Glucocorticoids restrain bronchial epithelial wound repair by decreasing fibroblasts keratinocyte growth factor expression

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Abstract: Glucocorticoids (GCs) are a first line drugs for asthma due to its inhibitory effects on airway inflammation, but they also restrain the repair of airway epithelial injury. Keratinocyte growth factor (KGF) is a kind of paracrine growth factors and abnormal expression of KGF has been involved in wound-healing defects. Several studies showed GCs reduced KGF transcription and secretion in vivo and in vitro. This work aimed to investigate the role of KGF in GCs induced inhibitory effects on bronchial epithelial wound repair. Human bronchial fibroblasts (FBs) obtained from non-asthmatic volunteer subjects were treated with different concentrations of dexamethasone (Dex) for 24 h or 100 nM Dex for different time periods, then the mRNA expression and concentration of KGF in culture medium were determined using qRT-PCR or ELISA. In addition, FBs were treated for 12 h with IL-1α (10 ng/ml), or TGFα (15 ng/ml) in the presence or absence of 100 nM Dex, and the mRNA levels of KGF were also measured. The culture medium from FBs stimulated with IL-1α in the presence or absence of Dex was collected and its effect on proliferation, migration, wound healing and MAPK pathway activation of human bronchial epithelial cells (BECs) was evaluated using CCK-8, transwell, wound closure and western blotting assays respectively. Dex remarkably suppressed not only basal KGF expression and secretion in FBs in a time- and dose-dependent manner, but also KGF expression stimulated with IL-1α and TGFα. The culture medium from FBs stimulated with IL-1α in the presence of Dex significantly promoted the proliferation, migration and wound healing, as well as p38 and Erk1/2 activation of BECs, whereas culture medium from FBs stimulated with IL-1α and Dex has no significant influence on these cell actions. In addition, blockage of KGF function using KGF receptor inhibitors or specific antibodies abolished the facilitating effects of culture medium from FBs on the proliferation of BECs and addition of KGF ameliorated the effect of culture medium from FBs stimulated with IL-1α and Dex on the proliferation, migration, wound healing, and p38 and Erk1/2 activation of BECs. In conclusion, the adverse impact of Dex on airway epithelial wound healing is at least partially due to its inhibition effect on KGF expression and secretion by FBs.

Keywords: Asthma, glucocorticoids, keratinocyte growth factor, fibroblasts, epithelium

Introduction

Asthma is a disease of chronic airways inflammation and affects more than 300 million people world-wide, which imposes a heavy social and economic burden on individuals, families and countries [1]. Airway inflammation and remodeling are two well-documented pathologic character of asthma. Due to its anti-allergy, anti-inflammatory and immunosuppressive pro-perties, glucocorticoids (GCs) are the first-line drugs used to control asthma symptoms. Epithelial damage is also a characteristic feature of asthma [2, 3], which accelerates the penetration of environmental insults. Evidence have been presented that GCs hinder the repair process of airway epithelial injury by inhibiting early-stage epithelial cells migration and proliferation [4, 5], whereas the molecular mechanisms responsible for the adverse effects of GCs on these processes remain largely unknown.

It is well documented that epithelial-mesenchymal interactions play a vital role in regulating epithelial injury repair and this interplay con-
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sists of three basic processes: production of soluble factors exhibiting autocrine and paracrine activities, cell-matrix interactions and signaling by direct cell-cell contact [6]. Keratinocyte growth factor (KGF), a member of the fibroblast growth factor (FGF) family, is a typical paracrine acting growth factor. KGF is produced by mesenchymal cells including fibroblasts, endothelial and smooth muscle cells and was found to be overexpressed during epithelial wound healing [7-9]. Accumulating studies have demonstrated KGF to be a protein mitogen for KGF receptor (KGFR)-positive epithelial cells and can restrain epithelium apoptosis and promote them differentiation [8, 10, 11]. Moreover, abnormal expression of KGF or absence of KGFR has been involved in defective wound healing. Maria Brauchle et al. reported that GCs treatment suppressed KGF expression in cultured fibroblasts and in mice with severe wound healing abnormality [12]. Marcio Chedid also found GCs decreased not only basal KGF expression, but also KGF expression stimulated by IL-lα, PDGF-BB, and TGFα as well, which might contribute to the impaired healing process associated with GCs use [13].

