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Functions and Mechanisms of AKBA in Inflammation Diseases and Cancer

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ABSTRACT

Bioactive molecules of traditional Chinese medicine have been gaining great momentum in the past few decades as treatments for many diseases. *Boswellia serrata*, via its active boswellic acids, appears to have promising anti-tumor and anti-inflammatory effects. Acetyl-11-Keto-β-Boswellic Acid (AKBA), is a major constituent and key bioactive molecule among boswellic acids. The potential roles of AKBA have been demonstrated in inflammatory diseases such as arthritis, inflammatory bowel disease, asthma and many types of tumors including glioma, leukemia, myeloma, pancreatic cancer, prostate cancer and other diseases. In this brief review, *in vitro* and *in vivo* functions of AKBA in inflammation diseases and tumors as well as the underlying mechanisms are discussed.

Keywords: AKBA, Boswellic acid, Inflammation, Cancer, Target

Abbreviations: AKBA: Acetyl-11-Keto-β-Boswellic Acid; IKK: IκB kinase; Akt: Protein Kinase B; TNF-α: Tumor Necrosis Factor α; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; MCP-1: Monocyte Chemoattractant Protein 1; VEGF: Vascular Endothelial Growth Factor; MMP-3: Matrix Metalloproteinase-3; LTB4: Leukotriene B4; NASID: Nonsteroidal Anti-inflammatory Drug; LPS: Lipopolysaccharides; ROS: Reactive Oxygen Species; LDL: Low-density Lipoprotein; PGE2: Prostaglandin E2; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; COX: Cyclooxygenase; Erk: Extracellular Signal–Regulated Kinases; DR5: Death Receptor 5; CXCR: CXC Chemokine Receptors; CXCL: Chemokine (C-X-C motif) Ligand

INTRODUCTION

Bowellic acids are a series of pentacyclic triterpene molecules which exist in the *Boswellia* genus. Many researchers have demonstrated that Boswellic acids exert bioactivity both *in vitro* and *in vivo* as the main components of frankincense, which is traditionally used for treating arthritis and wound healing [1-4]. Boswellic acids have been revealed to act as anti-inflammatory and anti-tumor agents partially through inhibition of 5-lipoxygense, topoisomerase and leukocyte elastase [5, 6] and other multiple mechanisms.

Among these Boswellic acids, AKBA is shown to be a major bioactive molecule displaying multiple functions in anti-inflammation and anti-tumor activity. Numerous studies focusing on AKBA have reported the beneficial and curative effects in treating inflammatory diseases and cancer. Published literature suggests that AKBA regulates a variety of molecular targets such as 5-lipoxygenase, NF-κB, LL-37, HIF-1 and other molecules that contribute to inflammation and tumor progression [7-9]. In this review, the *in vitro* and *in vivo* activity of AKBA on several inflammatory diseases and cancer will be discussed. In addition, the putative and possible mechanisms underlying this effective molecule may help tailor the future strategies for fighting against cancer and refractory inflammatory diseases.

Targets and Anti-inflammatory Mechanisms of AKBA

5-lipoxygenase

The resin of *Boswellic serrata* has been used in many countries as traditional medicine to treat inflammatory diseases. AKBA as one of the major constituents of

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Boswellic serrata, has been proved to inhibit 5-lipoxygenase (5-LOX) *in vitro* and in animal models [6,10-15]. Leukotrieneshas been implicated to have proinlfammatory properties in inflammation and hypersensitivity [16,17]. 5-lipoxygenase, as a key enzyme in the leukotriene synthesis, has been developed to be a major target clinically [18]. 5-LOX product from exogenous arachidonic acid of rat peritoneal PMNL, was inhibited by 15μM AKBA. Natural and synthetic analogues of AKBA were tested for inhibiting 5-lipoxygenase in intact rat neutrophils [19]. Moreover, AKBA showed efficient inhibition of 5-lipoxygenase product formation in isolated human neutrophils with IC_{50} of 2.8 to 8.8 μM, while failed to inhibit that of human whole blood [20]. Upon noninhibitory pentacyclic triterpenes such as amyrin, 5-LOX product formation was reversed [21]. As for the underlying mechanism of binding, AKBA was shown to directly target 5-lipoxygenase via a pentacyclic triterpene-selective binding site [11,13]. These researches indicate that AKBA may be a potential drug for 5-lipoxygenase contributing inflammatory diseases.

