Short Review

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The Molecular Mechanisms underlying the Therapeutic Effect of Berberine in Inflammatory Skin Diseases

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ABSTRACT

Clinical therapy of chronic inflammatory skin diseases such as atopic dermatitis is extremely difficult. Recently, the use of a number of traditional herbal medicines has been attempted to treat these skin diseases. Orengedokuto is a traditional herbal medicine consisting of four crude natural medicines, and in the field of dermatology, it is used to treat skin diseases accompanied by inflammation and pruritus. Our recent animal study showed that berberine, a major component of Orengedokuto, improves skin inflammation and itching in mice with atopy-like dermatitis. Furthermore, we identified EIF3F and MALT1 as factors involved in the suppression of cytokine production by berberine. In addition, berberine also activates AMP-activated protein kinase, which is involved in the expression of inflammatory and anti-inflammatory cytokines. In addition, berberine also attenuates epidermal hyperplasia though the inhibition of CDC6 expression. Taken together, these findings indicate that berberine improves inflammatory skin diseases by controlling gene expression related to both inflammation, anti-inflammation and keratinocyte hyperproliferation.

Keywords: Orengedokuto; Berberine; Inflammation; Pruritus; Cytokines; EIF3F; MALT1; AMPK

ABBREVIATIONS

AMPK: AMP-activated Protein Kinase

CDK: Cyclin-dependent Kinase

COX-2: Cyclooxygenase-2

E2F: E2 Transcription Factor

EIF3F: Eukaryotic Translation Initiation Factor 3 Subunit F

HO-1: Heme Oxygenase-1

IKK: I Kappa B Kinase

IL: Interleukin

INF-γ: Interferon- γ

JAK: Janus Kinase

MALT1: Mucosa-associated Lymphoid Tissue Protein 1

MCP-1: Monocyte Chemoattractant Protein-1

MIF: Macrophage Migration Inhibitory Factor

MMP-9: Matrix Metalloproteinase-9

NEMO: NF-κB Essential Modulator

NF-κB: Nuclear Factor-kappa B

Nrf2: NF-E2-related Factor 2

Rb: Retinoblastoma

STAT: Signal Transducer and Activator of Transcription

TAK1: TGF-β-activated Kinase1

TAB1-3: TAK-binding Protein1-3

TGF: Transforming Growth Factor-β

INTRODUCTION

Inflammatory skin diseases (e.g. atopic dermatitis and psoriasis) are accompanied by severe pruritus, which leads to a decrease in the quality of life (e.g. stress and sleepless) and interference with treatment of skin disease, such as cutaneous inflammation. Therefore, controlling the inflammation and pruritus is very important for treating skin diseases. Since existing medicines do not work, however, therapy for these symptoms is still extremely difficult. Thus, the search for and development of new medicines are required.

Berberine (5,6-dihydro-9,10-dimethoxy-benzo(g)-1,3-benzodioxolo(5,6-a) quinolizinium, Figure 1) is a plant alkaloid (e.g. Coptis japonica and Phellodendron amurense). The rhizome of *Coptis japonica* ("Ohren": *Coptidis rhizome*) and the bark of *Phellodendron amurense* ("Obaku": *Phellodendri cortex*) are used as crude drugs in natural medicine. Berberine exerts anti-inflammatory and anti-oxidant effects [1-4].

Traditional herbal medicines are being used increasingly frequently to treat intractable skin diseases, mainly in Asia. Orengedokuto, which contains berberine as a major component, is a traditional herbal medicine that consists of four crude drugs (*Coptidis rhizome*, *Phellodendri cortex*, *Scutellariae radix* and *Gardeniae fructus*). It is commonly used to improve symptoms, such as dry mouth, hot flashes, perspiration, inflammation and pruritus.

We herein review the molecular mechanisms underlying the therapeutic effect of berberine, as a major component of Oregedokuto, in inflammatory skin diseases.

THERAPEUTIC EFFECT OF ORENGEDOKUTO AND BERBERINE IN INFLAMMATORY SKIN DISEASES

In cases of atopic dermatitis with severe cutaneous inflammation and pruritus, Orengedokuto improves several symptoms [5,6].

