103:1243–52

Anderson ME, Siahaan TJ (2003) Targeting ICAM-1/LFA-1 interaction for controlling autoimmune diseases: designing peptide and small molecule inhibitors. *Peptides* 24:487–501

Bearden CM, Agarwal A, Book BK, Vieira CA, Sidner RA, Ochs HD *et al.* (2005) Rituximab inhibits the in vivo primary and secondary antibody response to a neoantigen, bacteriophage phiX174. *Am J Transplant* 5:50–7

Cavazzana-Calvo M, Sarnacki S, Haddad E, De Coene C, Calise D, Yvon E *et al.* (1995) Prevention of bone marrow and cardiac graft rejection in an H-2 haplotype disparate mouse combination by an anti-LFA-1 antibody. *Transplantation* 59:1576–82

Dengler TJ, Strnad N, Buhring I, Zimmermann R, Girgsdies O, Kubler WE *et al.* (1998) Differential immune response to influenza and pneumococcal vaccination in immunosuppressed patients after heart transplantation. *Transplantation* 66:1340–7

Gottlieb AB, Casale TB, Frankel E, Goffe B, Lowe N, Ochs HD *et al.* (2003) CD4+ T-cell-directed antibody responses are maintained in patients with psoriasis receiving alefacept: results of a randomized study. *J Am Acad Dermatol* 49:816–25

Kipnis CD, Myers WA, Opeola M, Gottlieb AB (2005) Biologic treatments for psoriasis. *J Am Acad Dermatol* 52:671–82

Krueger JG, Ochs HD, Patel P, Gilkerson E, Guttman-Yassky E, Dummer W (2008) Effect of therapeutic integrin (CD11a) blockade with efalizumab on immune responses to model antigens in humans: results of a randomized, single-blind study. *J Invest Dermatol* 128:2615–24

Langley RG, Carey WP, Rafal ES, Tyring SK, Caro I, Wang X *et al.* (2005) Incidence of infection during efalizumab therapy for psoriasis: analysis of the clinical trial experience. *Clin Ther* 27:1317–28

Strober BE, Clarke S (2004) Etanercept for the treatment of psoriasis: combination therapy with other modalities. *J Drugs Dermatol* 3:270–2

Vinuesa CG, de Lucas C, Cook MC (2001) Clinical implications of the specialised B cell response to polysaccharide encapsulated pathogens. *Postgrad Med J* 77:562–9

See related article on pg 2625

A Role for Th17 Cells in the Immunopathogenesis of Atopic Dermatitis?

Antonella Di Cesare[1,2], Paola Di Meglio[1], and Frank O. Nestle[1]

Atopic dermatitis (AD) is a common inflammatory skin disease. Both epidermal barrier dysfunction and immunodysregulation are suggested to influence the pathogenesis of AD. AD has been considered a paradigmatic T helper cell (Th) 2–mediated disease, with a switch to a Th1 cell environment during the chronic phase of the disease. Previously unreported findings now suggest a possible role for Th17 cells as well.

Journal of Investigative Dermatology (2008), **128**, 2569–2571. doi:10.1038/jid.2008.283

Atopic dermatitis (AD) is a common, chronic relapsing, inflammatory skin disease often associated with other systemic atopic disorders such as asthma, food allergy, and allergic rhinitis. The pathogenesis of AD has been attributed to a complex interaction among the environment and host susceptibility genes, altered skin barrier function, and the immune system (Bieber, 2008). Typically, AD has been considered the paradigm of an allergic T helper (Th) 2–mediated disease, characterized by abnormal IgE production, peripheral eosinophilia, mast cell activation, and induction of Th2 lymphocytes expressing IL-4, IL-10, and IL-13 but not IFN-γ (Wierenga *et al.*, 1991). However, observations on the clinical evolution of the cutaneous lesions from an acute phase (characterized by erythematous papules, intense itching, excoriation, and serous exudation) to a chronic phase (with lichenification) led to the development of models to study the progression of the disease. Sequential biopsies in AD patients after exposure to aeroallergens demonstrated a biphasic immunologic response characterized by antigen presentation, Th2 activation, IgE release, eosinophil recruitment, and a switch toward a Th1 phenotype in later phases of the disease (Grewe *et al.*, 1995). Eosinophils, together with infiltrating dendritic cells, are thought to be responsible for the Th2-to-Th1 switch.

> IL-17 and Th17 cells may have roles in AD.

