Article

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Testosterone Modulates Lipid Accumulation and Proliferation of Sebocytes through the Repression of Autophagy

Ying Xiong[1,2], Ting Chen[2], Jia Yu[2], Wenwen Sun[2], Bo Wu[2,*], Ledong Sun[1,*]

[1]Department of Dermatology, Guangdong Medical Products Administration Key Laboratory for Research and Evaluation of Drugs for Inflammatory Diseases, The Fifth Affiliated Hospital, Southern Medical University, 510900 Guangzhou, Guangdong, China
[2]Department of Dermatology, Shenzhen Maternity & Child Healthcare Hospital, 518028 Shenzhen, Guangdong, China
*Correspondence: bowu2004@hotmail.com (Bo Wu); sunledong126@126.com (Ledong Sun)
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Background: Androgen has been regarded as the strongest stimulator of sebum formation and sebocyte proliferation in individuals with acne. However, the underlying mechanisms remain to be elucidated. Recent studies suggest that autophagy is involved in lipid degradation and the regulation of cell proliferation. This study aims to explore the effects of testosterone on autophagy and its potential contribution to lipid accumulation and sebocyte proliferation.

Methods: Human SZ95 sebocytes were cultured with linoleic acid (LA) to induce sebum production. This study examined the role of testosterone in acne development by measuring autophagy, lipid accumulation, and cell proliferation. To determine whether testosterone's effects on acne depend on autophagy, the autophagy inducer rapamycin and the inhibitor 3-methyladenine (3-MA) were used in combination with LA.

Results: The results indicated that treatment with testosterone decreased the levels of LC-3II ($p < 0.01$) and Beclin 1 ($p < 0.01$) while increasing p62 level ($p < 0.05$) in SZ95 cells. Additionally, testosterone treatment induced lipid accumulation, as demonstrated by Oil Red O staining ($p < 0.01$), and increased Triglyceride (TG) content ($p < 0.01$) in SZ95 cells. Moreover, testosterone treatment increased cell viability in SZ95 cells according to the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay ($p < 0.01$) and increased the count of Ki67 positive cells in immunofluorescent staining ($p < 0.01$). Co-treatment with rapamycin reversed the effects of testosterone on autophagy ($p < 0.05$ or $p < 0.01$), lipid accumulation ($p < 0.01$), and sebocyte proliferation ($p < 0.01$). In contrast, treatment with 3-MA mimicked all the aforementioned effects of testosterone ($p < 0.05$ or $p < 0.01$). Furthermore, immunoblot analysis revealed that treatment with testosterone enhanced the phosphorylation of v-akt murine thymoma viral oncogene homolog (AKT) ($p < 0.01$) and the mammalian target of rapamycin (mTOR) ($p < 0.05$), which were counteracted by rapamycin ($p < 0.05$ or $p < 0.01$) but mimicked by 3-MA ($p < 0.05$).

Conclusions: These findings suggest that testosterone may facilitate acne progression by activating mTOR and subsequently inhibiting autophagy.

Keywords: androgen; acne; autophagy; mTOR; sebocyte

Introduction

Acne is a prevalent chronic inflammatory dermatosis [1,2], affecting approximately 33% of individuals and causing distress and low quality of life [3]. The excessive sebum production and the increased proliferation of sebocytes within the sebaceous glands, triggered by androgen stimulation, are crucial pathological processes in acne development [4,5]. Extensive clinical data and experimental studies strongly suggest that androgens play a significant role in stimulating sebum formation and sebocyte proliferation during acne progression [6,7]. However, the precise mechanisms by which androgens regulate sebum formation and sebocyte proliferation remain incompletely understood.

In general, lipid metabolism is maintained in a dynamic balance between synthesis and catabolism [8,9]. Enzyme-dependent lipolysis decomposes lipids into free fatty acids, which can then undergo further degradation through beta-oxidation in mitochondria. This process is considered the primary metabolic pathway that helps prevent the excessive accumulation of lipids in sebocytes [10, 11]. Apart from the traditional cytoplasmic lipolysis, recent studies have highlighted the significant role of autophagy in lipid degradation [12,13]. Moreover, emerging evidence suggests that autophagy may also play a role in regulating cell proliferation [14,15]. Interestingly, studies indicated a link between suppressed autophagy and the development of acne [16,17]. However, the precise mechanisms underlying this relationship remain largely unclear.

