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ORIGINAL RESEARCH

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APOBEC3G inhibits apoptosis and autophagy in cervical intraepithelial neoplasia W12 cells

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Abstract

Cervical intraepithelial neoplasia (CIN) is a collective term for specific precancerous lesions associated with cervical cancer (CC). Given the current poor prognosis, it is imperative to diagnose CIN at an early stage and identify the markers linked to its pathogenesis and prognosis, despite the disease's documented slow course and numerous levels of cellular alterations. We explored the expression level of the new marker apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G (APOBEC3G, A3G) and its regulatory effect on CIN. Cell proliferation were assessed using Cell Counting Kit-8 (CCK-8) and 5-ethynyl-2′-deoxyuridine (EdU) staining. Apoptosis rate was detected by flow cytometry. We used immunofluorescence to determine light chain 3B (LC3B) expression. Western blotting was used to detect Bcl2-Associated X (Bax), B-cell lymphoma 2 (Bcl-2), Cleaved caspase-3, p62, LC3-II/LC3-I, transforming growth factor-beta (TGF-β) and decapentaplegic homolog 2 (Smad2) expressions. A3G knockdown significantly inhibited cervical intraepithelial neoplasia cell proliferation, significantly increasing the apoptosis rate and the Bax/Bcl-2 ratio. Also, Cleaved-caspase-3 and LC-II expressions were significantly increased, and p62 expression was decreased. The TGF-β/Smad2 signaling pathway was significantly inhibited. In cervical intraepithelial neoplasia, APOBEC3G inhibits apoptosis and autophagy of W12 cells through TGFβ/Smad2 signaling pathway. In conclusion, we determined that APOBEC3G has a regulatory effect on CIN, which opens a new way to explore its pathogenesis and improve the accuracy of prognosis.

Keywords

Cervical intraepithelial neoplasia; APOBEC3G; Autophagy; Apoptosis; TGF-β/Smad2

1. Introduction

Cervical cancer develops from cervical intraepithelial neoplasia (CIN) [1]. Human papillomavirus (HPV) is considered one of Among the most common causes of CIN and cervical cancer is human papillomavirus (HPV), particularly HPV16 [2, 3]. Persistent HPV infection leads to cervical cancer progression [4]. Treatments for CIN and prevention of cervical cancer greatly benefit from understanding the molecular mechanism of CIN [5].

APOBEC3G (A3G) is a large apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC) family [6]. Researchers have confirmed APOBEC3G's association with viruses including Epstein-Barr virus, human T lymphocyte virus, *etc*. [7]. APOBEC family proteins encode HPV16 in CIN, and APOBEC3G has a highly mutagenic editing effect on HPV DNA [8]. Vartanian *et al*. [9] disclosed APOBEC3A's possible involvement in HPV infection. The authors demonstrate that significant hypermutations occur when APOBEC3A expression plasmids are co-transfected with HPV DNA, and that APOBEC3A suppresses retrotransposons and parvoviruses through a deaminase-dependent mechanism [8, 9]. Research has demonstrated that the expression of APOBEC3A in cervical cancer cells differentially inhibits the production of cytidine deaminase-dependent HPV E6 and E7, hence exerting anti-viral and anti-cancer effects [10]. As CIN progresses, APOBEC3G expression will increase. When HPV infections persist, its high expression contributes to CIN and cervical cancer [11]. Wang's research revealed that APOBEC3G inhibits DNA repair and the transforming growth factor-β (TGF-β)/mothers Against Decapentaplegic Homolog 2 (Smad2) pathway controls cell invasion [12]. Furthermore, APOBEC3G induces autophagic degradation, which regulates anti-viral resistance [13].

One of the most significant subtypes of the TGF family is TGF-β. As a polypeptide molecule, it regulates wound healing, differentiation, cell division and embryonic development. Elevated levels of TGF-β1 in tumor tissues, such as cervical carcinoma, frequently indicate more aggressive forms [14]. By analyzing exfoliated cells from cervical smears, some studies demonstrated that TGF-β expression is linked to CIN

development into cancer. TGF-β promoter's activity can be increased by the HPV16 E6 and E7 genes [15, 16].