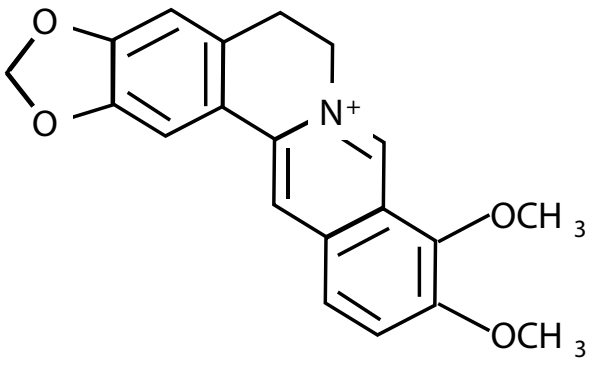

Figure 1. Structure of berberine.

In addition, skin inflammation and itch-related behavior in animal models of atopic dermatitis were also improved by repetitive oral administration of Orengedokuto [7] and berberine [8]. Orengedokuto also attenuates the inflammatory symptoms in mite-induced allergic dermatitis [9] and chemical allergen-induced contact dermatitis [10,11]. In addition to our report [8], berberine also exerts an anti-inflammatory effect in 12-O-tetradecanoylphorbol-13-acetate-induced dermatitis [12], allergic contact dermatitis [13,14] and fungus-induced dermatitis [5] in animals. These findings suggest that berberine (or Orengedokuto) is effective against inflammatory skin diseases.

ANTI-INFLAMMATORY MECHANISMS OF BERBERINE IN INFLAMMATORY SKIN DISEASES

Figure 2 shows a schematic illustration of berberine-regulated immune cells and inflammatory factors in the skin.

In a mouse model of atopic dermatitis, we showed that berberine [8] and Orengedokuto [7] inhibited the infiltrated eosinophils and mast cells, and the expression of eotaxin and Th2-type cytokines (IL-4, macrophage migration inhibitory factor (MIF)). A rat model of contact dermatitis also showed that berberine inhibits mast cell degranulation [13]. IL-4, which is released from Th2 cells [16] and mast cells [17], and MIF, which is released from mast cells [18], fibroblasts [19] and keratinocytes [19], play a role in mast cell recruitment [20,21]. IL-5, which is released from Th2 cells directly induces eosinophil infiltration [22,23]. We previously showed that, in murine fibroblasts, IL-4/MIF increases the expression of eotaxin [8], which is a chemokine that increases eosinophil infiltration [24-26]. These findings suggest that berberine regulates the recruitment of mast cells and eosinophils into the skin through its inhibitory action on Th2 cells (but not Th1 cells), mast cells and fibroblasts.

IgE plays an important role in the activation of mast cells. Berberine attenuated the serum IgE level in dermatitis mice [8]. IL-4 induces IgE production in B cells, and IL-5 enhances IL-4-induced IgE production [27,28]. Therefore, the inhibition of IL-4 and IL-5 expression by berberine is involved in the decrease in the serum IgE level in dermatitis mice and helps prevent the degranulation of mast cells. The arachidonic acid metabolite prostaglandin E_2 and its metabolic enzymes cyclooxygenase-2 (COX-2) are involved in inflammation [29] and berberine inhibits the production and transcriptional activity, respectively [2,3,30,31]. Matrix metalloproteinase-9 (MMP-9) [32] and IL-6 [33] are involved in inflammation. IL-6 also induces MMP-9 expression [34]. In human atopic dermatitis, MMP-9 [35,36] and IL-6 levels are increased [37]. Berberine inhibits the expression of both MPP-9 and IL-6 in keratinocytes [38].