Human leukocyte elastase

As is the case in many inflammatory diseases, levels of 5-LOX and elastase are increased simultaneously [22]. AKBA was reported to block the activity of human leukocyte elastase (HLE) in a dose-dependent manner *in vitro*, while other leukotriene biosynthesis inhibitors failed to inhibit HLE. In line with inhibition on 5-LOX, AKBA also exerts non-competitive mode of HLE blocking [5,10]. This unique dual inhibition of AKBA on both 5-LOX and HLE might provide us with better understanding about the pathophysiology of many inflammatory disease.

LL-37

LL-37, an antimicrobial peptide, also exerts immunomodulatory effects by induction of cytokines production of many immune and non-immune cells [23]. Macrophage-like cell lines produce TNF-α after LL-37 stimulation [24]. And mast cells release IL-2, IL-4 and IL-6 when stimulated with LL-37 [25]. As the sole member of cathelicidin with the immune modulating property, LL-37 contributes to many autoimmune disease development such as psoriasis, atherosclerosis, systemic lupus erythematosus and rheumatoid arthritis [26]. AKBA has been reported to directly bind to LL-37 using an unbiased target fishing approach and exert the inhibitory effect in a concentration dependent way [9]. Thus, AKBA may be a suitable and potential natural chemical to treat LL-37 associated diseases.

NF-Kb

NF-κB, due to its controlling of many pro-inflammatory and cell proliferation associated genes transcription, is involve in a large number of diseases including inflammatory diseases and cancers. AKBA has been reported to be a natural inhibitor of NF-κB in many studies through several different mechanisms. In PC-3 prostate cancer cells, AKBA was shown to directly bind to IKK, subsequently inhibiting NF-κB signaling pathway [27]. In accordance with this, AKBA was also reported to inhibit TNF-α induction by directly interaction with IKK and followed inhibition of NF-κB in LPS-stimulated human monocytes [28]. AKBA potentiated apoptosis induced by TNF, suppressed TNF-induced invasion and inhibited NF-κB ligand-induced osteoclastogenesis, all of which are considered to require NF-κB activation. However, this inhibition on NF-κB was not observed to act through direct binding to IKK, but through inhibition of Akt [29]. In the case of LPS-challenged $ApoE^{-/-}$ mice, AKBA treatment significantly reduced NF-κB activity and NF-κB-dependent genes such as MCP-1, VEGF, IL-1 and TF, resulting in reduced atherosclerotic lesion size [30]. Targeting NF-κB signaling, a pivotal cause in the pathogenesis of CD18hypo mouse model of psoriasis, with treatment of AKBA, NF-κB-dependent cytokine production, intradermal MCP-1, IL-12 and IL-23 expression as well as the aberrant proliferation of keratinocytes were suppressed and reduced abundantly [31]. These reports indicate that AKBA, as a natural inhibitor of NF-κB, may provide an effective tool for the treatment of many inflammatory diseases and cancers.

Potential Role of AKBA in Inflammatory Diseases

Arthritis

Osteoarthritis (OA) is the commonest form of inflammatory joint disease, characterized by articular cartilage degradation with an accompanying periarticular bone response [32]. Derivatives of boswellic acid have been demonstrated to suppress IL-β induced apoptosis of chondrocytes as well as TNFα induced production of MMP3 by synovial fibroblasts, thus demonstrated a clear therapeutic potential for the treatment of OA [33]. AKBA is a potent inhibitor of 5-lipoxygenase (5-LOX), an enzyme that catalyzes the generation of leukotrienes including LTB4, which is a molecule strongly implicated in osteoarthritis (OA)-associated inflammation [34,35]. Huh Luo Xiao Ling Dan (HLXLD), a Chinese herbal formula containing AKBA has been traditionally used to treat arthritis and other chronic inflammatory diseases [36]. Boswellic acid is reported to attenuate mouse model of osteoarthritis either orally or topically treated [37]. Based on these, several drugs which mainly contain enriched AKBA, have been reported to have therapeutic effects on OA treatment. In a double-blind, randomized, placebo-controlled study, patients who received 5-Loxin (containing 30% enriched AKBA) treatment, showed significantly improvements in pain scores and physical function scores, accompanying reduced synovial fluid matrix metalloproteinase-3 comparing to placebo group [38]. Considering the poor bioavailability of AKBA by oral administration of 5-loxin, a novel *Boswellia serrata* extract Aflapin was developed [39], which contained at least 20% of AKBA. Compared with 5-Loxin, Aflapin treatment increased the availability of alba in systemic circulation of

