Weibel-Palade bodies)	PSGL-1, Sialyl-Lewis on leukocytes	Attaching leukocytes to endothelium T _H 1 cell extravasation Recruitment of eosinophils Increased expression of P-selectin in AD triggered by TNF- α and IFN- γ
	E-selectin	Activated endothelial cells	Sialyl-Lewis on leukocytes; ESL-1 on myeloid cells	Adherence of leukocytes is enhanced Binding to CLA T _H 1 cell extravasation E-selectin in AD triggered by TNF- α and IFN- γ
	Soluble E-selectin	Serum	Sialyl-Lewis on leukocytes	Correlates with disease activity
Integrins	VLA-4 ($\alpha_4\beta_1$ -integrin)	Leukocyte membrane	VCAM-1	Attachment of leukocytes to high endothelial venules
	VLA-5 ($\alpha_5\beta_1$ -integrin)	Monocytes, macrophages	Fibronectin	
	LFA-1 ($\alpha_L\beta_2$ -integrin)	Monocytes, T-cells, macrophages, dendritic cells, neutrophils	ICAMs on endothelial cells	Enhanced in AD
	Mac-1 ($\alpha_M\beta_2$ -integrin)	Monocytes, macrophages, neutrophils	Only ICAM-1	
Ig superfamily	ICAM-1	Expressed on keratinocytes and fibroblasts after stimulation of TNF- α or IFN- γ	LFA-1, Mac-1	Contributes to leukocyte adhesion
	Soluble ICAM-1	Increased serum levels in AD, psoriasis, metastatic melanoma		Increased levels in AD
	ICAM-2	Endothelium (constitutively)	LFA-1	Constitutively expressed
	ICAM-3	Monocytes; lymphocytes; Langerhans cells	LFA-1 (CD11a/CD18)	
	Soluble ICAM-3	Increased levels in AD and psoriasis		
	VCAM-1	Activated endothelium	VLA-4	Extravascular migration of monocytes and eosinophils
	Soluble VCAM			Positive correlation between clinical stadium of AD and soluble E-selectin and soluble VCAM levels; also correlated with number of monocytes
	PECAM-1 (CD31)	Platelets, intercellular junctions of endothelium	CD31	Leukocyte passage from blood vessels

TABLE II. (continued)

CAM	Tissue distribution	Ligand	Effects
CLA	Expressed on T-effector cells		Binding to E-selectin Selective role of CLA in homing T cells to the cutaneous tissues and playing a role in skin inflammatory reaction CLA ⁺ T cells from patients with AD are able to produce higher levels of IL-31 in comparison with skin of patients with psoriasis and healthy skin

GlyCAM-1, Glycosylation-dependent cell adhesion molecule 1; *PSGL-1*, P-selectin glycoprotein ligand 1; *ESL-1*, E-selection ligand 1; *VLA*, very late antigen; *LFA-1*, leukocyte function-associated antigen 1; *PECAM-1*, platelet/endothelial cell-adhesion molecule 1.

tight adhesion of the leukocytes depends on CD11a-CD18 integrin binding to endothelial junctional adhesion molecule A. Recently, it was reported that members of the junctional adhesion molecule family, which localize to endothelial junctions, are also involved in transmigration.¹⁰

In general, the importance of integrins regulating leukocyte-endothelial interactions is well established. However, only few publications exist focusing on integrin expression in atopic skin. α_6 Integrin is highly expressed on endothelial cells in lesional and nonlesional skin in patients with AD.¹¹ Anti- β_2 integrin antibodies effectively suppressed eosinophil accumulation in both mediator-induced and allergic inflammation of guinea pig skin, and anti- α_4 antibodies attenuated eosinophilic cell recruitment in allergic skin. However, antibodies did not directly affect eosinophils, suggesting the participation of other cells involved in mediating the above-mentioned effect.¹²

SELECTINS

Selectins are a family of 3 c-type lectins. P-Selectin (CD62P) is intracellularly stored in platelets and endothelial cells (Fig 1). The main ligand for P-selectin is P-selectin glycoprotein ligand 1 expressed on myeloid, lymphoid, and dendritic cells.¹³ The other P-selectin ligand is CD24, which can mediate cell rolling on inflamed endothelium independent of P-selectin glycoprotein ligand 1. E-selectin (CD62E) is synthesized and expressed solely by endothelium. Expression is regulated by TNF- α , IL-1, IL-6, LPS, thrombin, and substance P, for example. E-selectin expression is detectable on the dermal endothelium of all inflammatory dermatoses.¹⁴

