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Int. J Cell Biol. Physiol. 2018: 1 (1-2), 5-13

Review Article

Immunomodulatory effects of tacrolimus (FK506) for the treatment of allergic diseases

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(Received Nov 20, 2018; Accepted December 10, 2018)

Abstract

Tacrolimus has been used to prevent allograft rejection and also used in kidney, liver and heart transplantations. Various preclinical and clinical studies demonstrated that Tacrolimus possess immunomodulatory and anti-inflammatory properties. The mechanism of action of Tacrolimus in allergic diseases involves calcineurin inhibition, and downregulation of T-cell reactivity, IgE degranulation, and its actions on mast cells, dendritic cells, basophils, eosinophils and inhibition of transcription of proinflammatory cytokines. Herein we reviewed the Pharmacotherapeutic mechanism of action of Tacrolimus in the prevention of asthma, atopic dermatitis, and allergic conjunctivitis.

Keywords: *Tacrolimus, FK506, calcineurin inhibitor, asthma, atopic dermatitis, and allergic conjunctivitis*

Tacrolimus, a calcineurin inhibitor was isolated from the fermentation broth of a soil sample from Tsukuba, Japan, and defined as Streptomyces tsukubaensis in 1984. Tacrolimus has a molecular weight of 822 Daltons and is classified as a hydrophobic macrolide lactone (Fig.1). Tacrolimus selectively inhibits calcineurin, thereby impairing the transcription of interleukin (IL)-2 and several other cytokines in T lymphocytes. Tacrolimus has been used as organ transplantation for over several decades. Tacrolimus

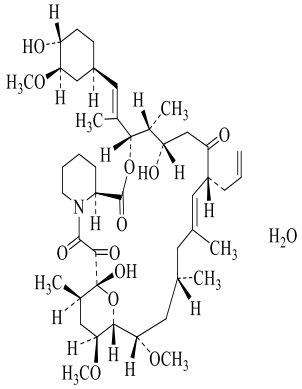

Figure 1. Chemical structure of Tacrolimus (FK506)

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also inhibits Th1 and Th2 responses and is used as a safe theapeutic for allergic diseases. The present review is focuses on the on its therapeutic effects against asthma, atopic dermat - itis, and allergic conjunctivitis. Immu-nomodulatory effects of Tacrolimus against allergic diseases, with a special focus on its pharmacokinetics.

Absorption and distribution.

Tacrolimus is absorbed in the small intestine, and plasma peak concentrations occur after one to eight hours. The oral bioavailability is limited (~20 percent for tacrolimus) as a result of poor absorption, partial metabolism by enzymes in the bowel mucosa, and first-pass hepatic metabolism (1, 2). Topical tacrolimus is minimally absorbed in patients with normal skin, but clinically significant absorption has been reported when used in patients with skin diseases (3).

Tacrolimus is lipophilic and undergoes extensive body distribution. In the blood, most of the absorbed drug is taken up by erythrocytes. In the plasma, tacrolimus binds albumin and alpha-1-acid glycoprotein. The plasma protein binding of tacrolimus is approximately 99 percent and is independent of concentration over a range of 5 to 50 ng/ml (4). Tacrolimus accumulates mainly in the lung, spleen, heart, kidney, and pancreas and cross the placenta and appear some extent in breast milk, but actual toxicity in breastfed infants appears to be rare (5).

Metabolism and elimination.

Tacrolimus is extensively metabolized by cytochrome P-450 CYP3A enzymes in the liver. There is also some metabolism in the gut mucosa. Tacrolimus is excreted in the bile. The elimination half-life can vary significantly among patients and is over 12 hours for immediate-release tacrolimus. The elimination half-life of extended-release tacrolimus tablets after oral administration of 2 mg once daily for 10 days was 31±8 hours in healthy subjects. The elimination half-life of extended-release tacrolimus capsules after oral administration of 4 mg capsules daily for 10 days was 38±3 hours in healthy subjects (6).

Effects of Tacrolimus on immune regulation

Immunomodulatory agents are commonly used for the treatment of severe and prolonged allergic diseases (7,8). Tacrolimus suppresses cell-mediated and humoral immune responses and inhibits activation of several pivotal immune cells and exerts immunomodulatory effects.

Effect of Tacrolimus on the innate and adaptive immune response

In cell mediate innate immunity eosinophils, macrophages, mast cells, dendritic cells, neutrophils, NK, and NKTcells play a role, whereas, in the humoral innate immune response complement system, C-reactive protein, antimicrobial peptides, mannose-binding lectins play a critical role. Whereas in cellular adaptive immunity T cells, B cell play role and in humoral adaptive immunity antibodies play

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immune function in response to allergens or antigens to control the immunological reactions.In allergic diseases, IgE production and infiltration immune cells like mast cells, eosinophils, and Th2 cells are observed (9-11). Innate type allergies are by various cytokine and innate lymphoid cells and induce allergic inflammation by the release of IL-4, IL-5, and IL13 cytokines. These reactions are observed in a variety of allergic diseases including AD, Asthma, and conjunctivitis. Tacrolimus cannot significantly alter the functions of innate and adaptive immune cells in the physiological status, but it can effectively delay allogeneic skin-graft rejection through ameliorating the T cell responses (12).