Based on the previous findings and discussion, we hypothesize GCs may restrain the repair of bronchial epithelial damage during asthma through inhibiting the secretion of KGF by fibroblasts. To test this, the isolated bronchial fibroblasts from non-asthmatics patients were administrated with GCs and the expression and secretion of KGF were measured using qRT-PCR and Elisa methods. Then, the cultured medium was collected and its influence on the proliferation, migration and wound healing of human bronchial epithelial cells (BECs) was evaluated using CCK-8, transwell and wound closure assays. In addition, the activation of mitogen-activated protein kinases (MAPKs) was detected by western blotting.

Materials and methods

Isolation and culture of human bronchial fibroblasts

Fibroblast cell lines were established from lung tissue obtained from patients undergoing resection of localized lung tumors. The experiment was approved by the hospital ethics committee and informed consents were obtained from all patients. The specimens obtained from adult male patients after total pneumonectomy were stored in sterile containers at 4°C. About 5 g of normal lung tissue was cut from the specimens and washed with PBS (pH 7.4) for several times. The bronchioles were isolated and cut into particles of < 1 mm³, which were implanted into 100 mm × 20 mm petri dishes containing 5 mL of DMEM medium supplied with penicillin (100 U/ml), streptomycin (100 μg/ml) and 10% FBs, and incubated at 37°C in a humidified atmosphere of air containing 5% CO₂. The culture medium was replaced every three or four days. The cell growth was observed under an inverted microscope, and the contamination of cancer cells was excluded. Fibroblasts were digested and dissociated using 0.25% trypsin and 0.53 mmol/L edetate disodium after reaching above 80% fusion and were carried on the passage with the ratio of 1:3. After repeated passage in common culture conditions, the doped macrophages and endothelial cells were naturally disappeared. Cultured fibroblasts were characterized by immunofluorescence and greater than 95% of the cells were stained positively for vimentin and human fibroblast antigen Ab-1. Cells at early passages (3 to 5) were used as described below.

Dexamethasone administration and KGF bioassay

Cultured fibroblasts were grown to confluency and subsequently incubated with serum-free DMEM for 12 h. Then different concentration of dexamethasone (Dex, D1756, Sigma) was added to the medium and cultured for different time periods. At the end of cell culture, the culture supernatants were collected for further use and determination of KGF secretion using ELISA kits (R&D Systems, Minneapolis, MN) according to the manufacturer’s instructions. KGF secretion was expressed as pictograms KGF per microgram of protein in the cell monolayer. The mRNA expression of KGF was measured using qRT-PCR as described below. In addition, to determine the effect of Dex on KGF expression in fibroblasts under stimulation of IL-lα and TGFα, the starved cells were treated with 10 ng/ml of IL-lα or 15 ng/ml of TGFα in the presence or absence of 100 nM Dex for 12 h, and then KGF mRNA expression was measured.
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qRT-PCR

Total RNA isolation from fibroblasts was performed using RNaio plus kit (TaKaRa). RNA purity and degeneration were determined using spectrophotometer and agarose gel electrophoresis. Then 2 μg of total RNA was reverse transcribed using the GoScript™ Reverse Transcription System (Promega) according to the manufacturer’s instructions, and then 1 μl of cDNA was used to perform quantitative real-time PCR (qRT-PCR) using SYBR® Premix Ex Taq™. The reaction system was constructed as the manufacturer’s recommendations. PCR reactions were performed for 30 cycles with denaturing at 95°C, annealing at 58°C, and extension at 72°C. β-actin was used as a reference for quantification, and the relative KGF expression level was calculated using the 2^ΔΔCt method. The primer sequences were as follows: KGF, F 5’-CACCAGGGCAGACAAACAGAT-3’ and R 5’-GTAAGTTCAGTTGGCTGTGACGCT-3’; β-actin, F 5’-GCTGGAAGGTGACAGCGAG-3’ and R 5’-TGGCATCGTGATGGACTCCG-3’ (Shanghai Institute of Biochemistry, China).

