MiR-34a Promotes Apoptosis and Inhibits Autophagy by Targeting HMGB1 in Acute Myeloid Leukemia Cells

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Abstract
Background: MiR-34a is identified as a tumor suppressor gene and involved in acute myeloid leukemia (AML) development. However, the regulatory mechanism of miR-34a in AML is unclear. Methods: The expression of miR-34a and HMGB1 in HL-60, THP-1 and HS-5 cells were detected by qRT-PCR and western blot. Lipofectamine 2000 was used to transfect with miR-34a mimics, miR-34a inhibitor, si-HMGB1, pcDNA 3.1-HMGB1, and corresponding controls. The apoptosis and autophagy of transfected AML cells were assessed by flow cytometry and western blot, respectively. Bioinformatics software and dual luciferase reporter assay were applied to predict and verify the target of miR-34a. The effects of miR-34a mimics or si-HMGB1 on chemotherapy-induced autophagy were further explored in HL-60 cells treated with all-trans retinoic acid (ATRA) along with lysosomal protease inhibitors E64d and pepstatin A. Results: MiR-34a was lower expressed and HMGB1 mRNA and proteins were both higher expressed in HL-60 and THP-1 cells compared with that in HS-5 cells. Higher expression levels of MiR-34 and lower expression levels of HMGB1 both significantly promoted apoptosis and inhibited autophagy in HL-60 and THP-1 cells. Dual luciferase reporter system confirmed that HMGB1 was a potential target of miR-34a. Moreover, overexpression of HMGB1 dramatically reversed the promotion of apoptosis and inhibition of autophagy mediated by higher expression level of miR-34a. Higher expression level of miR-34a and lower expression level of HMGB1 both inhibited chemotherapy-induced autophagy by stimulating the LC3 conversion. Conclusion: MiR-34a promoted cell apoptosis and inhibited autophagy by targeting HMGB1. Therefore, miR-34a may be a potential promising molecular target for AML therapy.

Introduction

Acute myeloid leukemia (AML), the most common acute leukemia in adults and a lethal hematological malignancy originated from myeloid progenitor cells, is characterized by...
by the uncontrolled proliferation, diverse clinical presentations and accumulation of dysfunctional hematopoietic progenitors along with blockage in normal hematopoiesis [1, 2]. Chemotherapy with hematopoietic stem cell transplantation for AML is the main treatment and preferred therapy [3]. Along with the high relapse rates in AML patients, the overall 5 year survival rate remains poor, approximately 30%-40%, although great advances in medicine and chemotherapy have been achieved [4]. The main cause of therapeutic failure and poor outcomes is the occurrence of chemotherapy resistance in leukemia cells [5]. Therefore, alternative therapies are urgently needed for patients with AML.

MicroRNAs (miRNAs) consist of a class of small noncoding regulatory RNAs of 19 to 25 nucleotides (nt) that are highly conserved [6]. MiRNAs negatively modulate gene expression at the post-transcriptional level by interacting with 3'-untranslated regions (3'-UTR) of their target gene mRNA, leading to mRNA degradation or translational repression of target gene [7, 8]. Accumulating evidence has demonstrated that miRNAs are closely associated with the regulation of cellular differentiation [9], cell proliferation [10], apoptosis, hematopoiesis [11], angiogenesis and carcinogenesis in various tumors [12]. In addition, miRNAs also function as an important regulator of autophagy, a lysosomal-mediated pathway that contributes to degradation of cell waste proteins and damaged organelles. Numerous studies have revealed that aberrant expressions of miRNAs are involved in AML pathogenesis and development. For example, Favreau et al. found that miR-199b functioned as a tumor suppressor and had prognostic significance in AML [13]. Huang et al. showed that miR-519 enhanced cell proliferation and induced cell apoptosis in AML HL-60 cell line by decreasing the level of RNA-binding protein human antigen R [14]. MiR-34a is the first identified tumor suppressor gene that is lower expressed in many forms of tumors, including breast cancer, lung cancer and AML [15-17]. MiR-34a plays a critical role in many cellular processes including p53-induced cell cycle arrest, apoptosis and other biological behaviors by negatively regulating its target genes [18, 19]. However, the regulatory mechanism of miR-34a in AML is still unknown.