Tacrolimus inhibits mast cell activation, dendritic cells, basophils, and eosinophils

Mast cells are immune cells of the myeloid lineage that are found beneath the surface epithelia and play an important role in host defense. Tacrolimus-loaded ethosomal preparations suppressed the increase in the number of mast cells in the model of DNFB-induced dermatitis (13). Previously, it has been reported that IgE antibodies induced histamine release was reduced upon tacrolimus administration (14, 15). Dendritic cells (DCs) are antigen-presenting cells which process antigens and present them to T cells to promote immunity to antigens and also secrete cytokines to regulate immune responses. Tacrolimus eye drops are an effective and safe treatment for palpebral conjunctiva in patients with vernal keratoconjunctivitis, and can rapidly inhibit the activity of dendritic cell count, total area, average size, perimeter, and diameter (16). Tacrolimus inhibits cytokine production following T cell activation and decreases Fc epsilon RI expression on dendritic cells in the skin in atopic dermatitis. Basophils are granular leukocytes that play a role in development and pathogenesis of allergic diseases and also Th2 cytokine-mediated inflammation (17). Tacrolimus targets Ca^{2+}-dependent protein phosphatase, calcineurin. FK506 also inhibits IgE-dependent histamine release from human lung mast cells and basophils (18). Eosinophils are bone marrow-derived granulocytes that develop in response to cytokines and GM-CSF and release into peripheral blood to the target organs in response to allergen exposure and play a critical role in the regulation of immunological reactions. Tacrolimus is reported as an effective therapy for allergic asthma in dust mite-sensitized mice via inhibition of IL-4, IL-5, and IFN-γ (19) and also control bronchial asthma in humans (20). Tacrolimus inhibits conjunctival infiltrations with lymphocytes and eosinophils in OVA-sensitized,

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experimental allergic/immune-mediated blepharoconjunctivitis in rats (21).

Blockade of T-cell receptor-mediated signal transduction by tacrolimus

The antigens bind to T-cell receptors which result in increased production of Ca^{2+}. The increased intracellular Ca^{2+} binds with calmodulin and activate and phosphorylates nuclear factor of activated T Cells. The dephosphorylated form ofcytoplasmic NF-AT translocate from the cytosol into the nucleus and forms a complex with the nuclear subunit of NF-AT, and can bind to the promoter region of several cytokine genes and induce gene transcription. On the other hand, after penetrating the cell membrane, tacrolimus binds to its intracellular receptor, the FK-binding protein complex and blocks the function of the Ca^{2+} and calmodulin-dependent

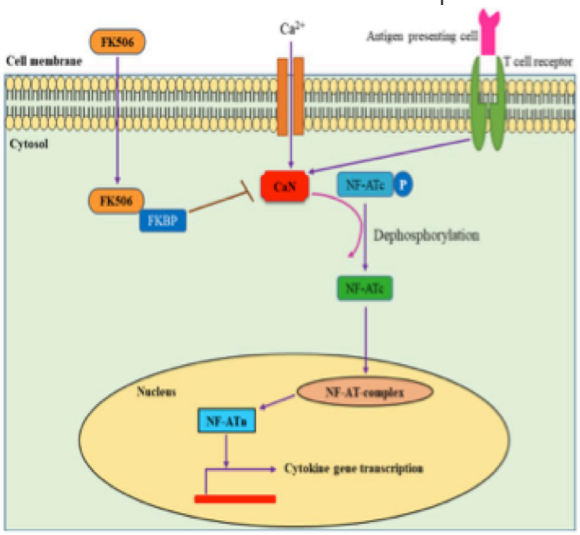

Figure 2. Blockade of T-cell receptor-mediated signal transduction by tacrolimus. FK506 bind with immnophyllin complex and inhibits nuclear translocation of the cytoplasmic subunit of the nuclear factor of activated T cells (NF-ATc) and prevents the formation of an NF-AT complex and inhibits, transcription of several cytokines and regulates immune responses.

phosphatase, calcineurin. This interaction results in suppression of NF-AT–dependent cytokine gene transcription and immunosuppression. Thus tacrolimus inhibits transcription of cytokines and suppresses T-cell prolifer- ation (Fig.2.)