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The potential effects of androgens on autophagy have been investigated. Findings have shown that testosterone can suppress autophagy in Sertoli cells, thereby extending the lifespan of the androgen-binding protein [18]. Additionally, treatment with dehydroepiandrosterone has been shown to induce the mammalian target of rapamycin complex 1 (mTORC1) activation and autophagy suppression in skeletal muscle [19]. In contrast, dihydrotestosterone has been observed to trigger cell death in autoreactive T cells by enhancing the process of autophagy [20]. Consequently, we hypothesized that androgens may be a key factor leading to autophagy suppression in sebaceous glands, potentially promoting the development of acne by inhibiting autophagy and lipid decomposition. Therefore, the present study investigated whether androgen could modulate lipid metabolism in sebocytes through the regulation of autophagy.

Materials and Methods

Reagents

Linoleic acid (LA, #L1012), testosterone (T, #T5411), rapamycin (Rapa, #V900930), 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT, #M5655), and Oil Red O (#O0625) were obtained from Sigma-Aldrich (Saint Louis, MO, USA). Additionally, 3-methyladenine (3-MA) was obtained from MedChem Express (Monmouth Junction, NJ, USA). Antibodies for LC-3-II (#3868P) and Beclin-1 (#3495) were acquired from Cell Signaling Technology (Danvers, MA, USA), Ki67 (#ab16667), v-akt murine thymoma viral oncogene homolog (AKT) (#ab8805), p-AKT (#ab81283), mTOR (#ab134903), and p-mTOR (#ab109268) were from Abcam (Cambridge, UK). The Triglyceride (TG) assay kit was produced by Nanjing Jiancheng Bioengineering Institute (#A110-1-1, Nanjing, China). The Bicinchoninic acid (BCA) protein assay kit (TJ272651) and the enhanced chemiluminescent (ECL) detection kit (#NEL105001EA) were obtained from Thermo Fisher Scientific (Waltham, MA, USA) and PerkinElmer (Waltham, MA, USA), respectively.

Cell Culture and Treatment

Human SZ95 sebocytes, obtained from the China Type Culture Collection Center (#BFN60807569, Wuhan, China), underwent mycoplasma testing and STR identification. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS) with penicillin (100 U/mL), and streptomycin (100 mg/mL), and incubated at 37 °C with 5% CO_2. The cells were divided into four groups: control group, LA+T group, LA+T+Rapa group, and LA+3-MA group. In the control group, cells were cultured with 10 M LA. Cells in the LA+T and LA+T+Rapa groups were co-treated with 10 M LA and 100 M testosterone in the absence or presence of Rapa (1 M) to investigate whether testosterone-induced lipid accumulation resulted from autophagy suppression. Cells in the LA+3-MA group were co-treated with 10 M LA and 3-MA (5 mM) to investigate whether inhibiting autophagy would replicate the lipid accumulation effects of testosterone.

Oil Red O Staining

After fixation with 4% paraformaldehyde (PFA) for 30 min, the cells were immersed in a solution of 60% isopropanol for 2 min, followed by staining with Oil Red O for 5 min. Subsequently, they were washed with a 60% isopropanol solution for approximately 2 s. Hematoxylin staining was performed for 3 min, and the cells were then sealed with glycerol gelatin for long-term preservation. Observation of cell staining was conducted using an inverted Olympus microscope.

TG Measurement

The SZ95 sebocytes were harvested using type IV collagenase digestion. Subsequently, the cells were lysed to determine the Triglyceride (TG) levels following the manufacturer's guidelines.

