

Tacrolimus: A new topical immunomodulatory therapy for atopic dermatitis

Abbreviations used

AD:	Atopic dermatitis
FcεRI:	High affinity IgE receptor
IDEC:	Inflammatory dendritic epidermal cell
LC:	Langerhans cell
NF-ATp:	Nuclear factor of activated T-cell protein

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease in which both inherited and environmental factors play a role in maintaining and exacerbating the condition.¹ Treatment options are few, with topical corticosteroids being the principal treatment for acute episodes. Secondary treatments with UV light irradiation or immune suppressive drugs generally do not replace topical corticosteroids but rather act as steroid-sparing therapies. The development of new corticosteroid preparations, with an aim to reduce side effects, has not significantly changed the benefit-risk ratio. The side effects of topical corticosteroids relate to the wide distribution of steroid-responsive elements in various cells and tissues. In general, the most clinically relevant are atrophogenicity, growth retardation in children, poor long-term control of AD, and, in some patients, therapeutic resistance.

Tacrolimus ointment, which recently received marketing approval in the United States under the trade name Protopic, offers the first new therapy for AD. Clinical studies performed in Europe, Japan, and the United States have shown short- and long-term therapy with tacrolimus ointment to be effective and safe for adults and children with moderate-to-severe AD.²⁻⁵ A major advantage over topical corticosteroid therapy is that skin atrophy does not occur.⁶ Tacrolimus ointment targets the local immune pathology of AD. The absence of a systemic effect is supported by minimal systemic exposure and by clinical findings that show no apparent increased risk of cutaneous or systemic infec-

tions.^{4,5,7} It is also of interest to note that long-term use of tacrolimus ointment in adult patients with AD did not reduce cell-mediated immunity, as assessed in the Recall Antigen Test,⁵ and was associated with a decrease in staphylococcal colonization.⁸

IMMUNE PATHOLOGY OF AD AND THERAPY AIMED AT LOCAL IMMUNE MODULATION

Inflammatory cells thought to play a role in producing and maintaining skin inflammation in AD include T cells, mast cells-basophils, eosinophils, and Langerhans cells (LCs).⁹⁻¹¹ Antigen presentation by LCs leads to the activation of T cells. The high-affinity receptor for IgE (FcεRI) on the surface of LCs binds peptide antigens by means of free IgE present in the inflammatory infiltrate. MHC II of LCs and the T-cell receptor play a role in this process (Fig 1). T cells are activated through a calcium-dependent pathway in which calcineurin dephosphorylates the nuclear factor of activated T-cell protein (NF-ATp). NF-ATp then migrates to the T-cell nucleus, where it leads to the transcription of IL-2 and other cytokines.

Tacrolimus blocks this process by binding to the FK506-binding protein, a 12-kd macrophilin (Fig 1, B). The FK506-binding protein/tacrolimus complex inhibits calcineurin and thereby the dephosphorylation of NF-ATp and expression of inflammatory T-cell cytokines, such as IL-2, IL-3, IL-4, IL-5, GM-CSF, IFN-γ, and TNF-α.^{12,13} In vitro studies have also shown that tacrolimus, through a mechanism that involves binding to the FK506-binding protein, also inhibits the release of inflammatory mediators from mast cells and basophils.¹⁴

In the February issue of the Journal, Panhans-Groß et al¹⁵ showed that in vitro tacrolimus downregulated the expression of FcεRI (Fig 1, B), whereas betamethasone upregulated its expression. Earlier, AD was shown to be characterized by strong expression of FcεRI on antigen-presenting epidermal dendritic cells (ie, LCs and related CD1a⁺ dendritic cells).¹¹ Thus the downregulation of FcεRI by tacrolimus is of potential clinical significance in the therapy of AD. It would be of interest to assess whether the action of tacrolimus on FcεRI depends on NF-ATp. LCs have been thought to originate from myeloid precursors; however, a recent study suggests they are more closely related to lymphoid precursors.¹⁶ Thus it is possible that their activation shares features in common with T-cell activation, such as dependence on calcineurin in the activation of a FcεRI-specific transcription factor.

