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Research Article

Cow's Milk Protein May Induce Allergy and Inflammation in Intestinal Epithelial Cells Through Regulating HOTAIR Expression and NF-κB Signaling Pathway

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Background: Cow's milk protein allergy (CMPA) is associated with activation of proinflammatory signaling pathways and overexpression of inflammatory mediators. Long noncoding RNA (LncRNA) HOX transcript antisense intergenic RNA (HOTAIR) is a LncRNA, which is involved in the occurrence and development of many biological processes and diseases. HOTAIR can prevent necrotizing enterocolitis. This study aims to explore the effect of milk protein on NCM-460 cells and its mechanism of action with HOTAIR.
Methods: NCM-460 cells were induced by cow's milk protein to establish in vitro cell models. CCK-8 and EdU staining were used for evaluating the effects of cow's milk protein on the viability and proliferation. ELISA was used for comparing the levels of inflammatory cytokines. TUNEL staining was conducted for evaluating the apoptosis. Expression levels of HOTAIR were detected by RT-qPCR. The expression of NF-κB signaling pathway–related molecules in cells was explored to evaluate the mechanism of HOTAIR in improving ALI.
Results: Cow's milk protein decreased the viability NCM-460 cells and also decreased the expression of HOTAIR. Moreover, it can induce the antiproliferative and proapoptotic effects on NCM-460 cells, and overexpression of LncRNA HOTAIR can partially reverse the effects of cow's milk protein. In addition, overexpression of LncRNA HOTAIR reversed the effects of cow's milk protein on NF-κB signaling.
Conclusions: Cow's milk protein may induce the allergy and inflammation in intestinal epithelial cells through regulating HOTAIR expression and NF-κB signaling pathways.

Keywords: cow's milk protein allergy; HOTAIR; intestinal epithelial cells; NF-κB

1. Introduction

Cow's milk protein allergy (CMPA) is a series of harmful immune reactions caused by the intake of milk protein, which is common in children [1–3]. There are four main types of allergens: globulin, lactoalbumin, β-lactoglobulin, and casein. The allergens in infants and young children, β-lactoglobulin and casein are commonly seen [4]. These proteins can enter the body through the intestinal barrier and may cause immune system response in susceptible individuals. Its pathogenesis can be divided into three types: IgE-mediated immune response, non-IgE–mediated immune response, or a mixture of both. It is reported that the incidence of milk protein allergy in children is about 2%–

7.5%. In the first year, CMPA symptoms often appear after formula milk or breast feeding [5]. In recent years, the incidence rate of CMPA has been rising. In clinical practice, most of the symptoms are gastrointestinal and skin symptoms, mainly manifested as vomiting, diarrhea, constipation, bloody stools, eczema, urticaria, and facial swelling [6]. A few children may experience shock symptoms. The prolonged presence of these symptoms in children can lead to malnutrition or delayed growth and development, as well as various emotional problems, including irritability, feeding difficulties, refusal to eat, partial eating, and restless sleep [7, 8]. Research has shown that CMPA children are more difficult to maintain compared to normal children. They have irregular diet, irregular sleep, and excessive activity, which increases the anxiety of the mother of the child.

There are many diagnostic methods for CMPA [9], including skin prick test (SPT), skin patch test (APT), oral food challenge (OFC) test, and atopic IgE measurement. There is experimental evidence that the gold standard for diagnosing food allergies is still the food provocation test [8]. Regarding the treatment of CMPA, studies have shown that avoiding the intake of allergic foods can alleviate clinical symptoms in children, and the detachment of allergens is one of the effective methods for treating allergic diseases [10, 11]. To meet the nutritional needs of children for normal development and ensure their healthy growth, it is necessary to pay attention to CMPA patients and intervene early.

Intestinal epithelial cells are normally exposed to large numbers of intact bacteria and high concentrations of bacterial products. Intestinal epithelial cells are the first component of the innate immune system to respond to intestinal microbial invasion. They effectively isolate intestinal flora from immune cells by constructing chemical and physical barriers, thus avoiding abnormal immune reactions. This mechanism not only protects the host from potential harmful microorganisms but also promotes the formation of healthy microbial communities. In addition, intestinal immune cells also play an indispensable role in this process. They participate in regulating and maintaining a balanced and healthy microbial community, while strengthening the function of epithelial barrier. This interaction ensures the stability of intestinal environment and is very important for the health of the whole host [12, 13]. These protective mechanisms of the epithelium include responding to enteric pathogenic bacteria and the compounds produced by these bacteria, such as cow's milk protein [14].

