

EDITORIAL

Calcineurin inhibitors for the treatment of skin disease: how do they work?

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Calcineurin inhibitors have been used for the treatment of skin disease for over 20 years following the observation in 1979 that psoriasis severity improved in patients receiving cyclosporin [1]. Formal randomized trials confirmed this observation [2] and cyclosporin is widely used in psoriasis management today although duration of therapy is often limited by side-effects.

Calcineurin antagonists which include cyclosporin, tacrolimus and ascomycins (e.g. pimecrolimus) act by inhibiting the activation of the nuclear factor for activated T cells (NFAT). The NFATs are a family of five transcription factors (NFAT1–5). NFAT1–4 show sequence homology; NFAT5 is included in the family because of homology of the DNA binding domain but is not regulated by calcineurin and in many ways is quite distinctive. In contrast, NFATs 1–4 are regulated by calcium and the calcium/calmodulin dependent phosphatase calcineurin. Elevation of intracellular calcium activates calcineurin which dephosphorylates NFAT, revealing a nuclear import region, with resulting nuclear translocation. In the nucleus NFAT binds with other transcription factors, for example activated protein-1 or GATA, to induce gene transcription. The NFAT signalling pathway has been extensively characterized in T cells and the known target genes in T cells include IL-2, IL-3, IL-4, IL-10, IFN- γ and granulocyte macrophage-colony stimulating factor [3]. Calcineurin inhibitors work by first binding to a cytoplasmic immunophilin protein; for example, cyclophilin for cyclosporin and FKBP12 for tacrolimus and ascomycin, respectively. The drug, immunophilin, calcineurin complex then inhibits calcineurin from activating NFAT [4].

The therapeutic effects of calcineurin inhibitors in skin disease were initially assumed to be acting via inhibition of T cell activation and proliferation. However, there is now firm evidence that the NFAT/calcineurin pathway is also active in other cells found in the skin and that calcineurin inhibitors exert therapeutic effects on a variety of non-immune cells.

NFAT isoforms are present in keratinocytes and calcineurin has been shown to be functionally active in keratinocytes [5, 6]. Induction of NFAT1 nuclear translocation in keratinocytes is blocked by treatment with either cyclosporin or tacrolimus [6]. Psoriasis is now generally thought of as a disease characterized by abnormal sustained T cell activation that results in increased keratinocyte proliferation although the development of a psoriasis-like phenotype in mice transgenic for constitutively active stat3, suggests that the interplay between keratinocytes and T cells may be more complex [7]. Cyclosporin remains one of the most effective therapies for psoriasis and this may be in part because of a combined effect on NFAT signalling in both T cells and keratinocytes.

Hailey–Hailey disease (familial benign pemphigus) is an autosomal dominant disorder characterized by faulty keratinocyte adhesion leading to recurrent vesicles and erosions affecting mainly but not exclusively flexural sites. The mutated gene is ATP2C1 which encodes a P-type Ca^{2+} -transport adenosine triphosphatase [8]. Several case reports and case series have described improvement of Hailey–Hailey disease in response to both oral cyclosporin and topical tacrolimus [9, 10]. Although randomized controlled trial data are lacking, in part because of the rarity of this disorder, these reports suggest that cyclosporin and tacrolimus may be exerting a therapeutic effect on human epidermis, as T cells are not thought to be involved in pathogenesis of Hailey–Hailey disease.

The importance of NFAT signalling in histamine release in basophils and mast cells has been established. For example, cross-linkage of the high-affinity receptor ($\text{Fc}\epsilon\text{RI}\alpha$) for IgE results in nuclear translocation of NFAT in the rat basophilic leukemia (RBL-2H3) mast cell line and rat bone marrow-derived mast cells [11]. Furthermore, calcineurin antagonists inhibit anti-IgE-induced histamine release from human basophils [12] and cyclosporin has been demonstrated by Grattan et al. [13] to be an effective treatment for chronic idiopathic urticaria.

Chronic urticaria describes the occurrence of weals occurring at least twice a week for greater than 6 weeks. In approximately 40% of these patients circulating histamine-releasing auto-antibodies can be identified [14] and this subset of patients may also be identified by the autologous serum skin test which shows a reasonable degree of sensitivity and specificity. These auto-antibodies have been shown to be directed against the α -subunit of the high-affinity IgE receptor ($\text{Fc}\epsilon\text{RI}\alpha$) found on basophils and mast cells and to a lesser extent IgE [15]. Binding of complement C5a to $\text{Fc}\epsilon\text{RI}\alpha$ can also induce histamine release [16].

The paper by Marsland et al. [17] published in this issue of Clinical & Experimental Allergy investigates further the mechanism of action of calcineurin inhibitors in patients with chronic autoimmune urticaria. Patients selected for study had chronic autoimmune urticaria as assessed by the ability of their serum to induce histamine release from human basophils. They demonstrated that therapeutically relevant concentrations of cyclosporin inhibited histamine release from basophils induced by patient's serum. The authors went on to dissect the effect of cyclosporin on histamine release induced by IgG and C5A and showed that the predominant effect is on histamine release induced by IgG with no inhibition of histamine release induced by C5A. Similar effects were observed with ascomycin but no effects were seen with antihistamines or methotrexate.

These data suggest that the therapeutic benefit of cyclosporin in chronic autoimmune urticaria may in part be because of direct effects on basophils or mast cells. The onset of action of cyclosporin in chronic urticaria is reasonably rapid, within 48 h [13], suggesting an early effect on histamine release. However, Grattan et al., observed no reduction in the autologous skin serum test response, using stored serum, after 4 weeks of cyclosporin which argues against a role for cyclosporin in regulating histamine release. Cyclosporin is also known to target eosinophils [18] and cyclosporin may also be inhibiting production of histamine releasing auto-antibodies as cyclosporin resulted in a significant reduction in the histamine releasing activity of serum [13]. It is therefore possible that cyclosporin is having effects on multiple responses in chronic urticarial patients. To further explore the clinical relevance of the findings reported by Marsland et al. [17], it would be interesting to study the effects of cyclosporin on human mast cells and to investigate whether systemic cyclosporin modulates the nuclear cytoplasmic ratio of NFAT isoforms within mast cells in the skin of patients with chronic urticaria. There is currently significant interest in the development of drugs that inhibit NFAT activation and this may lead to new therapies that are relatively specific for individual NFAT isoforms with improved side-effect profiles.

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