This study aimed to investigate whether A3G inhibits W12 cells proliferation and autophagy in cervical intraepithelial neoplasia through the TGF-β/Smad2 signaling pathway.

2. Method

2.1 Cell culture

Cervical epithelial neoplasia cells (W12, American Type Culture Collection) contain HPV16. We cultured W12 cells in Dulbecco's modified Eagle's medium (DMEM, 11885084) with 5% Fetal Bovine Serum (FBS, A5670701), 1% doublet antibody (15140122), 0.4 μg/mL hydrocortisone (S003K), 5 μg/mL insulin (A11382II), 8.4 ng/mL cholera toxin (C34775), 24 μg/mL adenine (MA1-12717), and 10 ng/mL epidermal growth factor (E3481) (All reagents are from Gibco Company, Grand Island, NY, USA). Culture conditions are 37 °C, 5% CO_2.

2.2 Cell transfection

Before transfection, 2×10^5 cells were seeded into a 6-well plate. Using Lipofectamine RNAi MAX reagent (R0541, Life Technologies, Carlsbad, CA, USA), siRNA targeting A3G (abx907826, Integrated DNA Technologies, Coralville, IA, USA) was transfected into cells in accordance with manufacturer's protocol. siA3G#1: forward (5′→3′), GGAAUAAUCUGCCUAAAUAUUAUAT; reverse (5′→3′), AUAUAAUAUUUAGGCAGAUUAUUCCAA. siA3G#1: forward (5′→3′), AGAUCAUGAAUUAUGACGAAUUUCA; reverse (5′→3′), CUUCUAGUACUUAAUACUGCUUAAAGU.

2.3 CCK-8

Stabled transfected W12 cells were seeded in a 96-well plate at 5×10^3 cells per well. After culturing for 24 h, Cell Counting Kit-8 (CCK-8, Beyotime, C0040, Nanjin, China) reagent was added. Absorbance at 450 nm were measured with a microplate reader (Bio-Rad Laboratories, Inc., imark, Hercules, CA, USA).

2.4 EdU incorporation assay

W12 cells were plated into a 96-well plate at 2×10^4 cells per well. After 24 h, 5-ethynyl-2′-deoxyuridine (EdU, Sigma-Aldrich, BCK-EDU488, St Charles, MO, USA) staining solution was added, followed by fixation and counterstaining. Observation and photography were performed using a fluorescence microscope (CKX41, Olympus, Tokyo, Japan).

2.5 Flow cytometry analysis

W12 cells were stained with Propidium Iodide (PI) and Annexin V-fluorescein isothiocyanate (BD 556547, BD Biosciences, Bedford, MA, USA) in the dark. Apoptotic cells were then examined using flow cytometry (BD FACSCanto, BD Biosciences, San Jose, CA, USA).

2.6 Immunofluorescence

W12 cells were cultured on coverslips in 6-well plates. Permeabilization and fixation of the cells were followed by blocking with 1% bovine serum albumin, incubation with LC3B (Sigma L7543, St Charles, MO, USA) primary antibody, and capture with a confocal microscope (Leica Microsystems GmbH, TCS SPE, Wetzlar, Germany).

2.7 Quantitative RT-PCR (qRT-PCR)

Total RNA was isolated from cell lines using Trzol reagent (Invitrogen, 15596026, Carlsbad, CA, USA). The iScriptTM cDNA Synthesis Kit (Bio-Rad, 1708890, Hercules, CA, USA) was used to create cDNA for reverse transcription. Real-time reverse transcription polymerase chain reaction (PCR) was performed using $2^{-\Delta\Delta ct}$ technique by ABI Prism 7500 equipment (Applied Biosystems, LAB-0001-0001-ABI, Foster, CA, USA) and SYBR Premix Ex Taq (Takara, RR820A, Tokyo, Japan) to measure target gene expression levels. Gene expression results were normalized through β-actin, an internal control.