Long noncoding ribonucleic acids (LncRNAs) are known as long chain RNA molecules that affect the expression level of their downstream targets [11, 15]. The roles of LncRNAs in milk related studies have been discussed previously. For example, Yan et al. reported the LncRNA profiles of human milk-derived exosomes and their possible roles in protecting against necrotizing enterocolitis; moreover, Zeng et al. explored the LncRNAs in bovine milk exosomes and their stability during digestion in vitro. HOX transcript antisense intergenic RNA (HOTAIR) is one of the most widely investigated LncRNAs that participate in the development of different diseases, i.e., cancers, nontraumatic femoral head necrosis, and cerebral infarction [16–18]. HOTAIR is overexpressed in myocardial cells of sepsis mice model, and transient knockdown of HOTAIR can improve cardiac functions of the septic mice [19]. Nevertheless, whether HOTAIR also participate in the pathogenesis of cow's milk allergy remains unknown.

Therefore, the current work explored the effects of cow's milk protein on intestinal epithelial cells and explored the potential mechanisms to provide experimental and theoretical basis for the clinical application for the management of CMPA.

2. Methods

2.1. Cell Culture. NCM-460 normal intestinal epithelial cells have been obtained from the American Type Culture Collection (ATCC). Cells have been treated by RPMI-1640 medium (Solebo, Beijing, China) with 10% fetal bovine serum (FBS, Gibco, America) at 37°C and 5% CO_2. Cells have been cultured and passaged, and the third generation of the cells has been used for the experiments. Cow's milk protein low group comprised of 50 μg/mL β-lactoglobulin, β-lactalbumin, and α-casein, cow's milk protein medium group comprised of 100 μg/mL β-lactoglobulin, β-lactalbumin, and α-casein, while cow's milk protein high group comprised of 200 μg/mL β-lactoglobulin, β-lactalbumin, and α-casein. Cells were treated by different concentrations of CMP for 72 h.

2.2. CCK-8 Assay. Cells at logarithmic growth phase have been placed on 96-well plates, and the cell viability was detected by CCK-8 kit (Beyotime, Haimen, China) base on the instruction proved by the manufacturer.

2.3. ELISA Assay. Cell culture supernatants have been collected at different time points, and then the levels of IL-1β as well as TNF-α have been determined based on the protocols of ELISA kit (Beyotime).

2.4. EdU and TUNEL Staining. Cells were stained according to the protocols of the EdU Cell Proliferation Kit with Alexa Fluor 488 (Beyotime) and Colorimetric TUNEL Apoptosis Assay Kit (Beyotime), respectively. The cells were then imaged by a microscope, and the cell proliferation and apoptosis were analyzed.

2.5. Cell Transfection Experiment. Suck up the culture medium in the Petri dish and wash it with PBS once. Replace serum-free medium. Prepare transfection preparation solution and prepare it with sterilized EP tube. Solution A: 200 nm HOTAIR siRNA was diluted with 200 μL Opti-MEM; Solution B: Dilute 5 μL lipo2000 with 200 μL Opti-MEM, mix solution A and solution B gently, and let it stand for 5 min, then add solution B into solution A, mix gently, and let it stand at room temperature for 20 min. Add

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transfection reagent into the culture medium of each well in the six-well plate, after 6 h, replace it with complete culture medium, and continue to culture for 24–48 h.

2.6. RT-qPCR. Total RNAs have been isolated from the cell samples by TRIzol (Invitrogen). Then cDNA has been reverse-transcribed by the kits purchased from Beyotime. RT-qPCR was conducted by ABI 7900 HT system with commercially available kits purchased from Beyotime according to the instructions provided by the manufacturer. Levels of HOTAIR in different samples have been quantified using the $2^{-\Delta\Delta C}$ method. GAPDH has been applied as the reference gene. The sequences of the primers are shown in Table 1.