Tacrolimus as a pharmacotherapy for allergic diseases

Allergic diseases of the biological system comprise a spectrum of diseases, with each condition being characterized by a complex immunopathology. Tacrolimus is a potent immunomodulator that is effective in the treatment of various allergic diseases by its pleiotropic immunosuppressive effects on the immune system.

Tacrolimus for the treatment of asthma

Asthma is a lifelong respiratory disease characterized by bronchoconstriction, airway hyper-responsiveness, mucus secretion, and chronic inflammation and requires pharmacotherapy to reduce the severity of asthmatic symptoms. Shin et al (22) demonstrated that FK506 decreases serum IgE, eosinophils, IL-5 levels reduce allergic rhinitis with ovalbumin sensitization in mice (22). Previously it was demonstrated that tacrolimus inhibits bronchoconstriction to aspirin-induced asthma by inhibition of cysteinyl leukotriene excretion, wherein aspirin-induced asthma is linked to inhibition of COX activity and massive release of cysteinyl

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leukotriene into the airway that cause bronchoconstriction (23). IL13 is a critical cytokine released in asthma. FK-506 inhibited IL-13 synthesis, upon stimulation of PBMCs by 12-O-tetradecanoyl phorbol-13-acetate (TPA)/ionomycin that induce IL-13 expression (24). Tacrolimus also was

Tacrolimus for the treatment of conjunctivitis

Conjunctivitis is the inflammation of the conjunctiva which lies in the white part of the eye. It is classified as vernal keratoconjunctivitis that is bilateral disease characterized with redness and itching of the eye and Atopic keratoconjunctivitis that is also a bilateral disease of ocular surface and lids. Conjunctiva may have papillae and cataract may also occur in these patients (26). In a previous multicenter, randomized, double-masked, placebo-controlled clinical trial study 0.1% tacrolimus ophthalmic suspension is effective in improving severe allergic conjunctivitis (27). Tacrolimus blocks cellular steroid receptors and inhibits mediator release from mast cells and this inhibition suppresses T-cell activation and further B-cell proliferation (28,29). Tacrolimus inhibits ocular itching and symptoms of allergic eye diseases, (27,30). Increased periostin expression is linked with allergic inflammation (31). Levels of tear periostin are also significantly elevated in atopic keratoconjunctivitis however topical tacrolimus reduces the tear periostin levels with the improvement of atopic keratoconjunctivitis (32).

Tacrolimus for the treatment of atopic dermatitis

Atopic dermatitis also is known as eczema is characterized by skin inflammation, redness, itching, and dryness of the skin. Atopic dermatitis patients skin lesions show epidermal hyperplasia, T-cell and dendritic cell (DC) infiltrates and increased production of inflammatory mediators with an increase in serum IgE levels (33-36). Topical calcineurin inhibitor tacrolimus has been shown as an effective and alternative therapy for corticosteroids in children and adults (37). Tacrolimus has been shown to suppress Th1/Th2 cell activation, mast cell granulation, primary sensory neurotransmitter release, desensitization of TRPV1 receptor, suppression of IL-31 production, IL-33, ST2 receptor mRNA expression, and suppression of impairment of TLR2/TLR1 balance, and periostin production and reduces itching, scratching behavior and preservation of lamellar liquid crystal reduction in atopic dermatitis (31).

Conclusion and future perspectives

Topical application of tacrolimus for atopic dermatitis is safe since the systemic absorption of tacrolimus from the ointment is minimal and unlike corticosteroids adverse events, tacrolimus ointment is not associated with skin atrophy, and minimal risk of toxic effects and it is a well-recommended treatment for atopic dermatitis. The potent effect of

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Tacrolimus include mast cell degranulation and mast cell cytokine

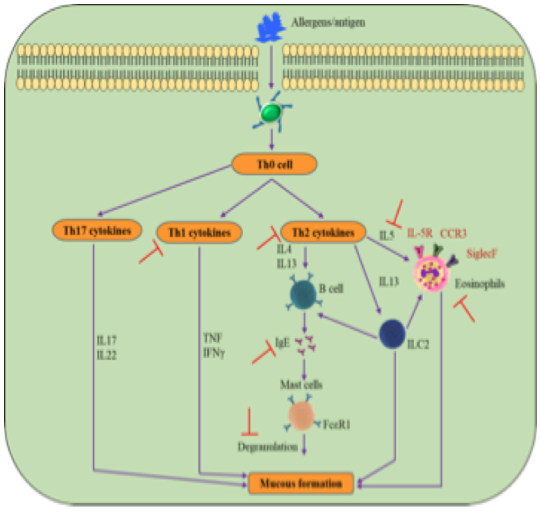

Figure 3. Tacrolimus action mechanisms in allergic diseases

expression and release, hence Tacrolimus is also an effective strategy for mast cell-mediated allergic diseases (Fig. 3).

Acknowledgements.

This work was supported in part by an NIH grant R01 AI080581 (AM).

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