experimental animals by 51.78%. Also, the inhibition of MMP-3 production was 14.83% better than 5-Loxin [33]. These investigations reveal that AKBA is potential and feasible to treat osteoarthritis as a alternative to NASID which exerts severe side effects such as stomach ulcers, heartburn, headaches, etc [40].

Atherosclerosis

Atherosclerosis is a inflammatory disease featured unresolved chronic inflammation condition [41]. During the inflammatory process of atherosclerosis, leukocyte adhesion and infiltration process lead to intimal arterial plaques formation, plaque rupture, thrombosis and finally occlusion [42]. NF-κB plays an important role in all stages of atherogenesis through genes, membrane and cellular proteins, polypeptides, chemokines and hormonal influence [43]. In the animal experiment, atherosclerosis lesions were induced by LPS injection in $ApoE^{-/-}$ mice. AKBA treatment reduced NF-κB activity and subsequent NF-κB-dependent genes expression such as MCP-1, MCP-3, MIP-2, VEGF and TF. Compared to LPS injection group, AKBA treated group exerted nearly 50% reduction of atherosclerotic lesion size. AKBA treatment did not affect the plasma concentration of triglycerides, total cholesterol, anti oxidized LDL antibodies and various subsets of lymphocyte-derived cytokines, indicating its non-toxicity and safety.

Inflammatory Bowel Disease

AKBA has been reported to attenuate indomethacin-induced ileitis, an experimental model of inflammatory bowel disease (IBD). Leukocyte-endothelial cell adhesive interactions and severe tissue injury were decreased with both low and high dose of AKBA treatment in a concentration-dependent manner [44]. A selective 5-LOX inhibitor, zileuton, was observed to significantly improve healing of dextran sodium sulphate-induced colitis rat model of IBD, through inhibition of neutrophil recruitment. This indicates that inhibitors of 5-LOX may playeffective therapeutic role in treating chronic intestinal inflammation [45]. Sphingomyelin phosphodiesterase (SMase) is regarded to contribute to several inflammation-related diseases including IBD. As a specific inhibitor of 5-LOX, AKBA was found to inhibit and decrease SMase activity and expression in Caco-2 cells, resulting in inhibition of cell proliferation [46]. Besides its effectiveness, AKBA was test for its safety for influence on integrity and function of the intestinal epithelium. 0.027 μg/ml of AKBA was administrated, and reduced NF-κB phosphorylation as well as ROS increased by H_2O_2 exposure, which indicated the antioxidant activity and intestinal epithelium barrier protection from inflammatory damage of AKBA. All together, AKBA is a potential and safe natural product for treating intestinal inflammatory disease including IBD [47].

Psoriasis

Psoriasis is an immune-mediated, chronic inflammatory skin disease which affects about 2-4% of the western population [48]. It is featured by disfiguring erythematous skin lesions covered with white silvery scales and often leads to discrimination of the patients. The relapse and life-long accompany of this disease also result in substantial reduction in the life quality of the patients [49]. Thus, it is urgent to develop medicines that exert few side effects and significant therapeutic effects against psoriasis. In the $CD18^{hypo}$ mouse model of psoriasis, systematically or locally treatment with AKBA was observed to profoundly suppress the NF-κB signaling and the subsequent NF-κB dependent TNF-α production by macrophages. In addition, administration of AKBA also attenuated the intradermal MCP-1, IL-12 and IL-23 expression level in previous skin lesions, which led to resolution of the abundant immune cell infiltrates and reduction of the aberrant proliferation of keratinocytes. All together, AKBA treatment largely improved the psoriasis disease activity score in the $CD18^{hypo}$ mice with a nearly normal phenotype [31]. This finding demonstrates the mechanism which might underly the effectiveness of AKBA for psoriasis treatment.