2.7. Western Blot Assay. Samples were collected and proteins were extracted with RIPA lysate (Beyotime, Shanghai), then the protein concentration was determined, and the samples were boiled for later use. The corresponding concentrations of separating gel and concentrating gel were prepared and subjected for the SDS-PAGE gel electrophoresis. After gel electrophoresis separation, the proteins on the gels have been electro-transferred to PVDF membranes (Millipore). Then they were sealed with 5% skimmed milk powder at room temperature for 1 h. The PVDF membrane was washed with PBST for 4 times (5 min/time), and the target protein bands were cut according to the Marker's position, put into an incubator incubated with the target protein rabbit primary antibody: NF-κB p65 (1:1000, Abcam, ab207297), p-NF-κB p65 (1:1000, Abcam, ab239882) and β-actin (1:1000, Abcam, ab8226). Then, wash the PVDF membrane with PBST for 4 times (5/min/time), add the secondary antibody (1:10,000, China Kangwei Reagent Biotechnology Co., Ltd.) combined with horseradish peroxidase according to the source of antibody species, and incubate for 1 h at room temperature and in the dark at the speed of 70–80 rpm. The PVDV film was washed with PBST for 4 times (5 min/time), and the signal of the combination of the secondary antibody and the primary antibody was detected by ECL color development. The photo was taken by chemiluminescence detection system, and the ratio of the optical density of the target strip to β-actin was detected by ImageJ.

2.8. Statistical Analysis. GraphPad Prism 7.0 (GraphPad Software Inc., CA, USA) has been applied for data analysis. Comparisons among the groups were analyzed by ANOVA. Data have been expressed as mean ± standard deviation (SD). $p < 0.05$ was considered as significant difference.

3. Results

3.1. Effects of Cow's Milk Protein on NCM-460 Cells In Vitro. First, we used cow's milk protein to construct an in vitro intestinal epithelial cell injury model. CCK-8 assay has been conducted for the detection of cell viability. ELISA has been performed for the detection of inflammatory cytokine. The viability of cow's milk protein–treated NCM-460 cells markedly decreased by cow's milk protein treatment (Figure 1(a)) in a dose-dependent manner. ELISA results showed that levels of IL-1β as well as TNF-α markedly increased by cow's milk protein treatment (Figure 1(b)) in a dose-dependent manner. This suggests that milk protein can inhibit cell viability and promote the release of inflammatory factors, indicating that this model can be used in subsequent experiments.

Table 1: Primer sequences.

Gene	Sequences	Product size (bp)
HOTAIR	F: AAGGCTGAAATG GAGGACCG R: GCTGGTTTAGGT TGCAGCAC	76
GAPDH	F: TGCAACCGGGAA GGAAATGA R: GCATCACCCGGAGGA GAAAT	148

3.2. Cow's Milk Protein Decreased HOTAIR Expression in the NCM-460 Cell Models. Moreover, the expression of HOTAIR was markedly decreased by cow's milk protein treatment (Figure 2). This suggests that milk protein can downregulate the expression of HOTAIR in NCM-460 cells.

3.3. Cow's Milk Protein Promotes Apoptosis of NCM-460 Cells via Regulating HOTAIR Expression. As shown in Figures 3 and 4, results of EdU and TUNEL staining showed that viability of NCM-460 cells was markedly decreased, while apoptosis of NCM-460 cells was significantly increased after cow's milk protein treatment, while the viability of NCM-460 cells was significantly increased, and apoptosis rate markedly reduced after transfection of HOTAIR OE (Figures 3 and 4). This suggests that milk protein can promote the apoptosis of NCM-460 cells by regulating HOTAIR.

3.4. Cow's Milk Protein Regulates NF-κB Signaling in NCM-460 Cells via Regulating HOTAIR Expression. Finally, to investigate the mechanism of the function of cow's milk protein, we explored the expressions of NF-κB signaling molecules in cells with different treatment. As shown in Figure 5(a), the expression of p-NF-κB markedly increased in cow's milk protein treatment group in comparison with the control, and the excretion of IL-1β as well as TNF-α also elevated (Figure 5(b)). Meanwhile, compared with cow's milk protein treatment group, NCM-460 cells treated by cow's milk protein + HOTAIR OE showed significant decrease of p-NF-κB expression as well as IL-1β and TNF-α secretion (Figures 5(a) and 5(b)). This suggests that milk protein can regulate NF-κB signaling pathway in NCM-460 cells by regulating the expression of HOTAIR.