High mobility group box 1 (HMGB1), a highly conserved DNA-binding protein, can repair DNA mismatch and regulate gene transcriptions. HMGB1 is higher expressed in various types of tumors and is closely associated with the inflammatory response, angiogenesis, tumor cells growth, invasion and metastasis [20-22]. It has been manifested that HMGB1 overexpression inhibited cell apoptosis, induced cells growth and functions as an anti-apoptotic protein in leukemia [23]. Additionally, HMGB1 improved chemotherapy resistance to anticancer drugs by inducing autophagy in human myeloid leukemia cells [24]. Therefore, targeting HMGB1 may be a crucial underlying application in leukemia treatment.

In this study, the expression level of miR-34a and HMGB1 were investigated in AML cells. Furthermore, the effects of miR-34a on cell apoptosis and autophagy and the potential mechanism were further investigated in AML cells.

**Materials and Methods**

**Cell lines and culture**

The human leukemia cell lines HL-60 and THP-1 were obtained from the Institute of Hematology at the China Academy of Chinese Medical Sciences (Beijing, China) and the human normal stromal cells HS-5 were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). All cells were cultured in complete medium (RPMI-1640; Invitrogen, Grand Island, NY, USA) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Invitrogen), penicillin (100 U/mL)/streptomycin (100 μg/mL) (Invitrogen), and 2 mM L-glutamine in a humidified air at 37°C with 5% CO₂.

**Cell transfection and treatment**

The synthetic miR-34a mimics, anti-miR-34a and negative control (miR-control) were obtained from GenePharma (Shanghai, China). SiRNA targeting human HMGB1 (si-HMGB1), siRNA control (si-control), pcDNA 3.1-HMGB1, and pcDNA 3.1-control were purchased from Ribobio (Guangzhou, China). After HL-60 and THP-1 cells (5 × 10⁵ cells/well) were cultured in 6-well plates for 24 h, miRNA mimics, miRNA inhibitor,
si-HMGB1, pcDNA3.1-HMGB1 or corresponding controls were transfected into HL-60 and THP-1 cells by Lipofectamine 2000 reagent (Invitrogen) in accordance with the manufacturer’s protocol, respectively. To assess autophagic flux under a stressed condition (chemotherapy), HL-60 cells transfected with miR-34a mimics or si-HMGB1 were treated with 1 μM ATRA (Sigma, St. Louis, MO, USA) for 24 or 48 h. Lysosomal proteases inhibitors, E64d (10 μg/mL; Sigma) and pepstatin A (Pep A) (10 μg/mL; Sigma), were added 2 h before protein extraction, followed by western blot analysis of the LC3 proteins.

Quantitative real-time PCR (qRT-PCR)

Total RNA was extracted from collected cells by using Trizol (Invitrogen) and an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc., Santa Clara, CA, USA) was used to check isolated RNA quality. Whole RNA (500 ng) was reversely transcribed into cDNA by miRNA-specific TaqMan miRNA assay kit (Applied Biosystems, Foster City, CA, USA). qRT-PCR was performed by the SYBR® Premix Ex TaqTMII (Perfect Real Time, Takara, Dalian, China) on a CFX 96 real-time PCR thermocycler (TaKaRa) to detect the expression levels of miR-34a. U6 small nuclear RNA was used as the internal control for miR-34a and the relative miR-34a amounts were performed using the 2^ΔΔCt method. The conditions of qRT-PCR reaction were used as follows: 92°C for 10 min, followed by 40 cycles at 92°C for 10 s and 60°C for 1 min. The miR-34a primers were as follows: forward 5′-GCCCTGGCAGTGTCTTAG-3′ and reverse 5′-CAGTGCGTGTCGTGGAGT-3′.