Culture of bronchial epithelial cells

The simian virus 40-transformed epithelial cell line 16HBE 14o_ derived from human bronchial epithelial cells (BECs) were obtained from the ATCC (Rockville, MD) and cultured in MEM (GIBCO) supplemented with 10% FCS, 1 mM glutamine, 1% penicillin/streptomycin solution (10,000 U/ml), and 25 mM HEPES (Invitrogen, Shanghai, China) in a humidified 5% CO₂ atmosphere at 37°C. The cells were passaged at 80%-90% confluence using 0.25% trypsin, 1 mM EDTA (GIBCO-BRL).

CCK-8 assay

Cell proliferation was evaluated using CCK-8 kits (Beyotime, China) according to the manufacturer’s instructions. Briefly, BECs were serum-starved for 12 h and then exposed to various factors as indicated for 48 h. In order to exclude the effect of Dex on cell proliferation, the culture medium of fibroblast treated with 100 nM of Dex for 24 h (FB CM (Dex)), and a combination of FB CM (Dex) and 10 ng/ml KGF (FB CM (Dex) + KGF) respectively. The migration of BECs was determined using transwell and wound closure assay. In the transwell assay, serum starved BECs were plated in the upper chamber of a transwell unit (Corning Inc., Corning, NY) at a concentration of 5 × 10⁵/ml. The lower chamber was filled with 600 μl of fresh culture medium (CM), fibroblast culture medium (FB CM), culture medium of fibroblast treated with 100 nM of Dex for 24 h (FB CM (Dex), and a combination of FB CM (Dex) and 10 ng/ml KGF (FB CM (Dex) + KGF) respectively. After incubated for 24 h at 37°C, the cell migrated through the permeable membrane were fixed with 4% paraformaldehyde, stained with Giemsa and counted under microscope in five randomly chosen fields. In the wounding-healing assay, HBES were seeded in 24-well plates at a density of 5 × 10⁵ cells per well. After the cells reached approximately 80%-90% confluence, a straight line was made across the center with a sterilized pipette tip. After washed with PBS, the cells were cultured with CM, FB CM, FB CM (Dex) and FB CM (Dex) + KGF respectively. Images of the wound area were recorded using a fluorescence microscope, immediately after wounding and after culturing for 24 h. Wound closure rate of each group was measured and calculated using image J software.

Western blotting

At the end of cell culture, the cells were collected and lysed in RIPA lysis buffer (Beyotime Inc., Nanjing, China) supplied with protease inhibitors (10 mg/ml aprotinin, 1 mM PMSF, 10 mg/ml leupeptin), and phosphatase inhibitors (1 mM sodium orthovanadate, 20 mM sodium pyrophosphate, 0.5 M NaF) at 4°C, and the total protein concentration was measured using a BCA protein assay kit (Applygen, China). Then, equal amounts of protein were separated on 10%-15% SDS polyacrylamide gels and transferred onto a PVDF membrane (Thermo Fisher Scientific, USA). After blocking, the membrane was incubated with anti-Retinoblastoma susceptibility gene product (Rb), Cdk2, cyclin D1, p15, p27 antibodies (Santa Cruz Biotechnology) and anti-p38, Erk1/2 and JNK1/2 anti-
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bodies (Abcam) at 4°C for 24 h. After 3 × 10 min washes with TTBS, the membranes were incubated with HRP-labelled second antibody for 1 hour at room temperature. The separated proteins were visualized using ECL kits (Amersham) and the optical density of these protein bands was quantified using the ImageJ software, using β-acting (Abcam) as an internal control.

Statistical analysis

All the experiments repeated at least for three times and data were expressed as the mean ± SD. The difference between two groups were analyzed using Student’s t-test, and P-values less than 0.05 and 0.01 were considered to be statistically significant.