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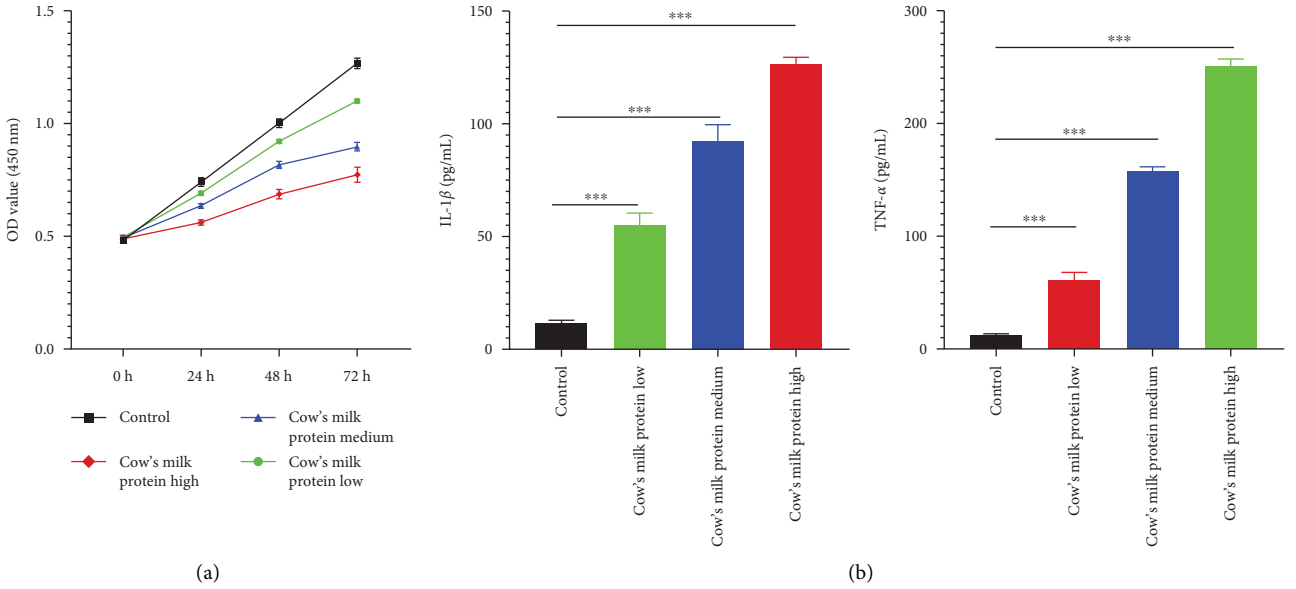

Figure 1: Effects of cow's milk protein on NCM-460 cells in vitro. (a) CCK-8 assay has been conducted for the detection of cell viability. (b) ELISA results showed that levels of IL-1β as well as TNF-α markedly increased by cow's milk protein treatment. $n = 3$, $^{***}p < 0.001$.

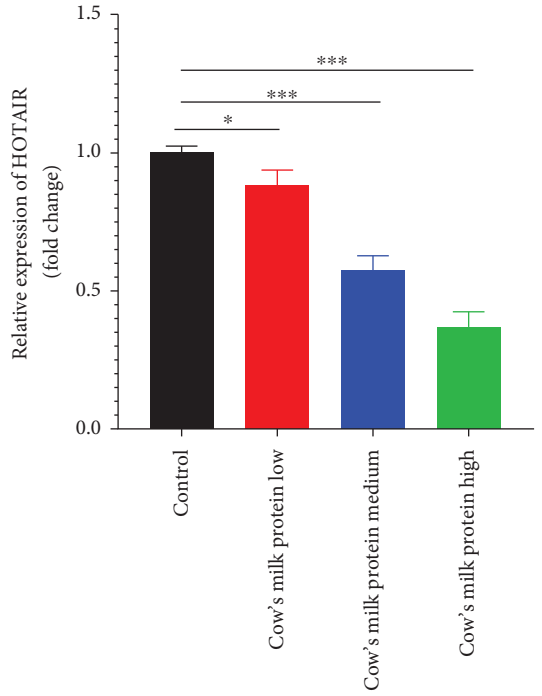

Figure 2: Cow's milk protein decreased HOTAIR expression in the NCM-460 cell models. $n = 3$, $^{**}p < 0.01$, $^{***}p < 0.001$.