Western blot assay

HL-60 and THP-1 cells were collected at 48 h post-transfection and lysed in M-PER mammalian protein extraction lysis buffer (Thermo Scientific, Hudson, NH, USA) for 30 min. Then total protein was extracted from collected cells with RIPA lysis buffer (Zhong-Shan JinQiao, Beijing, China). Protein concentrations were evaluated by BCA protein assay kits (CoWin Biotechnology, Beijing, China). Equal amounts of total proteins (40 μg) were subjected to 10% SDS–PAGE and subsequently transferred onto polyvinylidene difluoride membranes (PVDF; Millipore, Boston, MA, USA). Then the PVDF membranes were blocked with 5% milk for 1 h and incubated with primary antibodies (HMGB1 antibody, Bax antibody, Bcl-2 antibody, CytC antibody, Atg5 antibody, LC-3I antibody, and LC-3II antibody) (1:1,000; Cell Signaling Technology, Danvers, MA, USA) and β-actin (1:3,000; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA). Followed by 4°C overnight incubation, the membranes were further incubated with the appropriate horseradish peroxidase (HRP)-conjugated secondary antibody (Santa Cruz Biotechnology) and the protein bands were visualized by chemiluminescence using the ECL reagent (Millipore Corp., Billerica, MA, USA).

Dual luciferase reporter assay

The fragments of 3′-UTRs of HMGB1 mRNA containing the wild-type (wt) and the mutant (mut) binding sites of miR-34a predicted by Targetscan (http://www.targetscan.org/) [25] were cloned into the downstream of firefly luciferase coding gene in the pMIR-Report vector (Ambion Inc., Austin, TX, USA). The constructed luciferase reporters were called as pMIR-LUC-3′-UTR-WT HMGB1 and pMIR-LUC-3′-UTR-HMGB1-MUT. For luciferase assay, when HL-60 and THP-1 cells (5×10^4) were grown in 24-well plates to 80% confluence, miR-34a mimics or miR-control (100 nM) were cotransfected with reporters plasmids (100 ng) into HL-60 and THP-1 cells by Lipofectamine 2000 (Invitrogen). The luciferase activities were measured by using the Dual Luciferase kit (Promega, Madison, WI, USA) after 48 h transfection. Cells transfected with 100 ng pMIR-control vector was used to check transfection efficiency and Renilla luciferase was used as normalization control.

Cell apoptosis

Cell apoptosis was assayed using a commercially available Annexin V/FTC and PI apoptosis detection kit (Invitrogen) and flow cytometry. Briefly, the transfected HL-60 and THP-1 cells were trypsinized, harvested, washed and resuspended with 1 ml of 1 × binding buffer at a final concentration of 1 × 10^6 cells/ml. Then the cells were stained with 5 μl Annexin V/FTC followed by 1 μl PI and incubated in the dark for 15 min at room temperature. The apoptotic cells were analyzed by FACSCalibur flow cytometer (FACScalibur; BD, Franklin Lakes, NJ, USA).

Statistical analysis

The data are showed as the mean ± SD from three independent experiments. Statistical analysis was carried out with Student’s t-test or analysis of variance using Graphpad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA). Differences with P values of < 0.05 were considered to be statistically significant.
Results

**MiR-34a was lower expressed and HMGB1 was higher expressed in HL-60 and THP-1 cells compared with that in HS-5 cells**

To assess the effects of miR-34a and HMGB1 on AML cells, the expression levels of miR-34a and HMGB1 in AML and normal stoma cells were evaluated by qRT-PCR and western blot. The qRT-PCR results showed that the expression of miR-34a was significantly lower (Fig. 1A) and HMGB1 mRNA expression was markedly higher (Fig. 1B) in HL-60 and THP-1 cells than that in HS-5 cells. The western blot results indicated that HMGB1 protein levels in AML HL-60 and THP-1 cells were both dramatically higher than that in HS-5 cells (Fig. 1C and 1D).

**Higher expression level of miR-34a promoted apoptosis of AML cells**

To investigate the roles of miR-34a in the AML development, flow cytometry was used to detect cell apoptosis after the AML HL-60 and THP-1 cells were transfected with miR-34a mimics or miR-control. The flow cytometry results indicated that the apoptosis rates of AML cells HL-60 (Fig. 2A and 2B) and THP-1 (Fig. 2C and 2D) were significantly increased in miR-34a groups in comparison with that in miR-control groups. In addition, western blot results also showed that miR-34a mimics strikingly increased the levels of apoptosis-related proteins CytC and pro-apoptotic protein Bax while remarkably decreased anti-apoptotic protein Bcl-2 levels both in AML HL-60 (Fig. 2E and 2G) and THP-1 (Fig. 2F and 2H) cells compared with that in miR-control groups.