Both selectins were found to be expressed in the skin of patients with AD but, interestingly, not in the skin of nonatopic individuals. E- and P-selectin were highly expressed in the lesional skin of patients with AD and less pronounced in the nonlesional skin of patients with AD. However, there were no differences in the expression between the 2 different types of erythrodermia.⁹ It is

proposed that cytokines, such as TNF- α and IFN- γ , are responsible for the increased expression of selectins. Selectins facilitate T-cell (T_H1 but not T_H2) extravasation in the lesional but also in the nonlesional skin of patients with AD,¹⁵ thus explaining the presence of increased T cells in the nonlesional skin of patients with AD. Both selectins are highly expressed in lesional skin to facilitate the T-cell extravasation.¹⁶ Despite the homing receptor for T cells, cutaneous lymphocyte antigen (CLA), as a ligand for E-selectin, fucosyltransferase might be a prominent homing factor for eosinophils. Thus P-selectin might be an important mediator of eosinophil recruitment in AD.

Selectins can also be used as a marker for disease activity. The plasma concentration of soluble E-selectin in children significantly correlated with disease activity,¹⁷ whereas soluble P-selectin, soluble ICAM-1, and soluble VCAM-1 levels were unchanged. Soluble E-selectin appears to be the best serologic marker to determine disease activity in AD thus far.¹⁸ Plasma concentration of soluble E-selectin is a reliable marker of disease activity on treatment with cyclosporin A.

Recent findings indicate an important role of CLA, a counterreceptor of E-selectin, in the pathophysiology of AD. CLA is a glycoprotein leading to the homing of T cells specifically to the skin. The skin specificity of E-selectin/CLA binding makes this an attractive target for biologic therapy of inflammatory skin disease. Whether soluble E-selectin has any direct pathogenic role in AD or is merely a reflection of skin inflammation is still under debate.¹⁹

The last member of the selectin family is L-selectin. L-selectin is expressed on almost all leukocytes and involved in their rolling on inflamed vascular endothelium before firm adhesion and transmigration. CD62L expression on murine CD4⁺ T-cell subsets revealed that surface expression was maintained on T_H1 cells but not on T_H2 cells.²⁰ Therefore its role in the pathogenesis of AD needs to be elucidated.

Although selectins were originally investigated as adhesion molecules, there is now considerable interest in their role as signaling molecules.

TABLE III. Frontiers in vascular research in AD

Frontier	Possible therapeutic consequence	Selected reference
JAM-B and JAM-C contribute to leukocyte extravasation in murine skin	JAM-B and JAM-C as potential targets for cutaneous inflammation, including AD	Ludwig et al ³⁰
Histamine H4 receptor expressed on mast cells and leukocytes	Anti-H4 receptor treatment in AD	De Esch et al ³¹
IL-31	IL-31 involved in neurovascular modulation?	Sonkoly et al ³²
Chemokines	Small-molecule antagonists as potential therapy	Homey ³³
Integrins	Integrin inhibition as potential therapy for AD	Jung et al ¹⁰ and Teixeira et al ¹¹
Soluble E-selectin as marker for disease activity	Small-molecule antagonists as potential therapy for AD	Wolkerstorfer et al ¹⁶
E-selectin/CLA binding	Blocking of one or the other binding site to avoid homing of lymphocytes, especially to the skin	Wolkerstorfer et al ¹⁶
T _H 1-T _H 2 balance	SOCS suppressors of cytokine signaling proteins \geq lower number of T _H 2 cells	Kubo and Inoue ³⁴
	Immunosteroids produced by immunoregulatory cells	Matsuzaki et al ³⁵
PAR ₂	PAR ₂ inhibitors suppress vascular responses during AD	Steinhoff et al ^{23,36}
Neuropeptides	Antagonists for neuropeptides (SP, CGRP, PACAP) regulating neurogenic inflammation	Steinhoff et al ⁴

JAM, Junctional adhesion molecule; SOCS, suppressor of cytokine signaling; SP, substance P; CGRP, calcitonin gene-related peptide; PACAP, pituitary adenylate cyclase-activating polypeptide.