MTT

The cells were cultured in 96-well plates and incubated at 37 °C with an MTT solution (0.5 mg/mL) for 4 h. Then, the cells were dissolved in 150 µL of dimethyl sulfoxide (DMSO), and the 96-well plate was agitated at room temperature for 15 min. Finally, a microplate reader (VLBLATGD2, Thermo Fisher Scientific, Waltham, MA, USA) was used to measure the absorbance of the samples at 570 nm.

Immunofluorescence

The SZ95 sebocytes, cultured on coverslips, were fixed with 4% formaldehyde solution, then permeabilized with 0.1% Triton X-100, and blocked with phosphate-buffered saline (PBS) containing 1% bovine serum albumin (BSA). Primary antibodies against LC-3-II (#3868P, 1:50, Cell Signaling Technology, Danvers, MA, USA) or Ki67 (#ab16667, 1:50, Abcam, Cambridge, UK) were incubated with the blocking solution at 4 °C overnight. After washing, the cells were treated with Alexa Fluor 594 GAR (#R37117, 1:200, Molecular Probes, Carlsbad, CA, USA) or a 488-conjugated secondary anti-rabbit IgG secondary antibody (#35552, 1:100, Thermo Fisher Scientific, Waltham, MA, USA) at room temperature for 2 h and counterstained with DAPI. The immunofluorescence-stained images were then examined and captured using a Leica Imager microscope (Leica DM4000, Leica, Wetzlar, Hessen, Germany).

Western Blotting

Total protein was extracted using the cell lysis kit (FNN0011, Thermo Fisher Scientific, Waltham, MA,

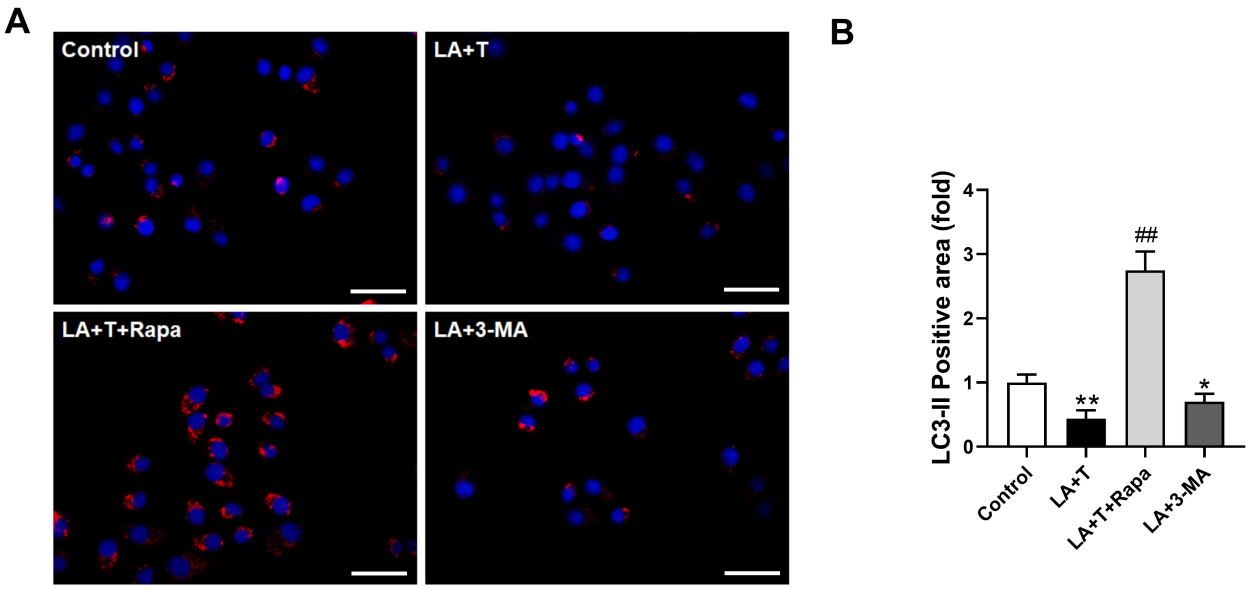

Fig. 1. Testosterone suppresses LC3-II expression in human SZ95 sebocytes. Following a 24-hour treatment with testosterone, the cells were subsequently fixed and subjected to immunofluorescence to observe the expression of (A) LC3-II protein and (B) the quantification of the relative positive area was performed. LA, linoleic acid (100 M); T, testosterone (100 M); Rapa, rapamycin (1 M); 3-MA, 3-methyladenine (5 mM). Scale bar: 50 µm. $^{*}p < 0.05$, $^{**}p < 0.01$, compared with the control group. $^{\#\#}p < 0.01$, compared with the LA+T group (n = 4).