4. Discussion

CMPA is a serious disease of children caused by acute inflammation, and the pathogenesis is not fully studied. Currently, there is no gold standard for the effective prevention and management for cow's milk protein [20]. Therefore, effective method for the treatment of CMPA is an area of focus, and the potential mechanism in the treatment of CMPA deserves further exploration. In current work, we explored the CMPA cell models, in order to provide a basis for the acquisition of new targets for CMPA.

The effects of different medications on epithelial cell inflammatory models have been discussed previously. For example, Xu et al. suggested that silibinin could alleviate lipopolysaccharide-induced inflammation in porcine mammary epithelial cells via mTOR/NF-κB signaling pathway; moreover, Xie et al. proved that porcine milk

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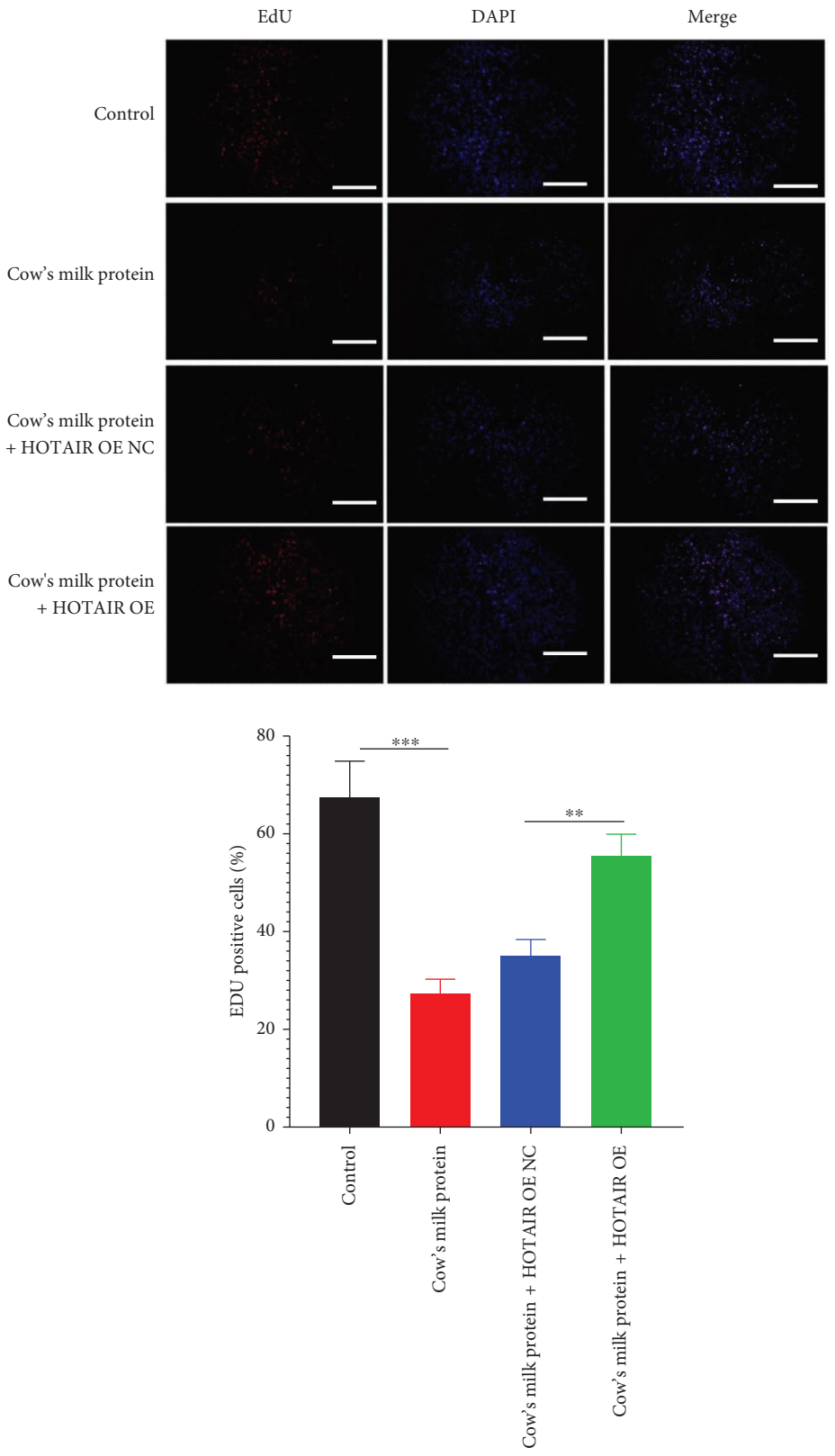