IG SUPERFAMILY

CAMs were first described as ligands or counter-receptors for integrins. They constitute 1 or more Ig-like domains and are characterized by fibronectin-repeat sequences. CAMs activate leukocytes, thereby increasing the avidity of binding to other leukocytes and endothelial cells to facilitate leukocyte migration (Fig 1). They also modulate activated fibroblasts and keratinocytes to enhance the capability of leukocyte recruitment to the site of inflammation.

ICAM-1 is rarely expressed by normal endothelium but is dramatically increased after stimulation by inflammatory mediators. ICAM-2, constitutively present on endothelium, is not increased by inflammatory stimuli. ICAM-3 is constitutively expressed by resting monocytes, lymphocytes, and Langerhans cells. It binds to leukocyte function-associated antigen 1 (CD11a/CD18). ICAM-1 contributes to leukocyte adhesion through leukocyte function-associated antigen 1 and Mac-1 β_2 -integrins. VCAM-1 expression is increased after cytokine stimulation and binds the $\alpha_4\beta_1$ -integrin, thereby mediating extravascular migration. Platelet/endothelial cell-adhesion molecule 1/CD31 is found in platelets and endothelium, where it contributes to leukocyte passage from blood vessels.

ICAMs and VCAM can be cleaved and released into tissue fluids in a soluble form. Soluble ICAM-1 is released by blood mononuclear cells but not by epithelial cells, fibroblasts, or the endothelium. Soluble ICAM-1 might be increased 2- or 3-fold in inflammation.²¹ Soluble ICAM-1 levels are increased in the serum of several dermatologic

diseases, including AD, psoriasis, and metastatic melanoma,²² and correlates with clinical severity. Soluble ICAM-2 does not exist. Soluble ICAM-3 is increased in the serum of patients with AD and psoriasis but is less relevant to disease activity than soluble ICAM-1. The role of soluble VCAM in AD is unknown, but expression of VCAM-1 was shown to be enhanced in patients with erythrodermic AD compared with AD lesions.⁹

MEDIATORS REGULATING ENDOTHELIAL CELL FUNCTION DURING AD

Histamine

Histamine is an important mediator of vascular function, causing vasodilation, increased vascular permeability, smooth muscle contraction, and sensory nerve stimulation through the histamine 1 receptor, thereby contributing to erythema, edema, and pruritus. Although an important role of histamines in allergic rhinoconjunctivitis and urticaria is well established, the effect of histamine and the histamine 1 receptor in patients with AD remains controversial because nonsedative antihistamines are not very effective in AD, and the concentrations of histamine are unchanged compared with those seen in control subjects.²³

Tryptase and proteinase-activated receptor 2

Mast cell tryptase mediates vasodilatation, edema, plasma extravasation, and mediator release from endothelial cells and smooth muscle cells²⁴ and cleaves the vasodilator calcitonin gene-related peptide. Tryptase

antagonists are beneficial for the treatment of asthma and atopic disease. The receptor proteinase-activated receptor 2 (PAR₂) is activated by tryptase on dermal endothelium, thereby stimulating ICAM-1 and E-selectin upregulation or activating nuclear factor κ B. The concentration of tryptase and the expression of PAR₂ is increased in the lesional skin of patients with AD, suggesting a role of tryptase and PAR₂ in vascular regulation during AD.²³

Cytokines and ILs

Thus far, 32 ILs have been defined, some of which contribute to vascular regulation. Cytokines can exert either proinflammatory or anti-inflammatory responses on microvascular endothelial cells, and various cytokines work synergistically during AD (Fig 1). IL-1 contributes to the activation of dermal microvascular endothelial cells through upregulation of ICAM-1 or E-selectin. IL-4⁺ mast cells are highly associated with the extent of immediate allergic wheal reaction in the skin. IL-6 is both generated by endothelial cells and can act on these cells through activation of the IL-6 receptor. As a general early proinflammatory mediator, IL-6 is not restricted to AD. Another cytokine, IL-13, acts as an anti-inflammatory agent by decreasing the production of inflammatory cytokines in endothelial cells. IL-17 induces IL-1 secretion and upregulation of CAMs, such as ICAM-1, from dermal endothelial cells.