2.8 Western blot analysis

We lysed and centrifuged W12 cells on ice to obtain protein determined the protein concentration. They were then separated and transferred to a membrane, and the obtained bands were blocked for 2 h. The strip was incubated with the primary antibody overnight at 4 °C, followed by the secondary antibody for 1 h. Images were obtained using a developing solution (R-03722-D50, Advansta, Menlo Park, CA, USA) and a chemiluminescence imager (1708265, Bio-Rad, Hercules, CA, USA). Grayscale value analysis was performed using Image J. Primary and secondary antibodies used are as follows: A3G (1:1000, ab302926, Abcam, UK), Bax (1:1000, ab32503, Abcam, UK), Bcl-2 (1:1000, ab182858, Abcam, UK), Cleaved caspase-3 (1:1000, ab32042, Abcam, UK), p62 (1:1000, ab207305, Abcam, UK), LC3-II/LC3-I (1:1000, ab192890, Abcam, UK), autophagy-related gene 5 (ATG5, 1:1000, ab108327, Abcam, UK), Beclin (1:1000, ab302669, Abcam, UK), TGF-β (1:1000, ab215715, Abcam, UK), p-TGF-β (1:1000, ab183037, Abcam, UK), Smad2 (1:1000, ab40855, Abcam, UK), p-Smad2 (1:1000, ab280888, Abcam, UK), glyceraldehyde-3-phosphate dehydrogenase (GAPDH, 1:1000, ab8245, Abcam, UK), secondary antibody (1:1000, cell signal technology).

2.9 Statistical analysis

Data analysis was performed using GraphPad Prism V8.0 (GraphPad Inc., La Jolla, CA, USA). Comparison between groups by t test. $p < 0.05$ indicates statistically significant differences.

3. Result

3.1 Knockdown of A3G inhibits the proliferation of W12 cells

The transfection of lentivirus eliminated A3G in W12 cells, which resulted in significant reductions in A3G expression was

significantly reduced (Fig. 1A). A3G knockdown decreased *HPV16* mRNA expression in cells (Fig. 1B). Compared with the siNC group, A3G deletion significantly inhibits cell viability, while EdU staining indicates A3G deletion significantly inhibits cell proliferation (Fig. 1C–E). For W12 cell proliferation, A3G protein is necessary.

3.2 Knockdown of A3G promotes apoptosis of W12 cells

To study the effect of A3G on W12 cell apoptosis, we used flow cytometry to measure the cell apoptosis rate and Western blot to measure protein expression. within comparison to the siNC group, A3G deletion significantly increase W12 cells apoptosis and the expression of Bax and Cleaved-caspase-3 (Fig. 2A,B). It also significantly inhibited Bcl-2 expression (Fig. 2B). A3G loss promotes W12 cells apoptosis.

3.3 Knockdown of A3G promotes autophagy in W12 cells

Autophagy is induced by the conversion of LC3-I to LC3-II, which represents autophagy. Hence, we used immunofluorescence to observe cells and Western blot to measure autophagy-related proteins. Compared to the siNC group, LC3-II/LC3-I, ATG5 and Beclin1 was significantly increased and p62 expression was significantly decreased after A3G deletion, which proved that autophagy increased after A3G knockdown (Fig. 3A). Immunofluorescence results revealed that fluorescent spots increased significantly after A3G deletion, indicating an increase in autophagy flux (Fig. 3B). A3G loss can promotes apoptosis of W12 cells apoptosis.

3.4 A3G activates TGF-β/Smad2 signaling pathway

Next, we investigated how knocking down A3G affected the TGF-β/Smad2 signaling pathway in W12 cells. We found that knocking down A3G did not reduce TGF-β and Samd2 expression, but it did reduce TGF-β and Samd2 protein phosphorylation when compared with the siNC group (Fig. 4). This proves that knocking down A3G inhibits the TGF-β/Samd2 pathway in W12 cells.