USA). A total of 40 µg of proteins were separated in a 10% sodium dodecyl sulfate (SDS) polyacrylamide gels and subsequently transferred onto polyvinylidene difluoride membranes (PVDF) (IPVH00010, Merck Millipore, Billerica, MA, USA). The membranes were then blocked for 30 min. After washing with TBST containing BSA, the membranes were incubated with the primary antibodies overnight at 4 °C. The primary antibodies used were against Beclin-1 (#3495, 1:1000, Cell Signaling Technology, Danvers, MA, USA), p62 (ab56416, 1:1000, Abcam, Cambridge, UK), p-AKT (ab81283, 1:1000, Abcam, Cambridge, UK), p-mTOR (ab109268, 1:1000, Abcam, Cambridge, UK), and Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (SC-32233, 1:1000, Santa Cruz Biotechnology, Santa Cruz, CA, USA). Subsequently, HRP-conjugated secondary antibodies against mouse (ab136815, 1:2000, Abcam, Cambridge, UK) or rabbit (ab136817, 1:2000, Abcam, Cambridge, UK) were applied to the membranes and incubated at room temperature 2 h. After three washes with TBST, the bands were detected with enhanced chemiluminescence reagents. Specifically, Western Lightning Plus-enhanced chemiluminescent (ECL) reagent (NEL105001EA, PerkinElmer, Waltham, MA, USA) was applied on the PVDF membrane, and the chemiluminescent was visualized using the Tanon 5200 Chemiluminescent Image System (Tanon, Shanghai, China). The bands were then analyzed and semi-quantified using Quantity One 4.6.2 software (Bio-Rad, Hercules, CA, USA).

Statistics Analysis

The data were presented as mean ± standard deviation (SD). The differences among the groups were determined using a one-way analysis of variance (ANOVA). The data were analyzed using GraphPad Prism (Version: 8.4.2, GraphPad Software, Inc., Boston, MA, USA). A *p*-value less than 0.05 was considered statistically significant.

Results

Testosterone Suppresses Autophagy in Sebocytes

Fig. 1 illustrates the immunofluorescent staining of LC3-II, a molecular marker of autophagy [21]. It was observed that treatment with testosterone reduced LC3-II levels in SZ95 cells ($p < 0.01$), indicating testosterone's inhibitory effect on autophagy in sebocytes. The suppressive effects of testosterone on LC3-II were reversed by the autophagy activator rapamycin ($p < 0.01$) [22], but mimicked by the autophagy inhibitor, 3-MA ($p < 0.05$) [19]. Consistent with these results, treatment with testosterone led to a decrease in Beclin 1 levels ($p < 0.01$), a molecular scaffold for the assembly of the autophagy machinery [23], which was inhibited by rapamycin but mimicked by 3-MA (Fig. 2). Conversely, treatment with testosterone increased the levels of p62 ($p < 0.05$), a protein degraded by autophagy [24] (Fig. 2). Additionally, the modulatory impact of testosterone on p62 was reversed by rapamycin ($p < 0.05$) but mimicked by 3-MA ($p < 0.0$) (Fig. 2). These findings indicate that testosterone inhibits autophagy in sebocytes.