**Lower expression level of HMGB1 promoted apoptosis of AML cells**

si-HMGB1 was used to further evaluate the effect of lower expression level of HMGB1 on apoptosis of AML cells HL-60 and THP-1 using flow cytometry. The flow cytometry results showed that the apoptosis rates of HL-60 (Fig. 3A and 3B) and THP-1 (Fig. 3C and 3D) cells were significantly increased in si-HMGB1 group compared with that in si-control group. Furthermore, western blot demonstrated that lower expression level of HMGB1 significantly improved the levels of Cyt-C and Bax and dramatically reduced Bcl-2 levels both in HL-60 (Fig. 3E and 3G) and THP-1 (Fig. 3F and 3H) cells.

Fig. 1. Expression of miR-34a and HMGB1 in human leukemia cells and normal stroma cells. The expression levels of miR-34a (A) and HMGB1 mRNA (B) in HL-60, THP-1 and HS-5 cells were detected by qRT-PCR. U6 snRNA was used as an internal control. (C and D) The levels of HMGB1 protein in HL-60, THP-1 and HS-5 cells were assessed by western blot. β-actin was used for normalization. Data are presented as mean ± SD. *P< 0.05.
Fig. 2. Effects of higher expression levels of miR-34a on AML cells apoptosis. Cells were transfected with miR-34a mimics or miR-control and cultured for 48h. The apoptosis of HL-60 (A and B) and THP-1 (C and D) cells was evaluated by flow cytometry using an Annexin V/PI detection kit. The levels of apoptosis-associated proteins Cyt-C, Bax, and Bcl-2 in HL-60 (E and G) and THP-1 (F and H) cells were analyzed by western blot and normalized to β-actin. Data are presented as mean ± SD. *P< 0.05.

Fig. 3. Effects of lower expression levels of HMGB1 on AML cell apoptosis. Cells were transfected with si-HMGB1 or si-control and cultured for 48h. The apoptosis of HL-60 (A and B) and THP-1 (C and D) cells was evaluated by flow cytometry using an Annexin V/PI detection kit. The levels of apoptosis-associated proteins Cyt-C, Bax, and Bcl-2 in HL-60 (E and G) and THP-1 (F and H) cells were analyzed by western blot and normalized to β-actin. Data are presented as mean ± SD. *P< 0.05.
Higher expression level of miR-34a inhibited autophagy of AML cells

MiR-34a mimics were used to study the effect of higher expression level of miR-34a on AML cell autophagy. The levels of autophagy-related proteins Atg5 and autophagy marker LC-3I and LC-3II were detected by western blot. The results revealed that higher expression level of miR-34a both in HL-60 cells (Fig. 4A and 4B) and THP-1 (Fig. 4C and 4D) cells dramatically decreased the levels of Atg5, LC-3I and LC-3II. The conversion of the cytosolic form of LC-3 (LC-3I) into the active membrane-bound form of LC-3 (LC-3II) in miR-34a group was also decreased in comparison with that in miR-control group.

Lower expression level of HMGB1 inhibited autophagy of AML cells

Si-HMGB1 was used to evaluate the effect of lower expression level of HMGB1 on autophagy of AML cells. The western blot results showed that the levels of Atg5, LC-3I and LC-3II as well as the conversion of LC-3I into LC-3II in HL-60 (Fig. 5A and 5B) and THP-1 (Fig. 5C and 5D) cells were both obviously reduced in si-HMGB1 group compared with that in si-control group.
MiR-34a directly regulated HMGB1 expression by binding to the 3'-UTR of HMGB1 in AML cells

The potential targets of miR-34a were predicted by Targetscan and the results showed that HMGB1 was a binding target of miR-34a. The predicted 3'-UTRs of HMGB1 binding to miR-34a were presented in Fig. 6A. To validate the interaction between HMGB1 and miR-34a, luciferase reporter vectors containing 3'-UTR-HMGB1-WT or 3'-UTR-HMGB1-MUT were cotransfected with miR-34a mimics or miR-control into HL-60 and THP-1 cells. The dual luciferase assays showed that miR-34a mimics obviously inhibited luciferase activity of pMIR-LUC-3'-UTR-HMGB1-WT vectors both in HL-60 (Fig. 6B) and THP-1 (Fig. 6C) cells, but not pMIR-LUC-3'-UTR-HMGB1-MUT vectors.