FIGURE 3: Cow's milk protein inhibits proliferation of NCM-460 cells via regulating HOTAIR expression. Results of EdU staining. $n = 3$, $^{**}p < 0.01$, $^{***}p < 0.001$. Scale bar = 100 μm.

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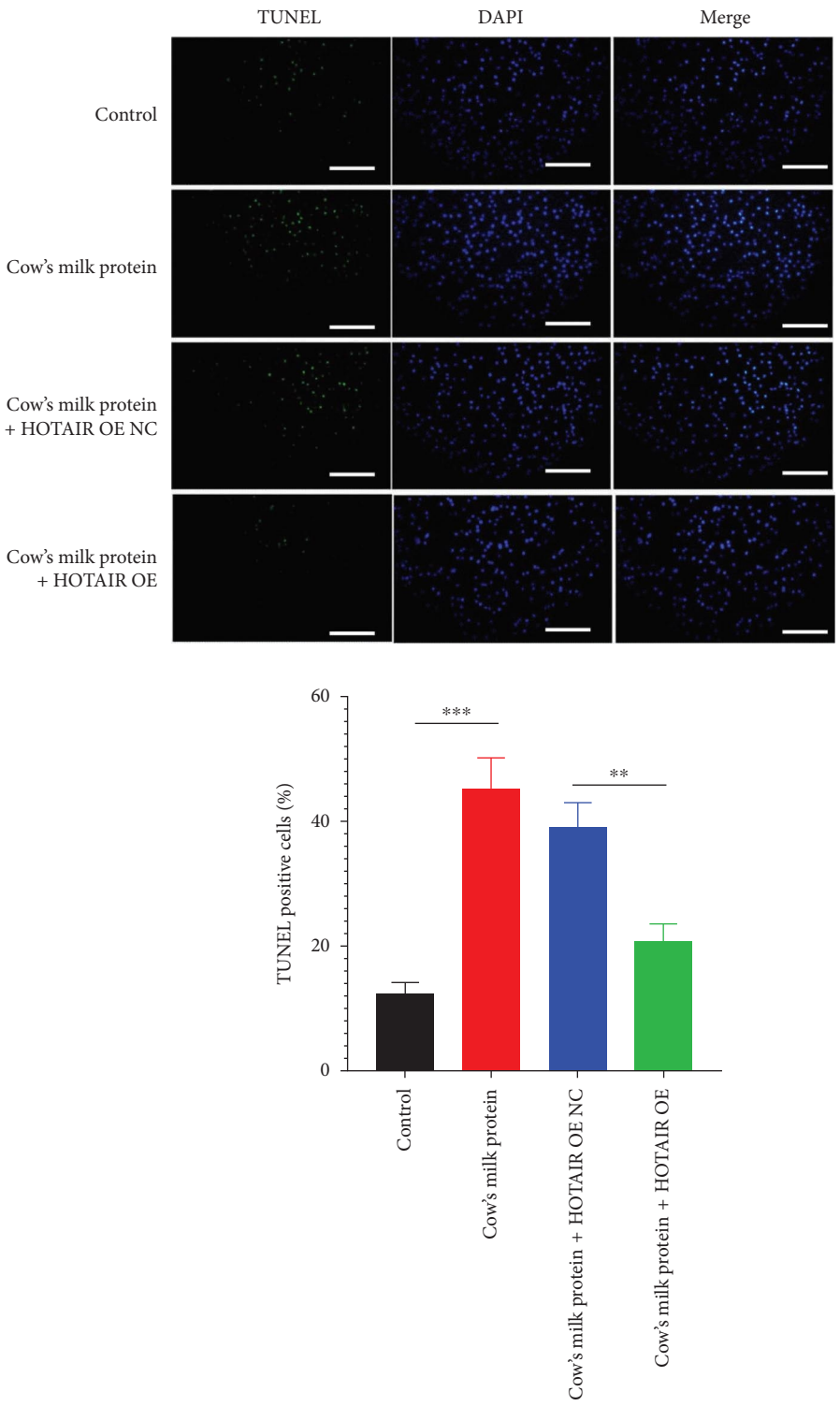