Several drugs have been developed and even come onto market which containing AKBA as the main effective component, for the treatment of psoriasis as a complementary and alternative medicine. A phase Ⅲ clinical trial of *Boswellia serrata* cream containing 5% of 95%AKBA revealed that 200 psoriasis patients enrolled showed marked improvement. A significant reduction in psoriasis activity severity index (PASI) score as well as biomarkers including TNF-α, VEGF, LTB4 and PGE2 were also observed [50].

Antitumor Effects

Anti-agiogenesis

Angiogenesis is essential for tumor growth and metastasis. There are a plenty of factors involving in the angiogenesis of tumor progression [51]. Fibroblast growth factors are a family of growth factors that are involved in many pathways that can contribute to carcinogenesis, and they also play a important role in angiogenesis. It has been reported that FGF acts synergistically with VEGF to promote angiogenesis and tumor maturation. Thus, targeting FGF is a potential strategy for inhibiting tumor angiogenesis [52]. AKBA was found to inhibit bFGF-induced angiogenesis in a Matrigel Plug Assay. Subcutaneous administration of AKBA for 10mg/kg/d inhibited Matrgel + bFGF-induced angiogenesis significantly comparing with indomethacin and cyclophosphamide at the same dose. Histological examination also revealed inhibition of blood vessels growth in comparison with the controlled group [7]. Besides, AKBA has also been reported to reduce and inhibit angiogenesis in prostate tumor growth and a mouse model of oxygen-induced retinopathy [53,54].

HIF-1

Hypoxia-inducible factor 1 (HIF-1), is a transcriptional activator that is highly involved in cancer pathogenesis and inflammatory disorders. Aberrant upregulation of HIF-1 is associated with aggressive tumor growth angiogenesis and metastasis, which makes it a feature of solid tumors [55]. Therefore, HIF-1 has been validated as a therapeutic target and inhibitors of HIF-1 have been considered to be a potential strategy against cancer [56]. In the screening of HIF-1 inhibitors from frankincense, molecularly imprinted polymer (MIP) was used. With quercetin, a known inhibitor of HIF-1, as the imprinted polymer, AKBA was then retained by solid phase extraction on MIP. AKBA effectively inhibited HIF-1 transcriptional activity and HIF-1α induction at concentration larger than 10Mm [57].

mi-RNA

AKBA has been reported to modulate miRNAs both *in vitro* and *in vivo*. In HCT116, HT29, SW480, and SW620 CRC cell lines, expression levels of let-7 and miR-200 families, which are putative tumor-suppressive mi-RNAs, were significantly up-regulated when treated with AKBA. Downstream targets of let-7 and miR-200, such as *CDK6*, *vimentin* and *E-cadherin*, were subsequently regulated. As in the case of orthotpoic CRC mouse model, the regulations of let-7, miR-200 and their target genes were identical with that in vitro [58]. In spite of let-7 and miR-200, AKBA has been reported to regulate miR-34a and miR-27a as well. In CRC cell lines including HCT116, RKO, SW480, SW620, HT29 and Caco2, AKBA inhibited cell proliferation, induced apoptosis and cell cycle arrest. Using gene expression array and *in-silico* analysis, miR-34a and miR-27a and their target genes were found to be regulated by AKBA. Furthermore, in a mouse xenograft model, AKBA showed tumor growth inhibition, which was consistent with *in vitro* findings [59]. These novel evidences of AKBA's anti-tumor effects via epigenetic machinery modulation provide a new insight into the application of AKBA.

Topoisomerase

In HL-60 AND CCRF-CEM cell lines, AKBA significantly reduced cell counts and thymidine incorporation in a concentration-dependent way, with its IC_{50} being 30μM. Then, in a DNA relaxation assay, AKBA was found to inhibit topoisomerase I at the concentration of from 10μM, suggesting that induction of apoptosis in these two leukemia cell lines by AKBA may be due to inhibition of topoimerase I [60].