Results

GCs suppress FBs KGF expression and secretion

Evidence showed that GCs hinder the repair process of airway epithelial injury by inhibiting early-stage epithelial cells migration and proliferation, whereas the molecular mechanisms remain largely unknown. KGF is a key paracrine growth factor and has been documented to promote epithelial proliferation, differentiation and migration. Thus we suspected that GCs
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might indirectly inhibit the proliferation and migration of epithelial cells through decreasing the expression of KGF by stromal cells. To test this, human FBs obtained from non-asthmatic volunteers were treated with 100 nM of Dex for different time periods or different concentrations of Dex for 24 h, and then KGF expression and secretion were determined using qRT-PCR and ELISA assays. It was found that Dex significantly decreased basal KGF expression and secretion in a dose- and time-dependent manner (Figure 1A-C). The expression of growth factors is increased in asthma due to the activation of fibroblasts by the inflammatory microenvironment. Here, we demonstrated IL-1α or TGFα simulation markedly increased KGF expression, which was also attenuated by Dex treatment (Figure 1D).

**GCs indirectly inhibit the proliferation of BECs by decreasing FBs KGF production**

To test whether FBs modulate epithelial proliferation through KGF secretion, the culture medium of FBs was collected after incubated for 24 h in the absence or presence of 100 nM of Dex. The proliferation of BECs was determined using CCK-8 kits after cultured for 48 h. It was found that compared with control, Dex-free culture medium of FBs (FBs CM) significantly promoted the proliferation of BECs, whereas culture medium of FBs containing Dex, FBs CM (Dex) did not show significant influence on the growth of BECs (Figure 2A). In addition, blockage of KGF using anti-KGF antibodies or KGFR inhibitors abolished the facilitating roles of FBs CM on BECs proliferation, indicating that the proliferation promoting effect of FBs CM on BECs was at least partly due to KGF. Furthermore, addition of KGF into FBs CM (Dex) restored the enhancement effect of FBs CM on BECs proliferation, which suggested that GCs indirectly inhibited BECs proliferation by decreasing FBs KGF production (Figure 2B). The effect of these culture media on the expression of proteins associat-
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ed with proliferation in BECs was detected using western blotting. It was found that FBs CM and FBs CM (Dex) + KGF significantly increased the expression of cyclin D1 and active form of cdk2, and Rb hyper-phosphorylation as well, while decreased p27 protein level (Figure 2C, 2D).

GCs indirectly suppress the migration of BECs through reducing FBs KGF secretion

Epithelial injury repair is a complex physiological process, which is constructed with cell extension, migration and proliferation. As the accelerating effect of KGF secreted by FBs on BECs proliferation has been confirmed, next we determined the influence of KGF derived from FBs on the migration of BECs using transwell and wound closure assays. It was observed that compared with the fresh medium (CM), culture medium of FBs (FB CM) observably facilitated the migration and wound healing, whereas culture medium from FBs treated with Dex, FB CM (Dex) had no significant influence on BECs migration (Figure 3). However, the combination of FB CM (Dex) and KGF could increase the number of migrated cells and wound closure rate (Figure 3), indicating that GCs could indirectly suppress the migration of BECs through reducing FBs KGF secretion.

GCs indirectly restrain p38 and Erk activation in BECs through downregulating FBs KGF production

One signaling pathway linked to growth factor response is comprised of the MAPK and the activation of p38 and Erk1/2 has been impli-
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Figure 4. KGF derived from FBs mediated the adverse effect of glucocorticoids on the activation of MAPK in BEC. BEC were serum-starved overnight (16-18 h) at 80-90% confluence and stimulated with the indicated agents, CM, FB CM, FB CM (Dex) and FB CM (Dex) + KGF (20 ng/ml) for 6 h. The status of active p38, JNK, and ERK1/2 was determined by Western blotting. The experiment was repeated three times with similar results. A. Representative protein bands measured with Western blotting. B. The intensity of individual bands was quantified using Image J software and expressed relative to β-actin signal as a control. *P < 0.05 and **P < 0.01 compared with control. &P < 0.05 and &&P < 0.01 compared with FB CM (Dex).