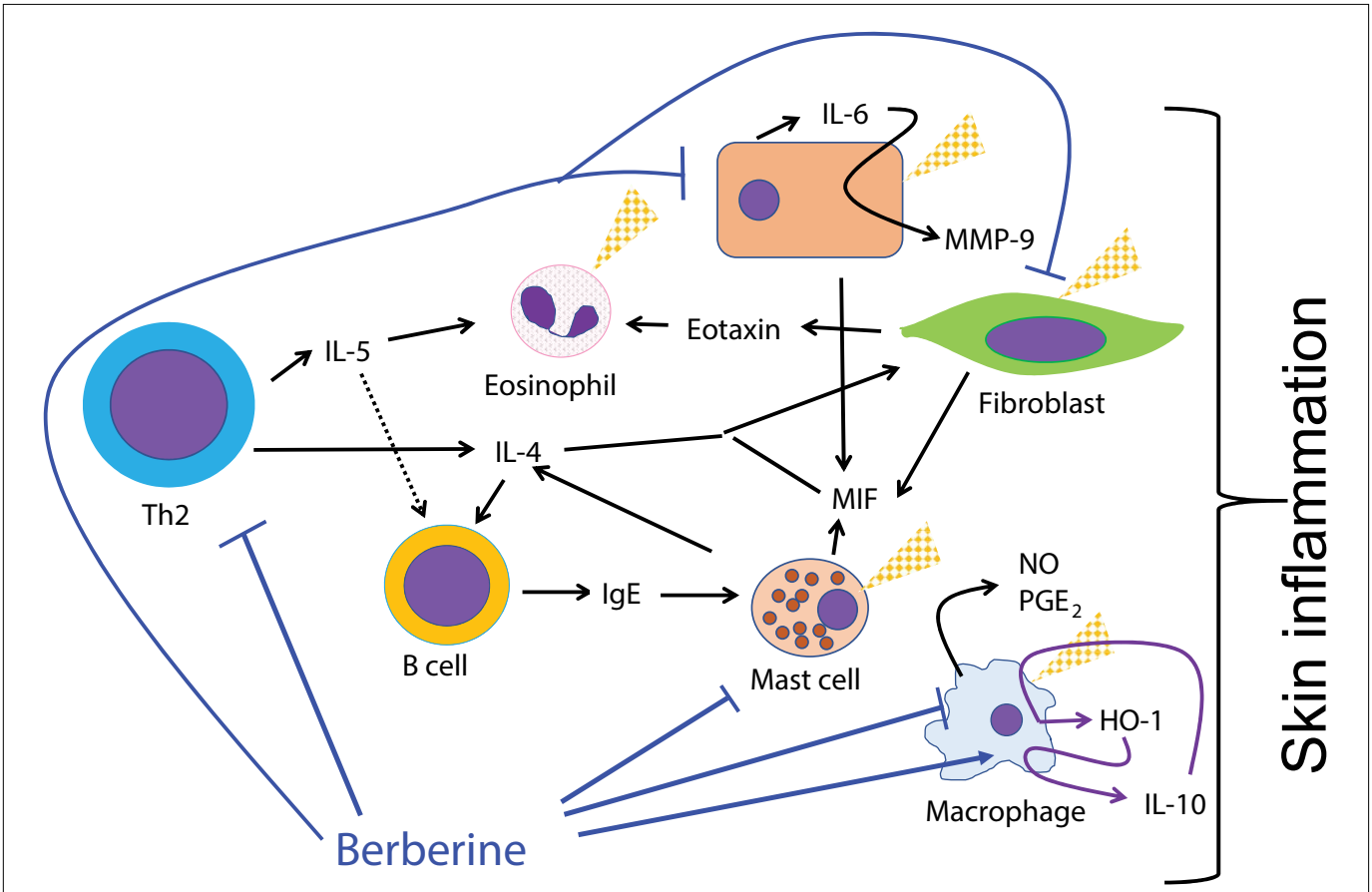

Figure 2: Schematic illustration of berberine-regulated immune cells and inflammatory factors in the skin..

Oxidative stress plays an important pathogenetic role in atopic dermatitis [39]. Heme oxygenase-1 (HO-1) regulates reactive oxygen species [40]. HO-1 inhibits the development of atopic dermatitis–like lesions in mice [41,42]. Berberine inhibits the expression of proinflammatory cytokines through HO-1 in macrophages [31,41]. Berberine also increases anti-inflammatory cytokine IL-10 in monocytes [43]. In macrophages, HO-1 contributes IL-10 production [44].

MOLECULAR MECHANISMS OF BERBERINE IN THE REGULATION OF INFLAMMATORY FACTORS

Figure 3 shows a schematic illustration of the molecular mechanisms underlying berberine-regulated inflammatory factors expression.

Berberine attenuates the expression of proinflammatory cytokines (e.g. IL-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1/CCL2) and inflammation-related enzymes (e.g. inducible nitric oxide synthase (NOS2) and COX-2) through the activation of the AMP-activated protein kinase (AMPK) pathway [2,31]. In brief, berberine induces AMPK phosphorylation [2,31,45] and inhibits the nuclear factor-kappa B (NF-κB) signaling pathway, as AMPK inhibits I kappa B kinase (IKK) activity or upstream proteins of IKK, such as TAK1, TAB1-3, and NEMO, and/or AMPK directly inhibits the DNA-binding activity of NF-κB [46]. In addition, berberine inhibits AP-1 binding, which is related to the expression of COX-2 [3].