AKBA has been reported as well to inhibit STAT-3 activation in human multiple myeloma cells [8].

AKBA Functions as an Anti-Tumor Agent

Glioma

AKBA has been demonstrated to exert the cytotoxic effect against malignant glioma cell lines including both long-term and glioma initiating cell lines by inducing apoptosis at low concentrations with approximate EC_{50} value being 20μM. This toxicity was obtained by inducing p53-dependent p21 expression, supporting by ectopic expression of p53. Nevertheless, treatment with AKBA of subtoxic concentration didn't interfere with the toxicity of other anti-cancer drugs toward glioma cells in acute cytotoxicity or clonogenic cell death assays. This indicates the effectiveness and safety of AKBA on human malignant glioma cells and makes AKBA a possible adjunct for the treatment of human malignant glioma [61]. In recent days, AKBA has been considered a useful adjunct agent for treating brain metastasis [62] and glioblastoma [63].

Colorectal cancer (CRC)

Colorectal cancer is the third most common cancer and the fourth most common cancer cause of death globally, accounting for roughly 1.2 million new cases and 600,000 deaths per year. The therapy for CRC patients with stage III/IV and high-risk stage II colon cancer are adjuvant chemotherapy [64]. AKBA has been reported to have chemoprevention effects on colorectal cancer both *in vitro* and *in vivo*. In the cases of CRC cell lines, AKBA induced HT-29 apoptosis slightly at the concentration of 30μM. It was observed that AKBA treated cells showed Akt activation by Ser473 and Thr308 phosphorylation. Inhibitors of PI3K pathway sharply enhanced AKBA induced HT-29 apoptosis, indicating that AKBA might induce CRC cell apoptosis through PI3K/Akt pathway [65]. Besides, AKBA was found to largely up-regulate let-7 and miR-200 expression in CRC cell lines, accompanied by modulated downstream target genes expression such as *CDK6*, *vimentin* and *E-adherin*. This was supported by the orthotopic CRC mouse model where AKBA modulated downstream target genes of let-7 and miR-200, suggesting that AKBA might modulate epigenetic machinery to achieve its anti-cancer activity [58].

AKBA was also demonstrated to inhibit colorectal cancer progression or intestinal adenomatous polypsis in animal models. Orthotropic human CRC mouse model orally administrated with AKBA exhibited decreased tumor volumes without significant body weight loss compared to vehicle treated group. In addition, AKBA suppressed ascites and metastasis of tumors to the liver, lung and spleen. Biomarkers of tumor including Ki-67, CD31, NF-κB, COX-2, cyclinD1, MMP-9 and VEGF were also inhibited by ABKA [66]. In $APC^{min/+}$ mice which is another human CRC mouse model, gavage administration of AKBA decreased polyps by approximately 50% both in the small intestine and colon, along with prevention of malignant progression of these polyps [67]. There is considerable evidence that aspirin is potential for prevention of colorectal cancer. Also, broader clinical recommendations for aspirin-based

chemoprevention strategy have been recently established [68]. However, in the *APC*$^{min/+}$ mouse model, AKBA exerted more potential prevention of small intestinal and colonic polyps than aspirin. And this efficacy of AKBA might contribute to its modulation of Wnt/β-catenin and NF-κB/COX-2 pathways [69].

Leukemia

AKBA has been reported to inhibit the proliferation and induce the apoptosis of several leukemia cell lines including HL-60 cells and CCRF-CEM cells [70-72]. DNA, RNA and protein synthesis were significantly inhibited by AKBA with IC_{50} values of 0.6, 0.5 and 4.1μM respectively [70]. AKBA induced HL-60 and CCRF-CEM cells apoptosis in a dose-dependent manner, which might be due to topoisomerase I inhibition [60,73]. These suggest that AKBA might be a promising approach for acute myeloid leukemia, though still needsmore investigations.