Discussion

Bronchial asthma (asthma) is a chronic airway inflammation characterized by airway inflammatory cell infiltration, airway hyperresponsiveness, mucus hypersecretion and airway remodeling. According to the latest version of the Global Initiative for Asthma (GINA), approximately 300 million people are suffering from asthma. Although clinical symptoms in most patients with asthma have been effectively controlled through the standardized treatment recommended by GINA, asthma is still a heavy burden on countries, families and individuals, especially children with asthma. Therefore, it is of great significance to explore the pathogenesis of asthma and to search for new therapeutic targets.

Glucocorticoids (GCs), mainly secreted by the adrenal cortex, are an important stress hormone in the body and are commonly used in clinical anti-inflammatory drugs. GINA and Guidelines for the Prevention and Treatment of Childhood Asthma in China both advocates inhaled corticosteroids (ICS) as the most effective drug for the treatment of bronchial asthma and chronic airway inflammation. GCs as the first-line drugs for the treatment of asthma, although can effectively relieve asthma symptoms, improve lung function, reduce airway hyperresponsiveness and eosinophilic inflammation, but also can inhibit the repair of the damaged airway epithelium [4]. Airway epithelium, as a physical barrier against external inflammatory and physical insults, plays an important role in the pathogenesis of asthma. Epithelial damage is a common finding in bronchial biopsies of patients with asthma, even when clinical dis-
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...e is judged to be mild [14-16]. Injuries to the airway epithelium facilitate the entry of pathogens into the bodies to cause respiratory tract infections and asthma attacks, even tissue damage [17, 18]. In addition, epithelial damage has also been related to disease chronicity, severity, altered epithelial phenotype, bronchial hyperreactivity and airway remodeling [19, 20]. Thus, the recovery of an intact epithelium is necessary for functional recovery and tissue homeostasis.

The inhibitory effect of GCs on the repair of injured epithelium has been observed in various tissues, including bronchus. Shin-ichi Ishimoto et al. reported systemic administration of GCs caused obvious healing impairment in perforated tympanic membrane (TM) of rats, and histologic studies of injured TM found epidermal migration was markedly inhibited by GCs treatment and no hyperplasia was observed in any layer at the perforation edge [21]. Zhou Fu et al. demonstrated that GC dexamethasone (Dex) significantly inhibited the proliferation and migration of a human airway epithelial cell line in vitro and delayed the repair of the airway epithelium in ovalbumin-induced mouse model of asthma [22, 23]. The deleterious effect of GCs on the wound healing process was traditionally attributed to the anti-inflammatory action of these steroids. Studies also demonstrated that GCs regulate the expression of various key regulatory molecules in wound repair process at the wound site, including cytokines, growth factors, enzymes, and extracellular matrix molecules [24]. Olivera Stojadinovic et al. compared the transcriptional profiles of cultured primary human keratinocytes in the absence and presence of DEX for 1, 4, 24, 48, and 72 h using large scale microarray analyses and found that GCs treatment influence the wound healing, tissue remodeling and scar formation by inhibiting cell motility, the expression of the proangiogenic factor, vascular endothelial growth factor, TGF1 and -2, MMP1, -2, -9, and -10 and inducing TIMP-2 expression [25]. A recent review by Emira Ayroldi et al. recommended GCs receptor modulator and GCs induced leucine zipper (GILZ) as targets for eschewing the side effects of GCs [26]. Zhou Fu et al. found GILZ gene silence significantly mitigated the inhibitory effect of Dex on the phosphorylation of Raf-1, Mek1/2, Erk1/2, proliferation and migration of a human airway epithelial cell line, and maintained the airway epithelium integrity of the asthmatic mice treated with Dex [22, 23].