Recently, the Th1/Th2 paradigm in autoimmunity and allergy has been revisited, including a role for a new population of IL-17–producing Th cells (Th17) (Weaver *et al.*, 2007). Transforming growth factor (TGF)-β, IL-1β, IL-6, and IL-23 seem to be key factors involved in naive Th-cell commitment to a Th17 phenotype, distinguishing Th17 cells from Th1 and Th2 populations. Moreover, Th17 cells are characterized by the production of inflammatory cytokines such as IL-17A, IL-17F, IL-22, and IL-26. Th17 cells have been implicated in several human autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and psoriasis, as well as in the clearance of extracellular pathogens (e.g., *Candida albicans*, *Borrelia burgdoferi*, *Mycobacterium tuberculosis*, and *Streptococcus pneumoniae*) (Tesmer *et al.*, 2008).

The role of Th17 cells in allergy is still largely unresolved. Increased levels of IL-17A have been reported in the peripheral blood, sputum, and airways of asthmatic patients and have been correlated with the degree of bronchial hyperreactivity (Tesmer *et al.*, 2008). IL-17A,

[1]*St. John's Institute of Dermatology, King's College London School of Medicine and NIHR Biomedical Research Centre, London, United Kingdom; and* [2]*Department of Dermatology, University of L'Aquila L'Aquila, Italy*

Correspondence: Professor Frank O. Nestle, St John's Institute of Dermatology, King's College London School of Medicine, Floor 9, Tower Wing, Guy's Hospital, London SE1 9RT, United Kingdom. E-mail: frank.nestle@kcl.ac.uk

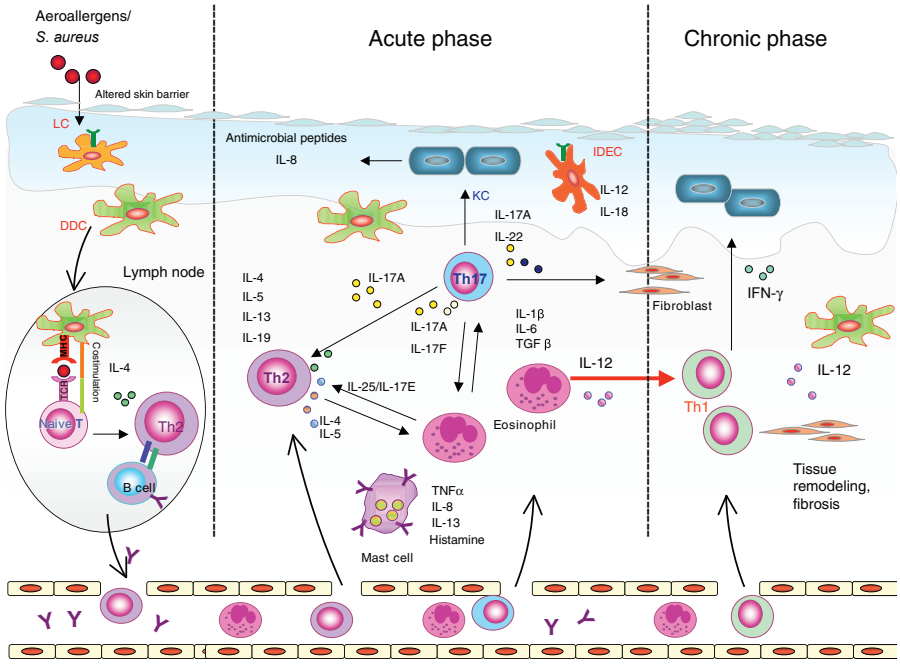

Figure 1. Model of sequential T helper cell involvement in AD. After the first contact with an antigen (e.g., aeroallergen or *Staphylococcus aureus*) during the elicitation phase, cutaneous professional antigen presenting cells migrate to regional lymph nodes, where they present processed peptides to naive T cells. In the presence of IL-4, naive T lymphocytes differentiate toward a Th2 phenotype and induce class switching of B lymphocytes to IgE production. Circulating IgE binds to high-affinity IgE receptors on tissue resident mast cells. A second exposure to the antigen causes cell reactivation, mast cell degranulation, and release of inflammatory molecules such as histamine, IL-8, and IL-13. This cytokine milieu causes an influx of Th2 lymphocytes and eosinophils into the skin, resulting in the production of Th2 cytokines (e.g., IL-4, IL-5, and IL-13), which in turn stimulate eosinophils to release IL-25, enhancing the Th2 environment. During the acute phase, eosinophils (producing IL-6, IL-1β, and transforming growth factor-β (TGF-β)) may support Th17 differentiation. Th17 cells may be recruited to the skin, where they interact with Th2 cells (potentially causing IL-19 release), keratinocytes (epidermal hyperplasia and release of antimicrobial peptides), and fibroblasts (tissue remodeling and fibrosis). IL-12 secreted by eosinophils, dermal dendritic cells (DDCs), and inflammatory epidermal dendritic cells (IDEC) drives the shift toward the chronic phase of AD, which is predominantly characterized by a Th1 phenotype. KC, keratinocyte; LC, Langerhans cell; MHC, major histocompatibility complex.