To further verify whether miR-34a regulated HMGB1 expression, miR-34a mimics, anti-miR-34a or miR-control were transfected into HL-60 and THP-1 cells to detect the expression levels of HMGB1. qRT-PCR results showed that miR-34a mimics significantly suppressed HMGB1 mRNA expression, while anti-miR-34a obviously promoted HMGB1 mRNA expression in HL-60 and THP-1 cells (Fig. 6D). The levels of HMGB1 proteins were dramatically decreased in miR-34a mimics group but strikingly increased in anti-miR-34a group in HL-60 (Fig. 6E and 6G) and THP-1 (Fig. 6F and 6G) cells compared with that in miR-control groups.

MiR-34a inhibited autophagy by targeting HMGB1 in AML cells

To study whether miR-34a inhibited autophagy by binding to HMGB1 in AML cells, miR-34a mimics were cotransfected with pcDNA 3.1-HMGB1 or pcDNA 3.1-control into HL-60 cells to investigate their effect on the expression of autophagy-related proteins Atg5, LC-3I...
and LC-3II. The results indicated that the miR-152 overexpression significantly decreased the levels of Atg5, LC-3I, LC-3II, as well as the conversion of LC-3I into LC-3II in HL-60 cells, which was completely overturned by HMGB1 overexpression (Fig. 7A and 7B), suggesting that restoration expression of HMGB1 by pcDNA 3.1-HMGB1 significantly relieved the inhibitory effect of miR-34a on autophagy in HL-60 cells.

**MiR-34a inhibited cell apoptosis by targeting HMGB1 in AML cells**

The apoptosis of AML cells with the same treatment as above was assessed by flow cytometry. The results showed that the expression levels of Cyt-C and Bax were markedly increased and Bcl-2 was conspicuously decreased by higher expression level of miR-34a in HL-60 cells, which was completely overturned by HMGB1 overexpression (Fig. 8A and 8B), suggesting that restoration expression of HMGB1 by pcDNA 3.1-HMGB1 significantly relieved the inhibitory effect of miR-34a on autophagy in HL-60 cells.

Higher expression level of miR-34a and lower expression level of HMGB1 both inhibited all-trans retinoic acid (ATRA)-induced autophagy in AML cells via stimulating the LC3 conversion

To further investigate the effects of high expression of miR-34a or low expression level of HMGB1 on autophagy under a stressed condition (chemotherapy), HL-60 cells transfected...
with miR-34a mimics or si-HMGB1 were treated with 1 μM ATRA along with lysosomal proteases inhibitor E64d and pepstatin A (Pep A) to block the fusion of autophagosome with lysosome. As shown in Fig. 9A and 9B, ATRA treatment significantly improved the level of the autophagosome-specific maker LC-3II at 24 h and 48 h, whereas miR-34a mimics and si-HMGB1 both significantly inhibited this effect in HL-60 cells treated or untreated with E64d + Pep A, suggesting that higher expression level of miR-34a or lower expression level of HMGB1 markedly suppressed chemotherapy-induced autophagy. More interestingly, we noticed that LC-3II conspicuously accumulated in the presence of E64d + Pep A under the chemotherapy condition, indicating that the accumulation of LC-3II was due to the stimulation of the LC3 conversion but not due to the inhibition of the fusion of autophagosome with lysosome. Taken together, these results revealed that higher expression level of miR-34a and lower expression level of HMGB1 both inhibited ATRA-induced autophagy in AML cells via stimulating the LC3 conversion.