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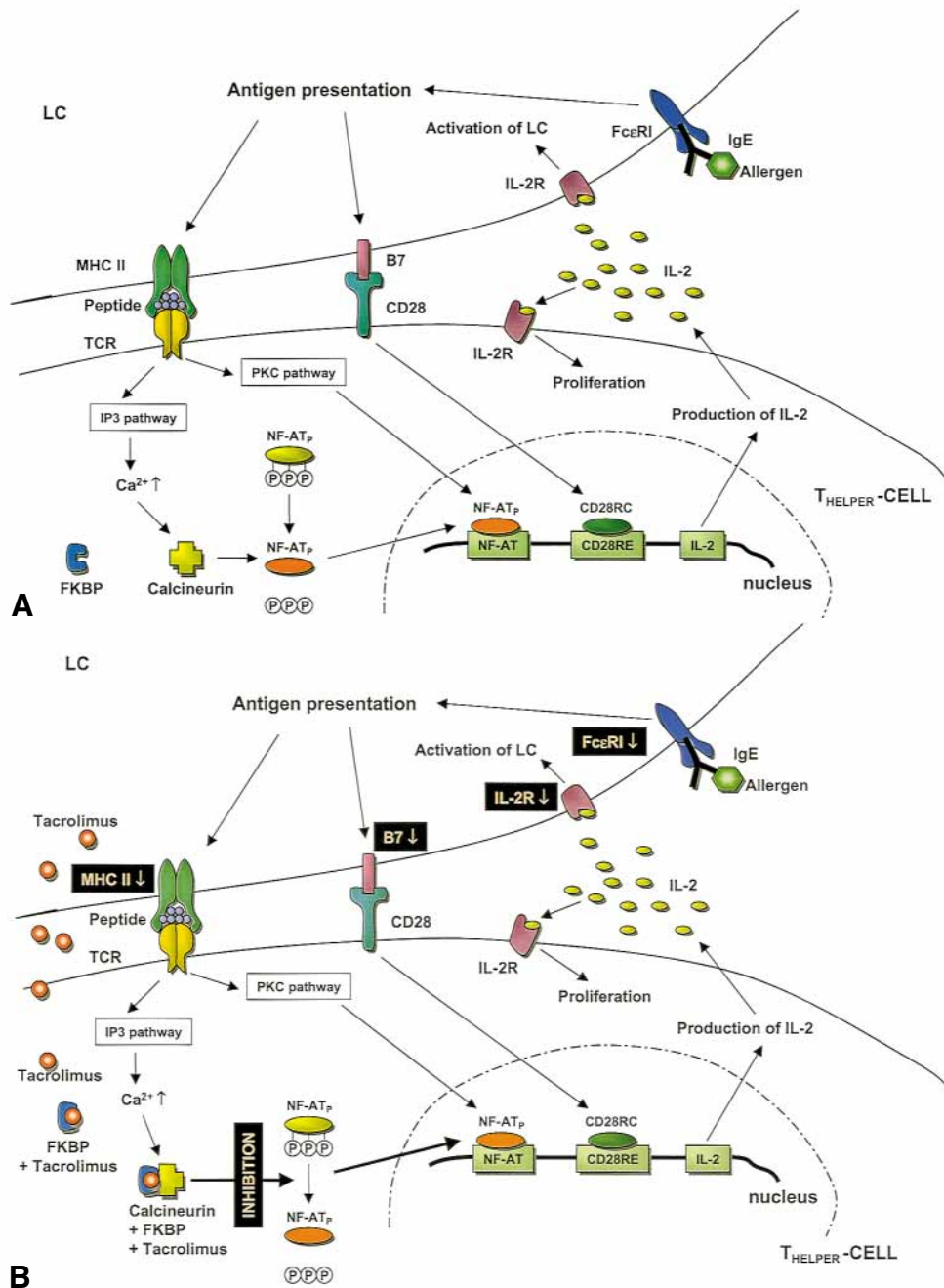


FIG 1. Antigen presentation by LCs and activation of T_H cells. **A**, Antigen presentation by LCs to T_H cells. **B**, Effect of tacrolimus (FK506) on antigen presentation by LCs and activation of T_H cells. Tacrolimus downregulates the expression of $Fc\epsilon RI$, $IL-2R$, $B7.1$, and $MHC II^{15}$ in LCs. In T_H cells tacrolimus inhibits the expression of inflammatory cytokines by blocking the dephosphorylation of $NF-AT$. **C**, Superantigens directly activate T_H cells through the $IP3$ /calcineurin pathway. Both $MHC II/TCR$ and $B7/CD28$ signals contribute to the activation of T_H cells. Whereas corticosteroids have a stronger inhibitory effect on the $B7/CD28$ route, tacrolimus specifically inhibits the $IP3$ /calcineurin pathway in T_H cells and at the same time downregulates both $MHC II$ and $B7.1$ in LCs, which are needed for the activation of T_H cells by superantigens. *FKBP*, FK506-binding protein; *IP3*, inositol-3-phosphate; *IL-2R*, $IL-2$ receptor; *NF-AT*, nuclear activator of T cell; *PKC*, protein kinase C; *TCR*, T-cell receptor.

In the present issue of the Journal, Wollenberg et al¹⁷ describe an in vivo intervention study with topical tacrolimus. An increased proportion of $CD1a^+$ cells in the epidermis of AD lesions decreased to normal during clinical improvement with tacrolimus ointment. The $CD1a^+$

population consisted of LCs and inflammatory dendritic epidermal cells (IDECs). An analysis of the relative proportion of these cell types showed that the decrease in $CD1a^+$ cells was mainly caused by a decrease in IDECs. The reduction in $CD1a^+$ cells during treatment with