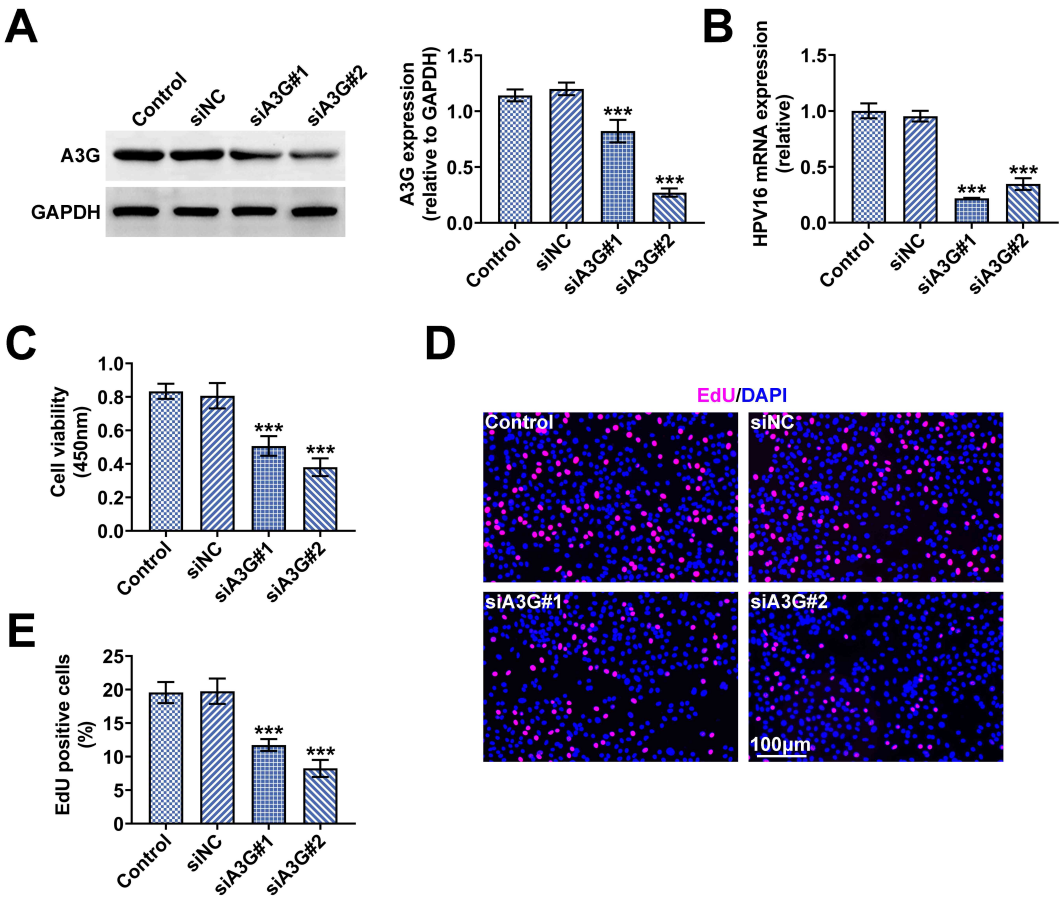

FIGURE 1. A3G knockdown inhibits W12 cell proliferation. (A) A3G protein expression. (B) *HPV16* mRNA expression. (C) Cell viability was assessed using CCK-8 assay. (D) Cell proliferation was measured by EdU staining and 1000 cells were counted in each group. (E) The ratio of the number of stained cells to the total number of cells. Values are presented as mean ± SD. ***$p < 0.001$ versus control group. n = 3. A3G: APOBEC3G; HPV: Human papillomavirus; siNC: negative control group; EdU: 5-ethynyl-2′-deoxyuridine; DAPI: 4′,6-diamidino-2-phenylindole.