TNF- α is a strong inducer of endothelial cell activation, resulting in nuclear factor κ B activation and regulation of CAMs. However, RNA and plasma levels of TNF- α , sTNF-R55, and sTNF-R75 were not different between atopic and nonatopic children.²⁵

Chemokines

During this multistep process, chemokines mediate the firm adhesion of receptor-bearing rolling leukocytes to the endothelium and initiate transendothelial migration (Fig 1). In peripheral tissues matrix-bound sustained chemokine gradients direct leukocytes to distinct anatomic locations. In this issue a review by Homey²⁶ provides an overview on the role of chemokines in the immunopathogenesis of AD.

Chemokines contribute to the bidirectional cross-talk between endothelial cells and leukocytes. In AD lesions dermal endothelial cells produce a variety of chemokines, which are secreted and presented at the luminal surface of the endothelium through glucosaminoglycan binding. Furthermore, endothelial cells are able to take up chemokines produced by keratinocytes, fibroblasts, and leukocytes within the vessel microenvironment through transcytosis and present them at the luminal side to circulating leukocytes. Endothelial cells not only express chemokine ligands but bear chemokine receptors on their cell surface (CCR3, CCR8, CCR10, CXCR2, CXCR3, and CXCR4). Chemokines can mediate angiogenic, as well as angiostatic, responses. In AD CCL1, CCL11, and CCL26 within lesional skin can interact with CCR8⁺ and CCR3⁺ endothelial cells to induce angiogenesis and tissue remodeling.

Prostaglandins

A body of evidence suggests that prostaglandins (PGs) are involved in vascular regulation, cutaneous inflammation, and pruritus of patients with AD. In AD enhanced local vasodilatation after intradermal injection of PGE₁, but not PGE₂, was observed. Accordingly, even at the highest concentrations of PGE₂, increased superficial blood flow but no protein extravasation was observed. Thus PGE₂ might be a histamine-supporting agent in AD. No significant differences in serum concentrations of PGE₁ were found in patients with AD compared with concentrations found in control subjects. Soluble phospholipase A-IIF (sPLA[2]-IIF) is expressed by capillary endothelial cells. Interestingly, IL-1 stimulated expression of COX-2 and microsomal PGE synthase induced by sPLA(2)-IIF, suggesting that sPLA(2)-IIF is a potent regulator of the arachidonic pathway and might participate in cutaneous inflammation.²⁷

REACTIVE OXYGEN SPECIES AND NITRIC OXIDE

Nitric oxide (NO) is a potent vasodilator regulating vascular tone and modulating vasodilator responses of other inflammatory mediators. NO plays a pivotal role in the regulation of inflammation, immunomodulation, and oxidative damage to cells and tissues. Endothelial NO synthesis is believed to be the main source of NO, although it can be also released from nerves and leukocytes. In AD lesions inducible nitric oxide synthase was closely associated with the upper dermal microvasculature of inflammatory, but not noninflammatory, lesions.²⁸ However, because of difficulties of direct NO measurement in the skin, the function of NO in AD is still poorly understood. Increased nitrate levels were found in infants with AD, stimulating vasodilation, edema, and probably expansion of T_H1 cells.²⁹ In contrast, others could not find a significant difference of nitrite-nitrate concentrations in patients with AD versus control subjects.

The correlation of oxidative stress and altered antioxidant defenses was studied in children with AD. Interestingly, urinary concentrations of certain oxidative stress markers (8-hydroxy-2'-deoxyguanosine, acrolein-lysine adducts, and bilirubin oxidative metabolites) were significantly higher in children with AD compared with those seen in control subjects. Thus oxidative stress and altered antioxidant defenses might be involved in the pathophysiology of AD. Finally, formation of reactive nitrogen species in eosinophils and an imbalance of NO metabolism seem to be involved in the pathophysiology of AD-like skin lesions in NC/Nga mice.

SUMMARY AND CONCLUSIONS

AD is associated with vascular responses, such as erythema, edema, leukocyte recruitment, and a paradox

vasoconstriction on cutaneous stimulation. The future challenge with regard to AD treatments will be to understand the molecular basis of these responses derived from the apparent inability to adequately regulate inflammatory stimuli. Further analysis of endothelial cell activation resulting in the release of a series of preformed and rapidly synthesized substances mediating the immediate onset of vasodilatation, vascular leakage, smooth muscle contraction, and nerve stimulation might result in novel tools for the treatment of early events during AD. Moreover, the effect of endothelial cell-derived mediators and receptors that interact with and activate T lymphocytes and other leukocytes in AD is only poorly understood. Thus the interaction of the cutaneous vascular system with the immune system remains a complex cascade and an exiting stage for future research (Table III).^{4,11,12,17,24,30-36}

We thank Brigit Schneider for the excellent drawing of Figure 1.