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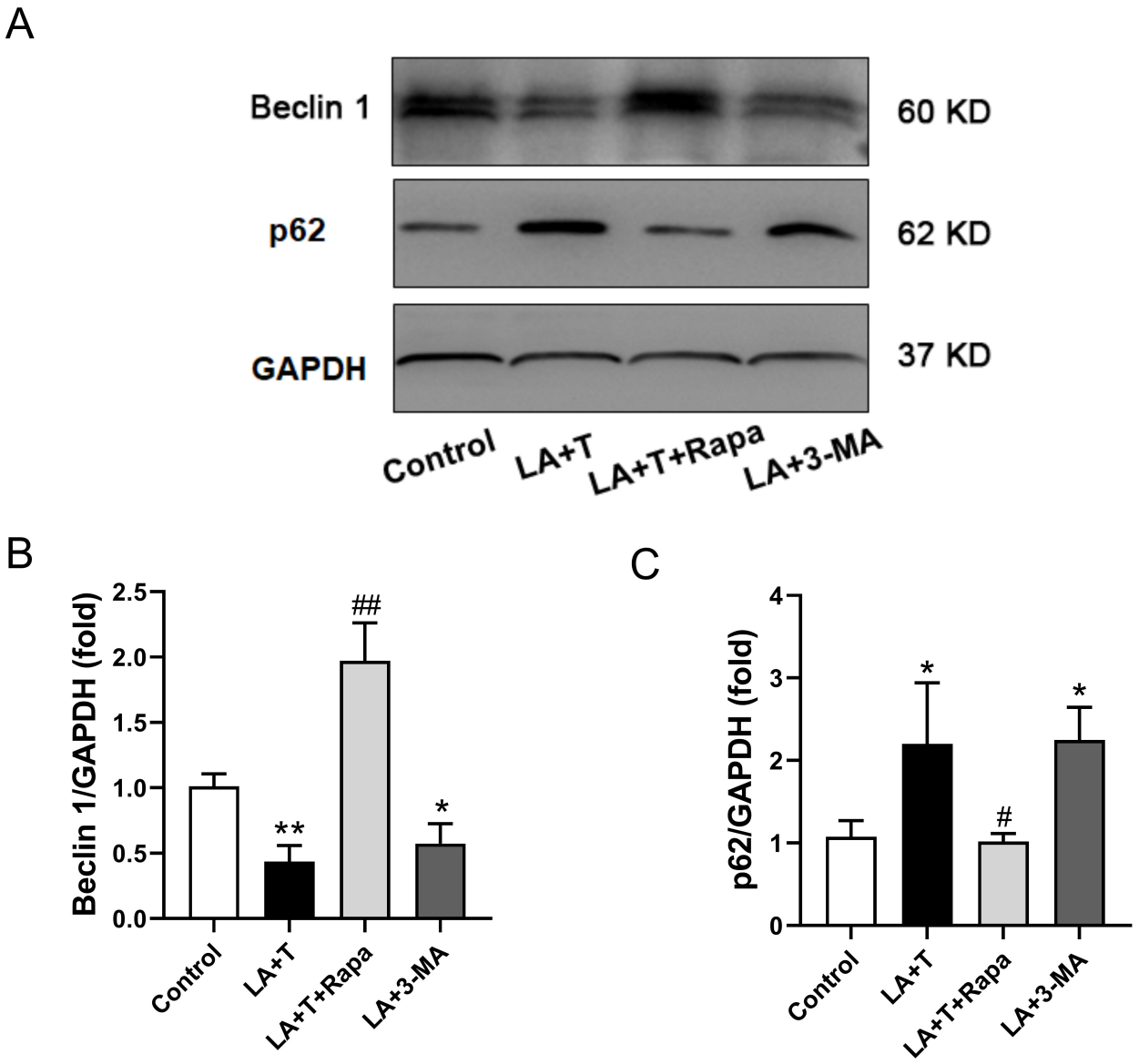

Fig. 2. Testosterone modulates Beclin 1 and p62 expression in human SZ95 sebocytes. (A) Following a 24-hour treatment with testosterone, the cells were harvested to assess Beclin 1 and p62 protein levels by Western blot analysis, with Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) serving as the internal standard for protein loading. (B,C) The blots were semi-quantified and the data were expressed as relative intensity levels. *$p < 0.05$, **$p < 0.01$, compared with the control group. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, compared with the LA+T group (n = 4).