Recently, we conducted a GeneChip analysis and found eukaryotic translation initiation factor 3 subunit F (*EIF3F*) and mucosa-associated lymphoid tissue protein 1 (*MALT1*) as genes that are increased by allergic reactions and suppressed by berberine in mast cells [8]. In addition to allergen-stimulated mast cells, the expression (gene and protein) of MALT and E1F3F was increased in the skin of dermatitis mice and was inhibited by berberine treatments [8]. Treatment with siRNA for *MALT* and *E1F3F* decreased the expression of not only MALT and E1F3F but also cytokines (MIF and IL-4) [8]. EIF3F is involved in the initiation of protein synthesis [47-49]) and FcεRI-mediated cytokine (e.g. IL-4) production by mast cells [50,51]. MALT1 controls the signaling to NF-κB,[52] which is involved in the expression of cytokines (e.g. MIF) [53]. Thus, these findings suggest that berberine regulated proinflammatory cytokine expression through the inhibition of the expression of *MALT1* and *E1F3F* in mast cells.

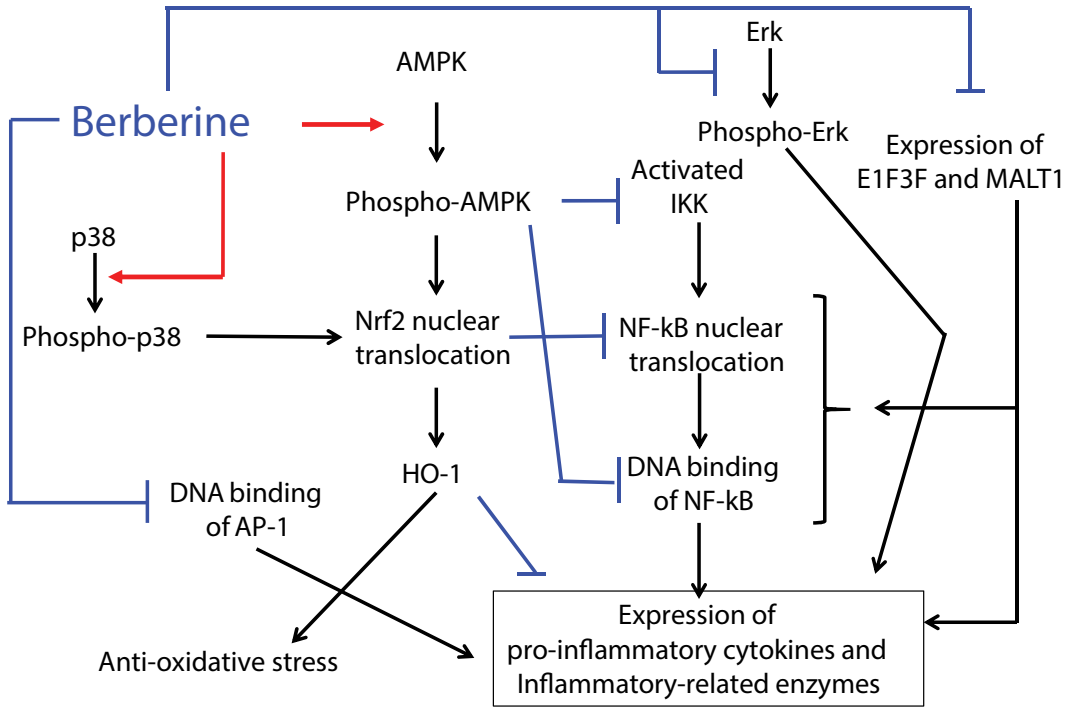

Figure 3: Schematic illustration of molecular mechanisms of berberine-regulated inflammatory factors expression. Red and blue lines indicate the activation and inhibition, respectively.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor, which regulates downstream target gene expression. The activated and translocated NF-κB induces the expression of proinflammatory cytokines (e.g. IL-1 and IL-6), NOS2 and COX-2 [54]. Nrf2 negatively regulates NF-κB signaling pathway. That is, Nrf2 prevents the IκB-proteasomal degradation and inhibits NF-κB nuclear translocation [55]. Since berberine activates Nrf2 [31,56,57], berberine inhibits the production of pro-inflammatory-related factors through Nrf2. In addition, heme oxygenase-1 (HO-1) has anti-inflammatory and anti-oxidative stress [58]. The expression of HO-1 is mediated by the activation of Nrf2 [59]. Berberine inhibits the expression of proinflammatory cytokines through the increase of HO-1, which is mediated by the promotion of the translocation of Nrf2 by the activation of AMPK and p38 [31,56,57].

The Erk pathway is involved in the pathogenesis of atopic dermatitis [60]. Berberine inhibits the proinflammatory cytokinin (e.g., IL-6) through the inhibition of Erk phosphorylation [38].