FIGURE 4: Cow's milk protein promotes apoptosis of NCM-460 cells via regulating HOTAIR expression. Results of TUNEL staining. $n = 3$, $^{**}p < 0.01$, $^{***}p < 0.001$. Scale bar = 100 μm.

exosome miRNAs attenuate LPS-induced apoptosis through inhibiting TLR4/NF-κB and p53 pathways in intestinal epithelial cells; Wang et al. suggested the LPS-induced reduction of triglyceride synthesis and secretion in dairy cow mammary epithelial cells via decreased SREBP1 expression and activity. In current study, we found that cow's milk protein markedly decreased the cell viability and increased the apoptosis of NCM-460 cells; moreover, cow's milk protein also increased the expressions of IL-1β and TNF-α, indicating that cow's milk protein could induce the injury of

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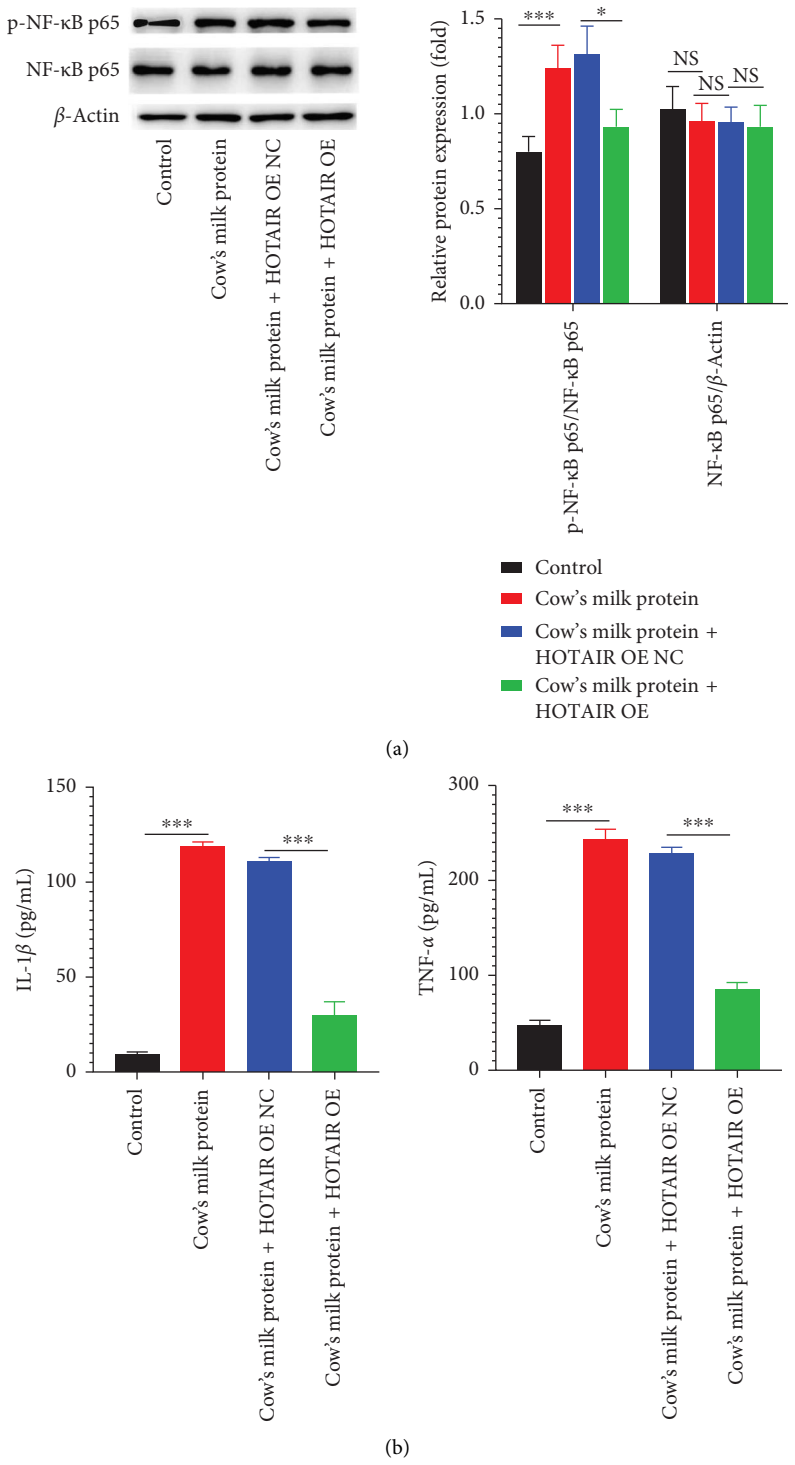