After epithelial injury, the surviving epithelial cells at the edge of the wound dedifferentiate, spread, migrate, proliferate and finally re-differentiate to reignite the epithelium [27]. These responses by epithelial cells may be regulated by the signals from underlying mesenchymal cells. It was found that lung fibroblasts (FBs) could accelerate wound closure in primary human alveolar epithelial cells (AECs) monolayers and in a co-culture system with FBs mainly through hepatocyte growth factor (HGF)/c-met signaling [27]. Keratinocyte growth factor (KGF) is another growth factor derived from FBs and has been documented to plays a vital in the restore of injured epithelium in lung through promoting epithelial cell proliferation, spreading, migration [28-30]. It was found that KGF could increase wound closure of primary cultures of human bronchial epithelial cells (HBEs) and a cell line of human airway epithelial cells, Calu 3 and overcame the inhibition of repair due to physiological levels of cyclic strain [31]. In addition, administration of KGF to mouse recipients of heterotopic syngeneic tracheal transplants led to more rapid repair of the tracheal epithelium, which was abrogated by blocking cytokeratin 5 positive circulating epithelial progenitor cells [32]. Moreover, intravenous administration of KGF into rats with chronic allergic asthma markedly limited the allergen-induced alterations in epithelium integrity [33]. Recently, in the ex vivo perfused human lung, it was found that the restorative function of intra-bronchial instillation of human mesenchymal stem cells on alveolar fluid clearance following endotoxin-induced lung injury is partly due to the release of KGF [34].

It was documented that GCs treatment could reduce KGF mRNA level in cultured FBs and rats with skin injury [12]. Marcio Chedid et al. also found GCs inhibited not only basal expression of KGF in primary dermal FBs, but also KGF expression stimulated by IL-1α, PDGF-BB, and transforming growth factor (TGF)α as well [13]. Shin-ichi Ishimoto et al. applied KGF, TGFα and basic fibroblast growth factor (bFGF) to the perforated tympanic membrane (TM) of rats in which wound healing had been impaired by systemic administration of GCs. Histologic...
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studies found only KGF induced marked hyperplasia in the epithelial layer at the perforation edge and improved epidermal migration in the TM [21]. Thus, we speculated that the deleterious effect of GCs on the wound healing of bronchial epithelium during asthma was partly due to its inhibitory effect on KGF production by bronchial FBs. Here, we found the mRNA expression and release of KGF by bronchial FBs were suppressed by Dex treatment. Since wound closure involves cell spreading, migration, and proliferation, we determined the influence of FBs conditioned medium on the proliferation and migration of HBEs. It was observed that Dex treatment attenuated the facilitating effect of FBs medium on the proliferation, migration and wound closure of HBEs, which was restored by addition of KGF into the medium. The data raise the possibility that KGF plays an important role in GCs induced impaired injury repair in asthma.

The interaction between KGF and KGFR, which are mainly expressed in epithelial cells, activates mitogen-activated protein kinases (MAPKs), including extracellular regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 kinase (p38) [9, 35, 36]. The activation of MAPKs pathways results in a wide range of cellular responses, including proliferation, differentiation, migration and apoptosis, and has been involved in wound healing. It was found that inhibition of ERK1/2 caused delayed wound closure and reduced proliferation in mucociliated human BECs cultures, whereas p38 MAPK inhibitor delayed early wound repair without having a significant effect on proliferation [4]. Zhou Fu et al. demonstrated that Dex induced GILZ inhibited the repair of human airway epithelial cells and ovalbumin-induced asthma airway epithelium injury in rats through suppressing the phosphorylation of Raf-1, Mek1/2, Erk1/2 [22, 23]. Guru-Dutt Sharma et al. found increased expression of KGF in a model of corneal wound healing induced rapid and marked activation of p38 and ERK1/2, and interruption of p38 and ERK1/2 pathways resulted in delayed corneal epithelial wound healing [37]. Here, we found KGF derived from FBs significantly promoted the activation of ERK1/2 and p38, but not of JNK, which was in accordance with previous reports [37, 38]. However, Yongsheng Chang reported KGF induces the expression of sterol-regulatory ele-

ment binding protein-1 through a PI3K and JNK/SREBP-1 pathway in H292 cells and induces cell proliferation and lipogenesis [39]. The reason for this may be that KGF may activate different MAPK pathways in different cell types or species to influence selective functions [38].

In summary, we found that Dex treatment reduced the expression and release of KGF by cultured human FBs. KGF derived from FBs significantly promoted the proliferation, migration and wound healing, as well as p38 and Erk1/2 activation of BECs. Thus, the impaired bronchial epithelial wound healing induced by GCs is at least in part due to its suppressing effect on KGF expression and secretion by FBs.

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Disclosure of conflict of interest

None.

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