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Short communication

Down-regulation of thymic stromal lymphopoietin by curcumin

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Abstract:
Background: Thymic stromal lymphopoietin (TSLP) is a cytokine implicated in the pathogenesis of allergic diseases such as asthma, atopic dermatitis and allergic rhinitis. Curcumin has various effects such as antidepressant, antioxidant, antihyperglycemic, antitumor and anti-inflammatory. However, the effect of curcumin on the production of TSLP has not been clarified. Thus, we investigated how curcumin inhibits the expression and production of TSLP in the human mast cell line, HMC-1 cells.
Methods: We used enzyme-linked immunosorbent assay, reverse transcription-polymerase chain reaction, luciferase assay, and caspase-1 assay to investigate the effects of curcumin.
Results: The results show that curcumin inhibited the production and mRNA expression of TSLP in HMC-1 cells: the maximal inhibition rate of TSLP production by curcumin (50 μM) was 59.16 ± 4.20%. In addition, curcumin suppressed the nuclear factor-κB luciferase activity induced by phorbol myristate acetate plus A23187. In the activated HMC-1 cells, caspase-1 activity was increased, whereas caspase-1 activity was decreased by pretreatment with curcumin.
Conclusion: These results suggest that curcumin can be used to treat inflammatory and atopic diseases through the suppression of TSLP.

Key words: thymic stromal lymphopoietin, curcumin, nuclear factor-κB, caspase-1

Abbreviations: NF-κB – nuclear factor-κB, PMA – phorbol myristate acetate, TSLP – thymic stromal lymphopoietin

Introduction

Atopic dermatitis is a chronic and relapsing eczematous skin inflammation associated with epidermal barrier dysfunction, intense pruritus, and cutaneous hyperreactivity to environmental triggers [8]. The lifetime prevalence of atopic dermatitis is estimated to be 15–30% in children and 2–10% in adults, while the incidence of atopic dermatitis has increased 2- to 3-fold during the past 3 decades in industrialized countries [1]. Thus, atopic dermatitis has significant socioeconomic and personal impacts in these countries [21].

Thymic stromal lymphopoietin (TSLP) was found to enhance potently the maturation of $CD11c^+$ dendritic cells, and TSLP-primed and activated dendritic cells promoted the differentiation of naive $CD4^+$ T

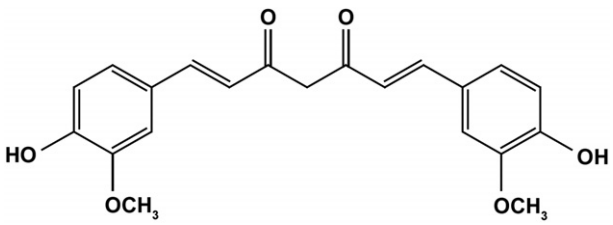

Fig. 1. Chemical structure of curcumin

cells into proinflammatory T_H2 cells [20]. A high expression of TSLP is a feature of keratinocytes in atopic dermatitis skin lesions, and the TSLP-priming of dendritic cells *in situ* may serve to induce or enhance T_H2 responses within the skin, as well as systemically. Consistent with this viewpoint, TSLP was originally reported to exert its T_H2-promoting properties through dendritic cell-mediated pathways in human beings that involved the induction of the OX40 ligand on dendritic cells [28]. TSLP has been implicated in the development of asthma and atopic dermatitis [13]. In atopic diseases such as asthma and atopic dermatitis, not only dendritic cells, epithelial cells, eosinophils, and T cells but also mast cells are important. A number of studies reported that mast cells are activated and infiltrated in the skin lesion of the atopic dermatitis animal model, suggesting the contribution of mast cells in atopic dermatitis [4, 9, 25, 30].

The cysteine protease caspase-1 is a member of the caspase family [6]. Quite unlike the role that most caspases have in apoptosis, caspase-1 mainly serves to cleave IL-1β and IL-18 from their inactive precursors to their active forms [2, 16]. In addition to the well-established roles of caspase 1 in the maturation of IL-1β and IL-18, caspase 1 is also capable of activating the nuclear factor (NF)-κB [15]. The activated caspase-1 activates NF-κB in HMC-1 cells [23]. NF-κB activated by caspase-1 mediates the induction of TSLP gene expression in airway epithelial cells [18].

Curcumin (Fig. 1) is the main constituent of the spice turmeric (*Curcuma longa*) [7, 33]. A number of studies have reported that curcumin has antidepressant, antioxidant, antihyperglycemic, antitumor, and anti-inflammatory activities [5, 10, 19, 29, 32]. However, the effect of curcumin on the production of TSLP has not yet been clarified. Thus, we investigated how curcumin suppresses the production of TSLP in mast cells.

Materials and Methods

Reagents

Phorbol myristate acetate (PMA), A23187, and curcumin were purchased from Sigma Chemical Co. (St. Louis, MO, USA). We purchased IMDM from Gibco BRL (Grand Island, NY, USA); caspase-1 inhibitor, caspase-1 assay kit, and TSLP antibodies from R&D Systems (Minneapolis, MN, USA); TMB substrate from Pharmingen (San Diego, CA, USA).

Cell culture

The human mast cell line, HMC-1 cells, was grown in IMDM and supplemented with 100 units/ml of penicillin, 100 μg/ml of streptomycin and 10% fetal bovine serum at 37°C in 5% CO_2 with 95% humidity.

Cytokine assay

We used the enzyme-linked immunosorbent assay (ELISA) method to assay the culture supernatant for TSLP [22, 24]. A sandwich ELISA for TSLP was carried out in duplicate in a 96-well ELISA plate. First, we coated the plate with 100 μl aliquots of mouse anti-human TSLP monoclonal antibody at 1.0 μg/ml in PBS at pH 7.4 and incubated the plate overnight at 4°X. The plate was washed in PBS containing 0.05% Tween-20 (Sigma) and blocked with PBS containing 1% BSA, 5% sucrose and 0.05% NaN_3 for 1 h. After additional washes, the culture supernatant and TSLP standards were added and incubated at 37°C for 2 h. After 2 h incubation at 37°C, the wells were washed and then each of the 0.2 μg/ml of biotinylated anti-human TSLP was added and again incubated at 37°C for 2 h. After washing the wells, streptavidin-peroxidase was added and the plate was incubated for 20 min at 37°C. The wells were again washed and the TMB substrate (Pharmingen) was added. Color development was measured at 450 nm using an automated microplate ELISA reader. A standard curve was run on the plate using recombinant human TSLP in serial dilutions.