FIGURE 5: Cow's milk protein regulates NF-κB signaling in NCM-460 cells via regulating HOTAIR expression. (a) WB expression of NF-κB p65. (b) ELISA results. $n = 3$, $^{**}p < 0.01$, $^{***}p < 0.001$.

intestinal epithelial cells. These results suggested the potential roles of cow's milk protein. However, the underlying mechanism requires further investigation.

Numerous studies have demonstrated that the regulatory functions of LncRNAs are essential for physiological balance. Researchers used the LPS-induced method to construct an inflammatory model of lung injury and found that LncRNA MALAT1 could regulate LPS-induced inflammatory response [21]. Li et al. [22] observed the decreased levels of LncRNA CASC2 in LPS-treated A549 cells as well as ALI mice models, and Xia et al. performed co-expression analysis of LncRNAs and mRNAs and at the

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same time identified potential regulatory LncRNAs involved in the inflammatory effects of lipopolysaccharide on bovine mammary epithelial cells. In current work, we found LncRNA HOTAIR was markedly decreased by cow's milk protein treatment. These results indicated that cow's milk protein increased epithelial cell injury through regulating LncRNA HOTAIR. Subsequently, HOTAIR was overexpressed in cow's milk protein treated cells, and results of CCK-8 assay as well as EdU assay showed that the viability and proliferation of NCM-460 cells markedly increased, while apoptosis decreased. These results indicated that cow's milk protein decreased the growth and increased apoptosis of NCM-460 cells by regulating the levels of LncRNA HOTAIR.

NF-κB pathway is a key pathway for the occurrence of inflammation and subsequent production of inflammatory factors, and the inhibition of the NF-κB signaling is the key to inhibit the release of proinflammatory factors [23–25]. We found that cow's milk protein could activate NF-κB signaling and increase levels of IL-1β and TNF-α, and the effects were partially abolished after HOTAIR siRNA transfection. These results suggested that cow's milk protein could regulate the phosphorylation level of NF-κB, possibly by upregulating HOTAIR expression, and consequentially inhibited secretion of proinflammatory cytokines. However, the results still need to be validated through further investigation.

5. Conclusion

In conclusion, cow's milk protein may induce intestinal epithelial cell injury, possibly via regulating the expression of LncRNA HOTAIR through NF-κB pathway. Our data may provide new evidences for the clinical management of CMPA. Further cell and animal studies are needed to strengthen our conclusion.

Data Availability Statement

The data are available from the corresponding authors on reasonable request.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

K.M.: conceptualization, writing–original draft, and writing–review and editing.

J.L.: validation and project administration.

D.L.: resources and supervision.

S.G.: data curation and supervision.

C.Z.: data curation and writing–original draft.

M.L.: data curation.

J.S.: conceptualization, funding acquisition, resources, supervision, and writing–review and editing.

J.W.: resources and visualization.

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