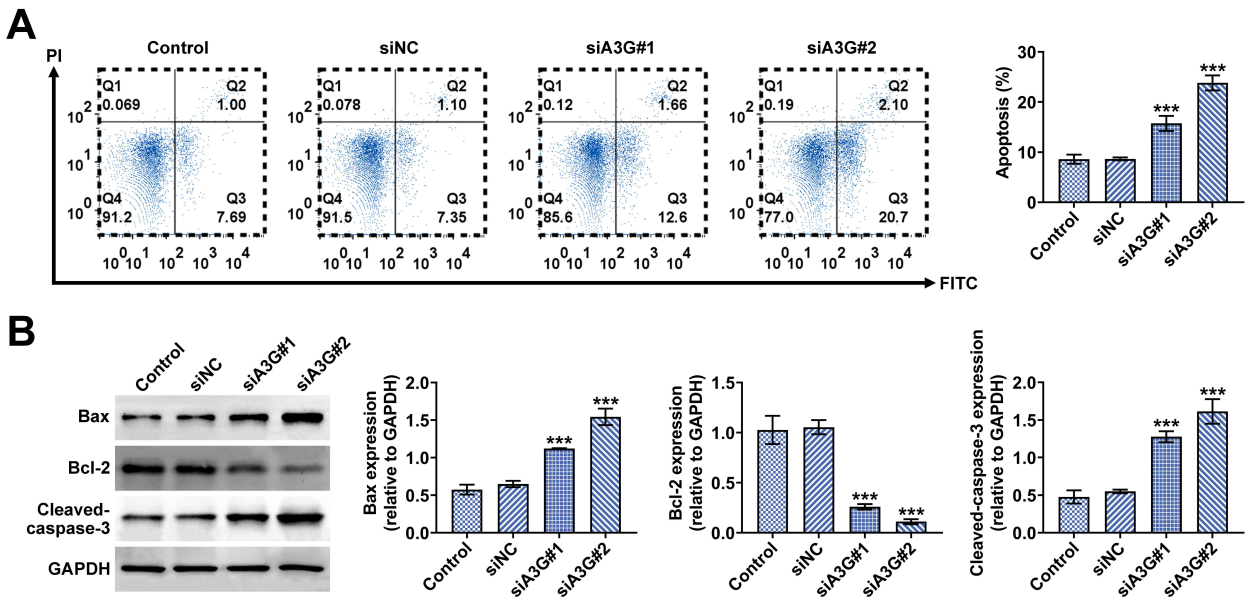

FIGURE 2. A3G knockdown promotes W12 cell apoptosis. (A) Measurement of cell apoptosis by flow cytometry. (B) Bax, Cleaved-caspase-3, Bcl-2 protein expression. Values are presented as mean ± SD. ***$p < 0.001$ versus control group. n = 3. A3G: APOBEC3G; siNC: negative control group; PI: Propidium Iodide; FITC: Fluorescein isothiocyanate; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; Bax: Bcl2-Associated X; Bcl-2: B-cell lymphoma 2.