together with IL-22, could be responsible for the acute inflammatory tissue remodeling promoting neutrophilic infiltration in the asthmatic airways through fibroblasts and epithelial cells, release of chemoattractants such as IL-8, and bronchoconstriction due to stimulation of airway smooth muscle cells (Galli *et al.*, 2008; Molet *et al.*, 2001). IL-17A is also able to induce IL-19 expression in airway epithelia synergistically with IL-4 and IL-13, enhancing a possible Th2 response (Huang *et al.*, 2008). Epicutaneous immunization in mice with ovalbumin can cause allergic skin inflammation resembling AD, cutaneous expression of IL-17A and IL-17F mRNA, and, subsequently, airway inflammation (He *et al.*, 2007). Another member of the IL-17 family, IL-17E, also denoted IL-25, has been implicated in Th2-mediated inflammatory responses, and IL-25 and IL-25R transcripts have been found to be elevated in AD lesions and in asthmatic lungs (Wang *et al.*, 2007).

In this issue, Koga *et al.* (2008) demonstrate the presence of Th17 cells and IL-17 in AD patients, suggesting participation by this newly recognized Th lineage in the development of the disease. Phenotypic analysis of peripheral blood mononuclear cells derived from AD patients demonstrated a marked increase in the IL-17$^+$CD4$^+$ T-cell population compared with healthy controls. The highest percentage of IL-17–producing cells was found in severe AD, suggesting a direct correlation between the presence of Th17 cells and severity of the disease. The mean percentage of IL-17–producing cells in psoriasis was slightly higher than that in severe AD, but the difference was not statistically significant. Increased levels of IL-17 were also reported in cutaneous lesions of AD patients; localization of IL-17–producing cells was greater in the upper papillary dermis, but they were also found in the epidermis. Of note, IL-17 expression was much more evident in acute than in chronic lesions, confirming findings previously reported by Toda *et al.* (2003). Koga *et al.* (2008) also investigated the effect of IL-17 and IL-22 on normal human keratinocytes *in vitro,* demonstrating a synergistic effect of the two cytokines in the induction of GM-CSF, IL-8, CXCL10, and tumor necrosis factor-α. In addition, IL-17 was also able to modulate vascular endothelial growth factor (VEGF) production.

How can we integrate the findings of Koga *et al.* (2008) into our current view of the pathogenesis of AD (see Figure 1)? The model of sequential activation of Th cells during the development of AD suggests the presence of an initial acute phase dominated by professional antigen-presenting cells encountering and processing antigens (e.g., aeroallergen, *Staphylococcus aureus*) and presenting peptides to naive T cells, which in turn differentiate into Th2 cells, induce a B-cell-class switch to IgE, and migrate to the skin. IL-4 and IL-5 released by Th2 cells recruit eosinophils to inflamed skin sites, which in turn produce IL-1β, IL-6, and IL-17E, the last being able to expand the numbers of Th2 cells and enhance Th2 cytokine production (Wang *et al.*, 2007). IL-1β and IL-6, together with TGF-β, which has been found to be increased in cutaneous lesions of AD (Toda *et al.*, 2003), could drive Th17 polarization. Cheung *et al.* (2008) demonstrated that IL-17A and IL-17F can promote eosinophil production of CXCL1, IL-8, and CCL4, as well as IL-1β and IL-6, indicating that there is possible cross-talk between Th17 cells and eosinophils in AD. Finally, eosinophils could contribute to the shift toward the late phase of AD by producing IL-12, which results in the Th2-to-Th1 switch.

A possible role for IL-17 in cutaneous remodeling in AD may be mediated by its ability to stimulate epithelial cells and fibroblasts to secrete proinflammatory

cytokines such as IL-8, IL-6, and IL-11 (Molet *et al.*, 2001). These IL-17 activities could promote tissue fibrosis, chronicity of the inflammatory process, and the evolution of chronic inflammatory cutaneous lesions. However, Koga *et al.* (2008) demonstrated lower levels of IL-17 during the chronic phase of AD, suggesting a possible Th17-to-Th1 shift in later phases of the disease. Their findings suggest a link between innate and acquired immunity in allergy, highlighting the relevance of balanced and reciprocal interaction among Th1, Th2, and Th17 cells in inflammation. Further studies are needed to clarify the role of Th17 cells in the pathogenesis of AD, especially identification of the stage of the disease in which Th17 might play a role.