Testosterone Promotes Lipid Accumulation through the Repression of Autophagy

As expected, treatment with testosterone promoted the accumulation of lipids in SZ95 cells, as visualized using Oil Red O staining, a widely used method for assessing intracellular lipid content [25] ($p < 0.01$) (Fig. 3). This effect was further confirmed by the TG content assay, which also showed a significant increase in lipid accumulation due to testosterone treatment ($p < 0.01$) (Fig. 4). Co-treatment with rapamycin reversed the stimulatory impact of testosterone on lipid accumulation ($p < 0.01$) and TG content ($p < 0.01$) (Figs. 3,4). In addition, treatment with 3-MA replicated the effects of testosterone on lipid accumulation ($p < 0.05$) and TG content ($p < 0.01$) (Figs. 3,4). Therefore, testosterone promotes lipid accumulation by inhibiting autophagy.

Testosterone Promotes the Proliferation of Sebocytes through the Repression of Autophagy

Testosterone has been shown to promote the proliferation of sebocytes, which contributes to the pathological roles of androgens in acne [11]. The MTT assay found that treatment with testosterone increased the number of viable SZ95 cells ($p < 0.01$), and this effect was reversed by rapamycin ($p < 0.01$) but mimicked by 3-MA ($p < 0.05$) (Fig. 5). Similarly, Ki67 staining for proliferating cells

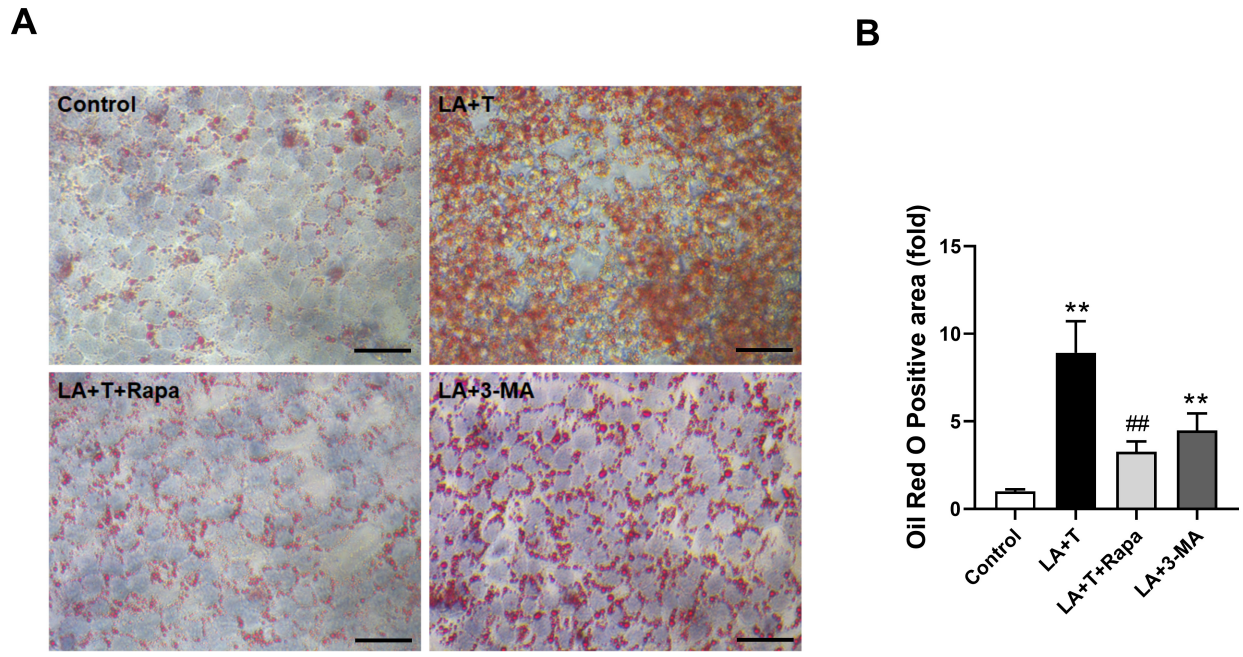

Fig. 3. Testosterone promotes lipid accumulation in human SZ95 sebocytes. (A,B) Following a 24-hour treatment with testosterone, the cellular lipid content was stained with Oil Red O to visualize and quantify the relative positive area. Scale bar: 50 μm. $^{**}p < 0.01$, compared with the control group. $^{\#\#}p < 0.01$, compared with the LA+T group (n = 4).