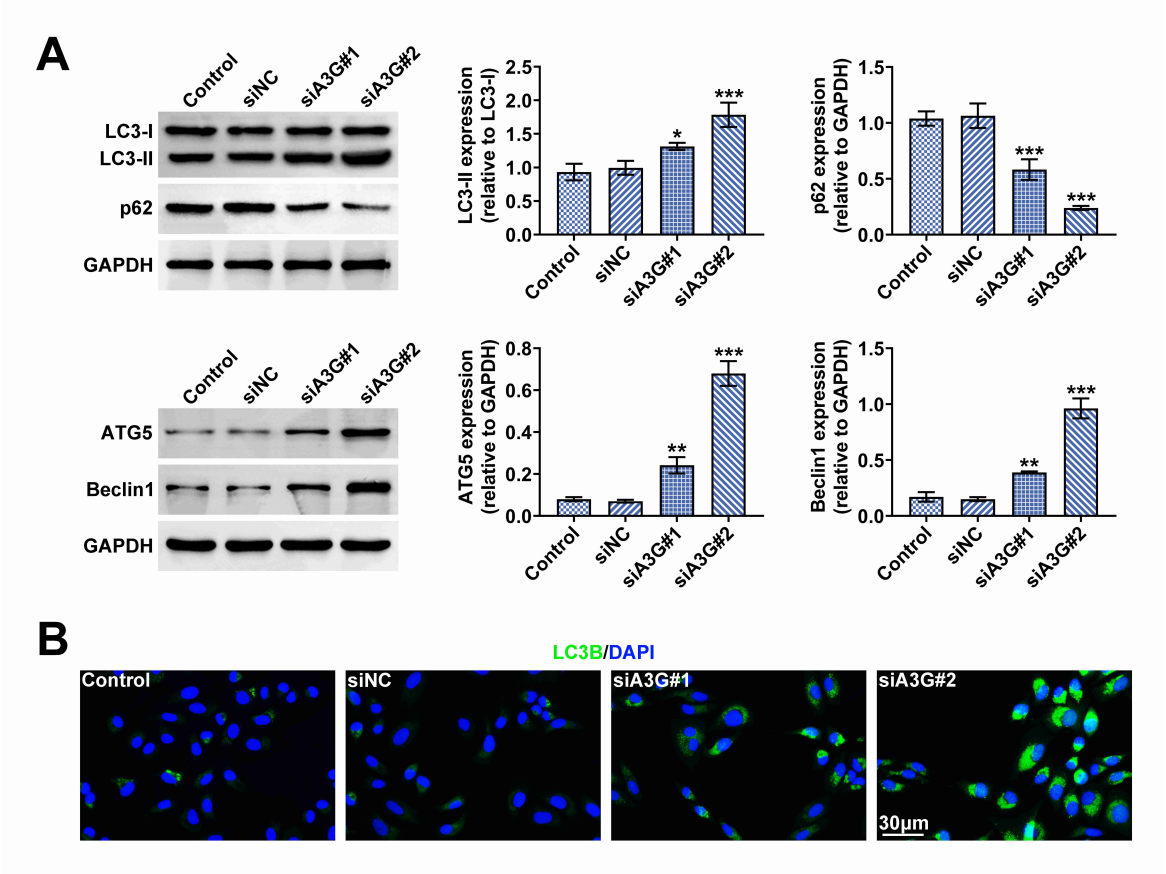

FIGURE 3. A3G knockdown promotes autophagy in W12 cells. (A) p62, ATG5, Beclin1 and LC-II protein expression. (B) Examine LC3B expression under a fluorescence microscope. Values are presented as mean ± SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus control group. n = 3. A3G: APOBEC3G; LC3: light chain 3; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; siNC: negative control group; ATG5: autophagy-related gene 5; DAPI: 4′,6-diamidino-2-phenylindole.