It will also be interesting to determine why, despite the presence of Th17 cells, there are no prominent neutrophilic infiltrates and no efficient protection against extracellular pathogens such as *Staphylococcus aureus* in AD. Th17 cells have been proposed to lead to neutrophil infiltration as a result of the production of IL-22 and IL-17A and the induction of IL-8 and antimicrobial peptides in epithelial cells. This cascade may have pathological relevance both in asthma and in psoriasis. Psoriasis and late-phase AD share many pathologic features, such as epithelial hyperplasia, abnormal differentiation of keratinocytes, and prominent T-lymphocyte and dendritic cell infiltration. Nevertheless, they have always been considered contrasting poles of immunopathologies because of the dichotomy of Th cells (Th2 versus Th1) and the presence of different subsets of leukocytes (eosinophils versus neutrophils) and dendritic cells. The presence of Th17 cells, in addition to Th1 cells, in AD provides a basis for a common effector pathway in AD and psoriasis, and this could partially explain some of their clinicopathologic similarities. Ultimately, this suggests that these inflammatory skin disorders might have common therapeutic targets.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENT

A.D.C. and P.D.M. contributed equally to this work.

REFERENCES

Bieber T (2008) Atopic dermatitis. *N Engl J Med* 358:1483–94

Cheung PF, Wong CK, Lam CW (2008) Molecular mechanisms of cytokine and chemokine release from eosinophils activated by IL-17A, IL-17F, and IL-23: implication for Th17 lymphocytes-mediated allergic inflammation. *J Immunol* 180:5625–35

Galli SJ, Tsai M, Piliponsky AM (2008) The development of allergic inflammation. *Nature* 454:445–54

Grewe M, Walther S, Gyufko K, Czech W, Schopf E, Krutmann J (1995) Analysis of the cytokine pattern expressed *in situ* in inhalant allergen patch test reactions of atopic dermatitis patients. *J Invest Dermatol* 105:407–10

He R, Oyoshi MK, Jin H, Geha RS (2007) Epicutaneous antigen exposure induces a Th17 response that drives airway inflammation after inhalation challenge. *Proc Natl Acad Sci USA* 104:15817–22

Huang F, Wachi S, Thai P, Loukoianov A, Tan KH, Forteza RM *et al.* (2008) Potentiation of IL-19 expression in airway epithelia by IL-17A and IL-4/IL-13: important implications in asthma. *J Allergy Clin Immunol* 121:1415–21, 1421.e1–3

Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y (2008) Possible pathogenic role of Th17 cells for atopic dermatitis. *J Invest Dermatol* 128:2625–30

Molet S, Hamid Q, Davoine F, Nutku E, Taha R, Page N *et al.* (2001) IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. *J Allergy Clin Immunol* 108:430–8

Tesmer LA, Lundy SK, Sarkar S, Fox DA (2008) Th17 cells in human disease. *Immunol Rev* 223:87–113

Toda M, Leung DY, Molet S, Boguniewicz M, Taha R, Christodoulopoulos P *et al.* (2003) Polarized in vivo expression of IL-11 and IL-17 between acute and chronic skin lesions. *J Allergy Clin Immunol* 111:875–81

Wang YH, Angkasekwinai P, Lu N, Voo KS, Arima K, Hanabuchi S *et al.* (2007) IL-25 augments type 2 immune responses by enhancing the expansion and functions of TSLP-DC-activated Th2 memory cells. *J Exp Med* 204:1837–47

Weaver CT, Hatton RD, Mangan PR, Harrington LE (2007) IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 25:821–52

Wierenga EA, Snoek M, Jansen HM, Bos JD, van Lier RA, Kapsenberg ML (1991) Human atopen-specific types 1 and 2 T helper cell clones. *J Immunol* 147:2942–9

See related article on pg 2686

Notch and Melanocytes: Diverse Outcomes from a Single Signal

Masatake Osawa[1] and David E. Fisher[1,2,3]

Notch signaling is an evolutionally conserved pathway that serves as a critical regulator of cell fate. From a series of studies, including a report in this issue, researchers have begun to elucidate the critical functions of Notch signaling in the regulation of melanocyte lineage development. With evidence of a recently identified role for Notch signaling in melanomagenesis, characterization of downstream molecular events may offer potential avenues for the development of novel therapeutic strategies.

Journal of Investigative Dermatology (2008), **128**, 2571–2574. doi:10.1038/jid.2008.289

Single signal, diverse outcomes: a critical question in developmental biology

Tissue organogenesis is governed by a remarkably small set of evolutionally conserved signaling pathways. These signals, which may be termed a "developmental toolkit," include the BMP, FGF, Notch, Hedgehog, and Wnt signaling pathways (Canestro *et al.*, 2007). During development, these toolkit signaling pathways are utilized in a diverse range of discrete cell lineages in a spaciotemporally regulated manner to build a wide variety of

Correspondence: Dr David E. Fisher, Department of Dermatology, Massachusetts General Hospital, Thier 204, 55 Fruit Street, Boston, Massachusetts 02114, USA. E-mail: dfisher3@partners.org

[1]Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts, USA; [2]Melanoma Program, Department of Medical Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA and [3]Pediatric Hematology/Oncology, Harvard Medical School, Boston, Massachusetts, USA