THE MOLECULAR MECHANISMS OF BERBERINE INHIBITS EPIDERMAL HYPERPLASIA

Most of inflammatory skin diseases (e.g. atopic dermatitis and psoriasis) show epidermal hyperplasia that is seen as a thickening of the epidermis in human patients [61,62] and in mouse models [8,62]. In mouse model of atopic dermatitis [8] and psoriasis [62], berberine inhibits epidermal hyperplasia. Epidermal hyperplasia is based on keratinocyte hyperproliferation. Cell division cycle 6 (CDC6) is an essential regulator of DNA replication and is involved in cell proliferation [63-66]. Recent study has been shown that CDC6 is involved in keratinocytes hyperproliferation [62]. Following to cyclin D expression through Janus kinase (JAK)- signal transducer and activator of transcription (STAT) 3 pathway, the activation of cyclin D-cyclin dependent kinases (Cdk) 4/6-retinoblastoma protein (Rb)-E2F pathway leads the expression of CDC6 [64,67]. Several cytokines (e.g, IL-6 and IL-22), which are activated JAK-STAT3 pathway, are known to be involved in the pathology of skin lesions and keratinocyte proliferation [62,68]. Berberine alleviates keratinocyte hyperproliferation through the inhibition of the expression of CDC6 by the regulation of JAK-STAT3 pathway (Figure 4) [62].

CONCLUSION

In summary, berberine improves skin inflammation through the inhibition of the expression of inflammation-related factors (e.g., cytokine and enzymes) and the induction of anti-inflammatory factors (e.g., IL-10 and HO-1). The activation of AMPK and the inhibition of MALT1 and E1F3F are involved in the anti-inflammatory effects of berberine. In addition, berberine also inhibits epidermal hyperplasia

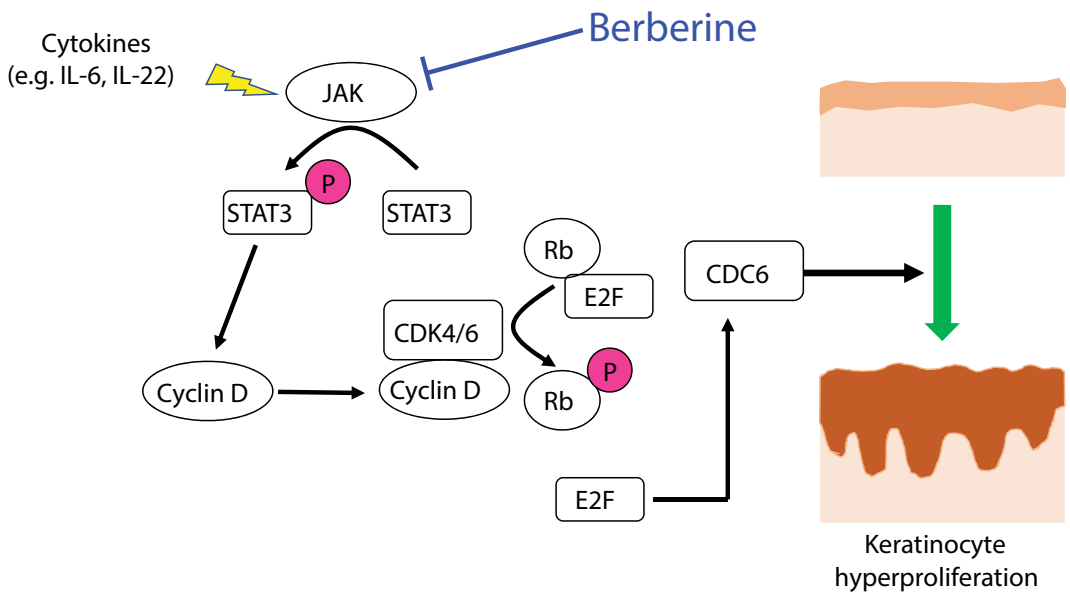

Figure 4: Schematic illustration of molecular mechanisms of berberine-regulated keratinocytes hyperproliferation. The activation of JAK induces the expression of cyclin D following to STAT3 phosphorylation. Cyclin D-CDK4/6 complex phosphorylates Rb and increases CDC6 expression following the activation of E2F. CDC6 accelerates keratinocyte hyperproliferation. Berberine inhibits the activation of JAK and leads to inhibit keratinocyte hyperproliferation.

through the inhibition of CDC6 expression following to inhibit the activation of JAK. These suggest that berberine effectives the improvement of inflammatory skin diseases (e.g. atopic dermatitis and psoriasis).

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INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

CONFLICTS OF INTEREST

The authors of this study declare no conflict of interest in publishing this manuscript.

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