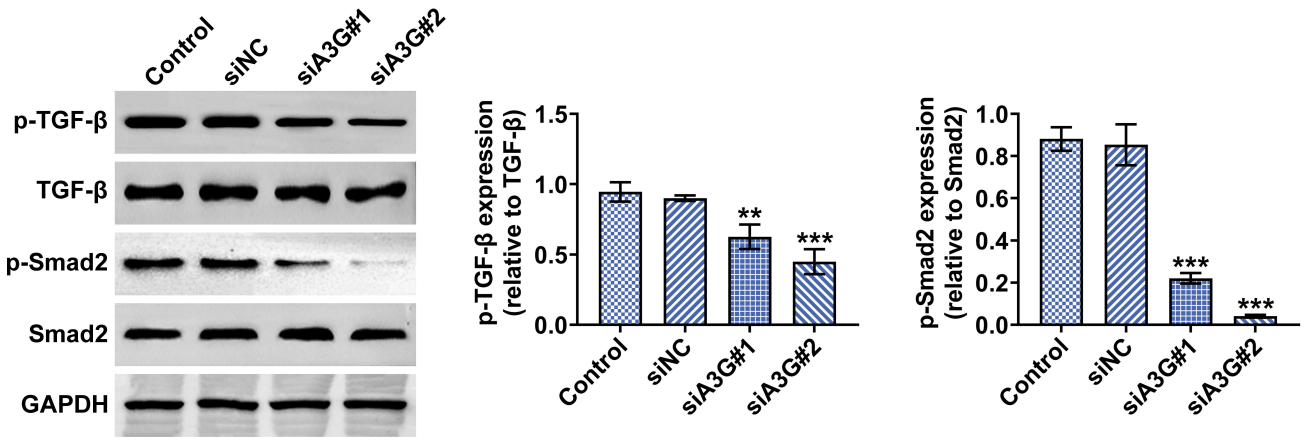

FIGURE 4. A3G activates TGF-β/Smad2 signaling pathway. TGF-β and Samd2 protein expression; Phosphorylated expression of TGF-β and Samd2 proteins. Values are presented as mean ± SD. $^{**}p < 0.01$, $^{***}p < 0.001$ versus control group. n = 3. A3G: APOBEC3G; TGF-β: transforming growth factor-beta; Samd2: decapentaplegic homolog 2; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; siNC: negative control group.

4. Discussion

This study demonstrated that A3G knockdown inhibited the TGF-β/Smad2 signaling pathway. It inhibited the proliferation of W12 cells containing HPV16 appendages and promoted their apoptosis and autophagy. In this way, it appears to have inhibitory activity on cervical intraepithelial neoplasia cells.

Long-term CIN often precedes cervical cancer [17]. Despite HPV infection being common, some subtypes, such as HPV16 can lead to CIN and cervical cancer [18]. In organisms, autophagy is a tightly regulated cellular process that eliminates damaged organelles, cell membranes and proteins through lysosomes. HPV16 inhibits autophagy, which captures and degrades intracellular pathogens [19].

The TGF-β pathway, however, regulates the HPV16 gene expression. There is a crucial role for TGF-β signaling in apoptosis, proliferation and autophagy [20].

A better understanding of CIN's molecular mechanisms helps to treat CIN and prevent cervical cancer. The A3 family is closely related to viruses. Recent studies have shown that it also plays a role in malignant tumor development and drug resistance [21]. A3G regulates human immunodeficiency virus type 1 (HIV-1) infectivity by inducing autophagy degradation [13]. APOBEC3G, however, controls glioma cell invasion through the TGF-β/Samd2 pathway [12]. In spite of this, it is still unclear how it affects CIN.

Autophagy is a strictly regulated cell that maintains energy homeostasis by eliminating damaged cells recovery [22]. Besides regulating many cell behaviors including apoptosis, it also plays an essential role in cancer and infectious diseases [23]. An autophagy process produces LC3-II from LC3-I. p62 is a connexin involved in autophagy and apoptosis [24]. Caspase-8-mediated apoptosis through autophagy-related proteins LC3 and p62 [25]. Bax and Bcl-2 are markers of apoptosis. They can change mitochondria permeability and cause the release of cytochrome c, initiating apoptosis [26]. In this study, A3G knockout significantly enhanced LC-II expression and inhibited p62 expression. Moreover, after knocking down A3G, the W12 cells' apoptosis rate was significantly increased, Bax/Bcl-2 ratio was significantly increased, Cleaved-caspase-3 expression was also significantly increased, and cell proliferation was inhibited. As a result, A3G inhibition inhibits cervical intraepithelial neoplasia cell proliferation by promoting apoptosis and autophagy.

TGF-β plays a key role in cancer. Increased TGF-β activity is associated with poor clinical outcomes in tumors [27]. TGF-β can bind to TGF-β type I and type II semi-receptors in plasma membranes, phosphorylating Smad2 and Smad3, thereby interacting with Smad4 [28]. Our findings demonstrated that A3G knockdown inhibited TGF-β/Smad2 signaling pathway transmission, suggesting that A3G knockdown may promote apoptosis and autophagy of W12 cells through TGF-β/Smad2 signaling pathway, thereby inhibiting proliferation.

5. Conclusions

In summary, this study confirms that A3G in CIN exerts anti-autophagy and anti-apoptotic effects through the TGF-β/Smad2 pathway. Furthermore, A3G should be studied *in vivo* and clinically for CIN treatment.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

YRL and LS—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. YRL, ZZ and JTG—supervised the data collection, analyzed the data, interpreted the data. All authors

have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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