Hepatocellular carcinoma

In liver cancer HepG2 cells, AKBA decreased cell viability as well as [3H] thymidine incorporation, and strongly induced apoptosis accompanied by activation of caspase-3, caspase-8 and caspase-9 [74]. Dose-dependent increase in caspase-3 activity, TNF-α level and IL-6 level was observed in HepG2 cells. Besides, AKBA protected anti-cancer drug Doxorubicin induced hepatic toxicity in Wistar rats [75].

Meningioma

Meningioma cells established from surgically removed meningioma specimens, when treated with AKBA, exhibited decrease in viable cells and inhibition of Erk-1/2 pathway [76].

Prostate cancer

Prostate cancer is the most common malignancy in men and a major cause of cancer deaths contributing to 1-2% deaths in men [77]. Since reduction of androgen stimulation in prostatic cells is one of the main treatment strategies for prostate cancer and expensive drugs for this disease, new agents targeting this disease in a different mechanism are needed to be developed.

AKBA has been reported to inhibit chemoresistant androgen-independent PC-3 prostate cancer cells proliferation and elicit cell death *in vitro* by specifically inhibiting IKK activity and NF-κB signaling pathway. Topical application of AKBA on PC-3 tumors xenograft and nude mice implanted with PC-3 tumors inhibited tumor growth without systemic toxicity [27]. As androgen receptor-mediated signaling is crucial for the progression and development of prostate cancer, AKBA was demonstrated to inhibit androgen receptor by interruption on Sp1(specificity protein 1) binding activity in prostate cancer cells [78]. Sp1 was suggested to be a possible target for treatment of prostate cancer for use of natural and synthetic compounds used to inhibit Sp1in prostate cancer [79]. In addition, human prostate tumor xenograft mice treated with AKBA shoed reduced tumor growth, which was well correlated with suppression of angiogenesis. *In vitro* experiment showed that AKBA inhibited VEGFR-2 phosphorylation and downstream protein kinases, indicating that AKBA might inhibit prostate tumor growth via intercepting VEGFR2 signaling pathway [53].

A novel mechanism of AKBA inhibition of prostate cancer cell lines was demonstrated as well. AKBA elicited apoptosis of LNCaP and PC-3 cells at concentrations above 10μg/ml. Caspase-8 was activated in AKBA treatment, which correlated with DR5 increase. Knocking down of DR5 by its shRNA inhibited AKBA-induced prostate cancer cell apoptosis and caspase-8 activation, suggesting that AKBA may induce apoptosis in prostate cancer cells through a DR-5-mediated pathway [80].

The anti-prostate cancer effect of AKBA through multiple targets and pathways demonstrates that AKBA has a large potential in strategies for treating prostate cancer.

Pancreatic cancer

Targeting CXCR4/CXCL12 pathway has been considered a promising strategy for treating tumor growth and metastasis of many types of cancers [81]. AKBA has been reported to suppress CXCR4 expression in PANC-28 cells *in vitro* and in orthotopic pancreatic cancer mouse model, with reduced tumor growth and metastasis [82,83]. Besides, pancreatic cancer cell lines including AsPC-1, PANC-28, MIA PaCa-2 cells proliferation were inhibited by AKBA treatment, which correlated with NF-κB and its modulating target genes suppression. In the orthotopic human pancreatic animal model, AKBA also down-regulated Ki-67, CD31, COX-2, MMP-9 and VEGF expression [82].

CONCLUSIONS

This reviewed data suggest that AKBA can target and regulate multiple cell signaling pathways which contribute to the pathogenesis and development of inflammatory diseases and various types of tumors. These functions of AKBA make it a potential and useful natural molecule for treatment of many diseases including arthritis, inflammatory bowel disease, psoriasis, colorectal cancer, glioma, leukemia, prostate cancer and also as a alternative to NASID. In spite of the efforts that have been made through different methods including nanomicelles loaded with AKBA and transdermal microemulsions, there remains improvement for higher bioavailability of AKBA *in vivo*. Although the anti-inflammatory and anti-cancer effect of AKBA have been demonstrated *in vitro* and *in vivo*, resolving the problem of AKBA's bioavailability and enhancing its bioactivity in human patients will endow AKBA with more applications clinically in the future.

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