Discussion

The miRNAs have drawn more attention during the past few years due to the effect of miRNAs in AML pathogenesis and its availability in early diagnosis and prognosis of AML. MiR-34 family, including miR-34a, miR-34b and miR-34c, is a type of conserved miRNAs widely distributed in mammals and is involved in AML development [26]. Many researchers have investigated the role of miR-34 family in leukemia, especially miR-34a. For instance, Li et al. reported that miR-34b was significantly lower expressed in AML blood samples and AML cell lines, and miR-34b inhibited cell viability and promoted cell apoptosis in AML cells by targeting HSF1 [27]. Yang et al. showed that miR-34c was lower expressed and served as a biomarker in predicting prognosis in patients with AML [28]. Wang et al. reported that miR-34a expression was reduced and acted as a tumor suppressor and a potential immunotherapeutic target by targeting PD-L1 in AML [17]. Zauli et al. found that miR-34a decreased the levels of oncogenes E2F1 and B-Myb in leukemic cells [29]. Ichimura et al. showed that miR-34a suppressed cell proliferation by inhibiting mitogen-activated
protein kinase kinase 1 (MEK1) during megakaryocytic differentiation of chronic myelocytic leukemia cell line K562 [30]. In the present study, in accordance with previous reports, we demonstrated that miR-34a expression was significantly decreased in HL-60 and THP-1 cells compared with that in HS-5 cells and miR-34a overexpression by miR-34a mimics promoted cell apoptosis and inhibited cell autophagy, suggesting that miR-34a plays a crucial role in AML progression.

Recent reports showed that higher expression level of HMGB1 contributed to tumourigenesis and the development of cancers. For example, Huber et al. reported that HMGB1 played an important role in murine B16 melanoma growth and metastasis [31]. Xi et al. found that HMGB1 knockdown and cordycepin had synergistic effect in promoting apoptosis, inhibiting proliferation and adhesion in chronic myeloid leukemia cells [32]. In our study, HMGB1 protein and mRNA was found to be higher expressed in AML cells, as compared with human bone marrow stromal cell line. Besides, lower expression level of HMGB1 by si-HMGB1 significantly promoted cell apoptosis and suppressed autophagy in AML cells.

More importantly, the present study demonstrated that HMGB1 was identified as a binding target of miR-34a by Targetscan, which was further confirmed by dual luciferase assay. Besides, it was verified that miR-34a targetedly regulating the expression of HMGB1. In addition, it was found that miR-34a promoted cell apoptosis and repressed autophagy by targeting HMBG1. Moreover, the study further revealed that higher expression level of miR-34a or lower expression level of HMGB1 could suppress chemotherapy-induced autophagy via stimulating the LC3 conversion. It has been reported that the lower expression level of miR-34a in cervical and colorectal tissues had an inverse correlation with HMGB1 levels and higher expression level of miR-34a inhibited cell proliferation, migration and invasion in human cervical and colorectal cancer by targeting HMGB1 [33].

Previous studies have demonstrated that miR-34a is a direct downstream target of p53, which is a tumor suppressor whose transcriptional targets regulate cell cycle, cell senescence, DNA repair, apoptosis and other biological behaviors [34, 35]. The p53-miR-34a network plays a crucial role in tumorigenesis. For example, perturbation of miR-34a expression contributed to tumorigenesis by strongly attenuating p53-mediated apoptosis in human cancers [36]. In addition, p53 was found to monitor the expression of miR-34a after cisplatin and miR-34a targeted to MYCN to sensitize lung cancer cells to cisplatin [37]. It has been shown that miR-34a was identified as the most significantly highly expressed miRNA among TP53 alteration-associated miRNA profiles in acute myeloid leukemia with complex karyotype (CK-AML) [38]. Besides, low expression of miR-34a and TP53 alterations predicted for chemotherapy resistance and inferior outcome in CK-AML clinically [38]. However, it was reported that HL-60 cells did not express p53 [39, 40] and THP-1 cells expressed mutant inactive p53, thus lacking functional p53 [41, 42]. Therefore, the biological role of miR-34a in AML cells used in our study was independent of p53 activity.

In conclusion, our results demonstrated that miR-34a was lower expressed in AML cells, accompanied with the increased levels of HMGB1. Lower expression levels of HMGB1 accelerated cell apoptosis and suppressed autophagy. MiR-34a promoted cell apoptosis and inhibited autophagy by targeting HMGB1. miR-34a upregulation and HMGB1 downregulation both suppressed ATRA-induced autophagy via stimulating the LC3 conversion in AML cells. Therefore, miR-34a may be a potential promising molecular target for AML therapy.

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Disclosure Statement

None.
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