REFERENCES

- Schallreuter KU, Pittelkow MR, Swanson NN, Beazley WD, Komer C, Ehrke C, et al. Altered catecholamine synthesis and degradation in the epidermis of patients with atopic eczema. *Arch Dermatol Res* 1997;289:663-6.
- Boguniewicz M, Leung DY. 10. Atopic dermatitis. *J Allergy Clin Immunol* 2006;117(suppl):S475-80.
- Wright RJ. Stress and atopic disorders. *J Allergy Clin Immunol* 2005; 116:1301-6.
- Steinhoff M, Stander S, Seeliger S, Ansel JC, Schmelz M, Luger T. Modern aspects of cutaneous neurogenic inflammation. *Arch Dermatol* 2003;139:1479-88.
- Radeke HH, Ludwig RJ, Boehncke WH. Experimental approaches to lymphocyte migration in dermatology in vitro and in vivo. *Exp Dermatol* 2005;14:641-66.
- Raap U, Goltz C, Deneka N, Bruder M, Renz H, Kapp A, et al. Brain-derived neurotrophic factor is increased in atopic dermatitis and modulates eosinophil functions compared with that seen in nonatopic subjects. *J Allergy Clin Immunol* 2005;115:1268-75.
- Raap U, Kapp A. Neuroimmunological findings in allergic skin diseases. *Curr Opin Allergy Clin Immunol* 2005;5:419-24.
- Nockher WA, Renz H. Neurotrophins in allergic diseases: from neuronal growth factors to intercellular signaling molecules. *J Allergy Clin Immunol* 2006;117:583-9.
- Sigurdsson V, de Vries IJ, Toonstra J, Bihari IC, Thepen T, Bruijnzeel-Koomen CA, et al. Expression of VCAM-1, ICAM-1, E-selectin, and P-selectin on endothelium in situ in patients with erythroderma, mycosis fungoides and atopic dermatitis. *J Cutan Pathol* 2000;27:436-40.
- Liang TW, Chiu HH, Gurney A, Sidle A, Tumas DB, Schow P, et al. Vascular endothelial-junctional adhesion molecule (VE-JAM)/JAM 2 interacts with T, NK, and dendritic cells through JAM 3. *J Immunol* 2002;168:1618-26.
- Jung K, Imhof BA, Linse R, Wollina U, Neumann C. Adhesion molecules in atopic dermatitis: upregulation of alpha6 integrin expression in spontaneous lesional skin as well as in atopen, antigen and irritative induced patch test reactions. *Int Arch Allergy Immunol* 1997;113: 495-504.
- Teixeira MM, Robinson MK, Shock A, Hellewell PG. alpha(4) integrin-dependent eosinophil recruitment in allergic but not non-allergic inflammation. *Br J Pharmacol* 2001;132:596-604.
- Laszik Z, Jansen PJ, Cummings RD, Tedder TF, McEver RP, Moore KL. P-selectin glycoprotein ligand-1 is broadly expressed in cells of myeloid, lymphoid, and dendritic lineage and in some nonhematopoietic cells. *Blood* 1996;88:3010-21.
- Groves RW, Ross E, Barker JN, Ross JS, Camp RD, MacDonald DM. Effect of in vivo interleukin-1 on adhesion molecule expression in normal human skin. *J Invest Dermatol* 1992;98:384-7.
- Astrup F, Vestweber D, Borges E, Lohning M, Brauer R, Herz U, et al. P- and E-selectin mediate recruitment of T-helper-1 but not T-helper-2 cells into inflamed tissues. *Nature* 1997;385:81-3.
- Satoh T, Kaneko M, Wu MH, Yokozeki H, Nishioka K. Contribution of selectin ligands to eosinophil recruitment into the skin of patients with atopic dermatitis. *Eur J Immunol* 2002;32:1274-81.
- Wolkerstorfer A, Laan MP, Savelkoul HF, Neijens HJ, Mulder PG, Oudesluys-Murphy AM, et al. Soluble E-selectin, other markers of inflammation and disease severity in children with atopic dermatitis. *Br J Dermatol* 1998;138:431-5.