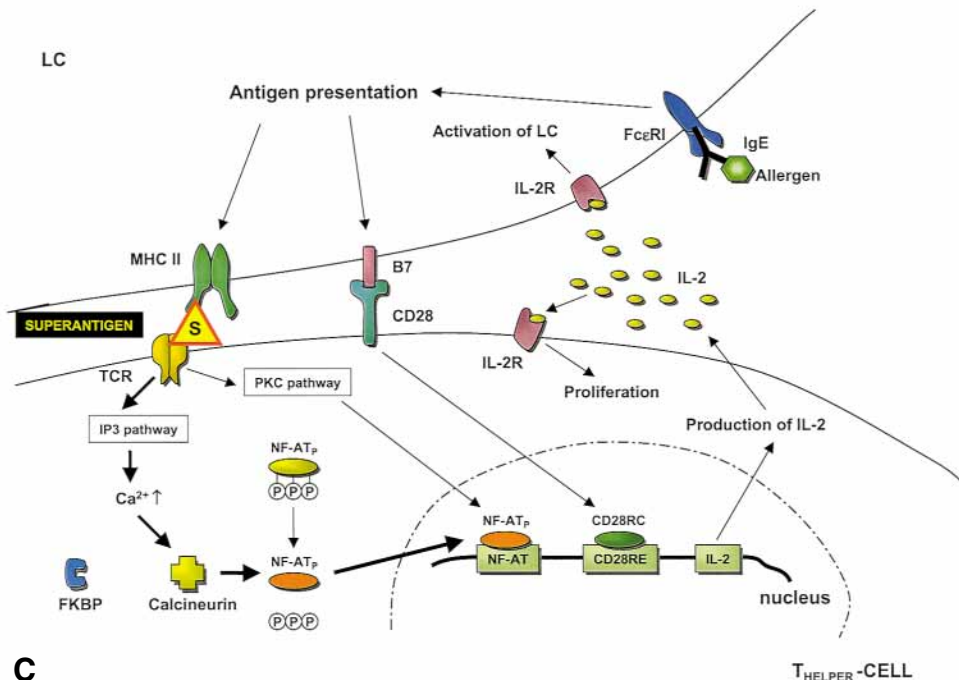


FIG 1. Continued

tacrolimus ointment was associated with downregulation of FcεRI expression in both IDECs and LCs. The authors concluded that the CD1a⁺ dendritic cells could represent a target of tacrolimus in AD therapy.

IS IgE CENTRAL TO AD AND ITS THERAPY?

As assessed by the proportion of patients with AD who have elevated serum IgE levels, approximately 80% have extrinsic AD, and approximately 20% have an intrinsic (non-IgE-related) form of the disease.¹⁸ One proposed explanation for the cause of AD in patients with intrinsic AD is that enterotoxins released by *Staphylococcus aureus* act as superantigens, which, independently of IgE, promote the release of proinflammatory molecules, such as IL-1 and TNF-α, from monocytes and dendritic cells and activate T cells. There is also evidence indicating that allergen-specific T cells, independently of IgE, play a role in the immune pathology of intrinsic AD.^{18,19} T cells are equally important in extrinsic AD. Increased IL-13 expression by T cells from lesions of patients with extrinsic AD is considered to account for increased IgE production through stimulation of B cells.¹⁹ It seems feasible that allergen-specific T cells can serve as a triggering factor in extrinsic, as well as intrinsic, AD.

Several studies have demonstrated that colonization of AD skin with superantigen-producing *S aureus* contributes to the severity of atopic skin disease.²⁰⁻²² Superantigen-mediated activation of T cells is resistant to corticosteroids, which may, in part, account for the increased clinical severity.²³ In the February issue of the Journal, Hauk and Leung²⁴ showed that tacrolimus specifically blocks *S aureus* superantigen-induced T-cell proliferation in AD. Specifically, tacrolimus had a strong inhibitory



FIG 2. A 27-year-old patient who was insensitive to topical corticosteroid therapy quickly responded to 0.03% tacrolimus ointment. Left, Before treatment with 0.03% tacrolimus; right, 48 hours after application of 0.03% tacrolimus.

effect on proliferation induced by the staphylococcal enterotoxin B in PBMCs from patients with AD and healthy volunteers compared with dexamethasone. Antigen processing by LCs seems not to be involved in this process. As Hauk and Leung point out, the recent finding suggesting that NF-ATp controls superantigen-induced shock²⁵ is relevant in terms of the inhibitory effect of tacrolimus on calcineurin-mediated dephosphorylation of NF-ATp (Fig 1, C). The fact that this path is independent of the glucocorticoid receptor^{23,24} could account for the positive therapeutic response observed with tacrolimus ointment in patients with AD who are clinically insensitive to topical corticosteroid therapy (Fig 2).

There remains the question of what came first, the chicken or the egg. FcεRI and IgE certainly play an important role in the immune pathology of AD in that they are required for optimal activation of T cells, but do they represent the principal anomaly in AD? The fact that AD can persist without apparent involvement of IgE (eg, in intrinsic AD) and that antigen processing by LCs seems not to be essential for T-cell activation (eg, in *S aureus* superantigen-induced T-cell proliferation) suggests that other possibilities should be considered. This is an exciting area of research, with research into the mechanism of action of tacrolimus perhaps leading to important discoveries about the immune pathology of AD and, more importantly, improved treatment for this common and debilitating skin disease.

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