- Gutgesell C, Heise S, Seubert A, Stichtenoth DO, Frolich JC, Neumann C. Comparison of different activity parameters in atopic dermatitis: correlation with clinical scores. *Br J Dermatol* 2002;147:914-9.
- Biedermann T, Schwarzler C, Lametschwandner G, Thoma G, Carbalido-Perrig N, Kund J, et al. Targeting CLA/E-selectin interactions prevents CCR4-mediated recruitment of human Th2 memory cells to human skin in vivo. *Eur J Immunol* 2002;32:3171-80.
- Savage ND, Harris SH, Rossi AG, De Silva B, Howie SE, Layton GT, et al. Inhibition of TCR-mediated shedding of L-selectin (CD62L) on human and mouse CD4+ T cells by metalloproteinase inhibition: analysis of the regulation of Th1/Th2 function. *Eur J Immunol* 2002;32:2905-14.
- Gearing AJ, Newman W. Circulating adhesion molecules in disease. *Immunol Today* 1993;14:506-12.
- Hirai S, Kageshita T, Kimura T, Tsujisaki M, Okajima K, Imai K, et al. Soluble intercellular adhesion molecule-1 and soluble E-selectin levels in patients with atopic dermatitis. *Br J Dermatol* 1996;134:657-61.
- Steinhoff M, Neisius U, Ikoma A, Fartasch M, Heyer G, Skov PS, et al. Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci* 2003;23:6176-80.
- Steinhoff M, Buddenkotte J, Shpacovitch V, Rattenholl A, Moormann C, Vergnolle N, et al. Proteinase-activated receptors: transducers of proteinase-mediated signaling in inflammation and immune response. *Endocr Rev* 2005;26:1-43.
- Laan MP, Koning H, Baert MR, Oranje AP, Buurman WA, Savelkoul HF, et al. Levels of soluble intercellular adhesion molecule-1, soluble E-selectin, tumor necrosis factor-alpha, and soluble tumor necrosis factor receptor p55 and p75 in atopic children. *Allergy* 1998;53:51-8.
- Honey B, Steinhoff M, Ruzicka T, Leung DYM. Cytokines and chemokines orchestrate atopic skin inflammation. *J Allergy Clin Immunol* 2006;118:178-89.
- Murakami M, Yoshihara K, Shimbara S, Lambeau G, Gelb MH, Singer AG, et al. Cellular arachidonate-releasing function and inflammation-associated expression of group IIF secretory phospholipase A2. *J Biol Chem* 2002;277:19145-55.
- Rowe A, Farrell AM, Bunker CB. Constitutive endothelial and inducible nitric oxide synthase in inflammatory dermatoses. *Br J Dermatol* 1997; 136:18-23.
- Taniuchi S, Kojima T, Hara Mt K, Yamamoto A, Sasai M, Takahashi H, et al. Increased serum nitrate levels in infants with atopic dermatitis. *Allergy* 2001;56:693-5.
- Ludwig RJ, Zollner TM, Santoso S, Hardt K, Gille J, Baatz H, et al. Junctional adhesion molecules (JAM)-B and -C contribute to leukocyte extravasation to the skin and mediate cutaneous inflammation. *J Invest Dermatol* 2005;125:969-76.
- de Esch IJ, Thurmond RL, Jongejan A, Leurs R. The histamine H4 receptor as a new therapeutic target for inflammation. *Trends Pharmacol Sci* 2005;26:462-9.
- Sonkoly E, Muller A, Lauerman AI, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006;117:411-7.
- Honey B. Chemokines and inflammatory skin diseases. *Adv Dermatol* 2005;21:251-77.
- Kubo M, Inoue H. Suppressor of cytokine signaling 3 (SOCS3) in Th2 cells evokes Th2 cytokines, IgE, and eosinophilia. *Curr Allergy Asthma Rep* 2006;6:32-9.
- Matsuzaki J, Tsuji T, Imazeki I, Ikeda H, Nishimura T. Immunosteroid as a regulator for Th1/Th2 balance: its possible role in autoimmune diseases. *Autoimmunity* 2005;38:369-75.
- Steinhoff M, Vergnolle N, Young SH, Tognetto M, Amadesi S, Ennes HS, et al. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000;6:151-8.