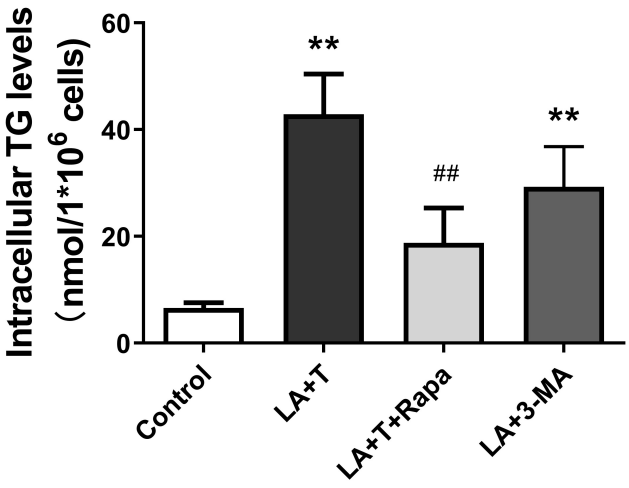

Fig. 4. Testosterone increases TG content in human SZ95 sebocytes. Following a 24-hour treatment with testosterone, the Triglyceride (TG) content in the cells was measured. $^{**}p < 0.01$, compared with the control group. $^{\#\#}p < 0.01$, compared with the LA+T group (n = 8).

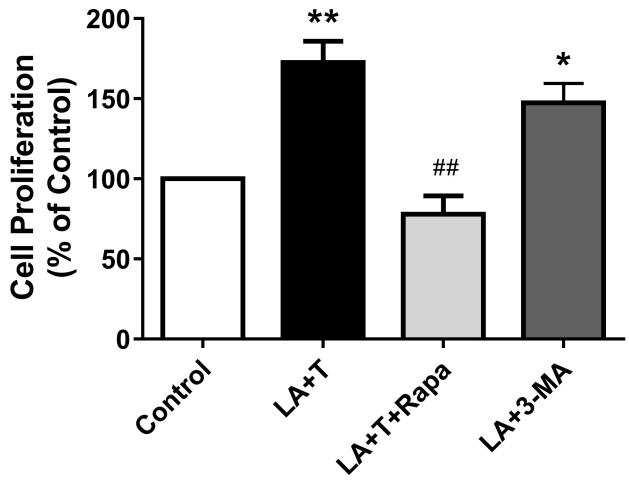

Fig. 5. Testosterone promotes the proliferation of human SZ95 sebocytes. Following a 24-hour treatment with testosterone, the cell proliferation was measured using the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay. $^{*}p < 0.05$, $^{**}p < 0.01$, compared with the control group. $^{\#\#}p < 0.01$, compared with the LA+T group (n = 8).

also resulted in comparable findings ($p < 0.05$ or $p < 0.01$) (Fig. 6). These results indicate that testosterone stimulates the proliferation of sebocytes by suppressing autophagy.

Testosterone Activates the AKT-mTOR Pathway

The AKT-mTOR pathway plays a crucial role in autophagy [26]. Immunoblot analysis revealed that treatment with testosterone significantly increased the phosphorylation of AKT ($p < 0.01$) and mTOR ($p < 0.05$). Concurrent administration of rapamycin reversed the stimulatory effect of testosterone on AKT ($p < 0.01$) and mTOR ($p < 0.05$), while the application of 3-MA replicated the effect of testosterone on mTOR phosphorylation ($p < 0.05$) (Fig. 7). Therefore, testosterone activates the AKT-mTOR pathway, subsequently inhibiting autophagy.

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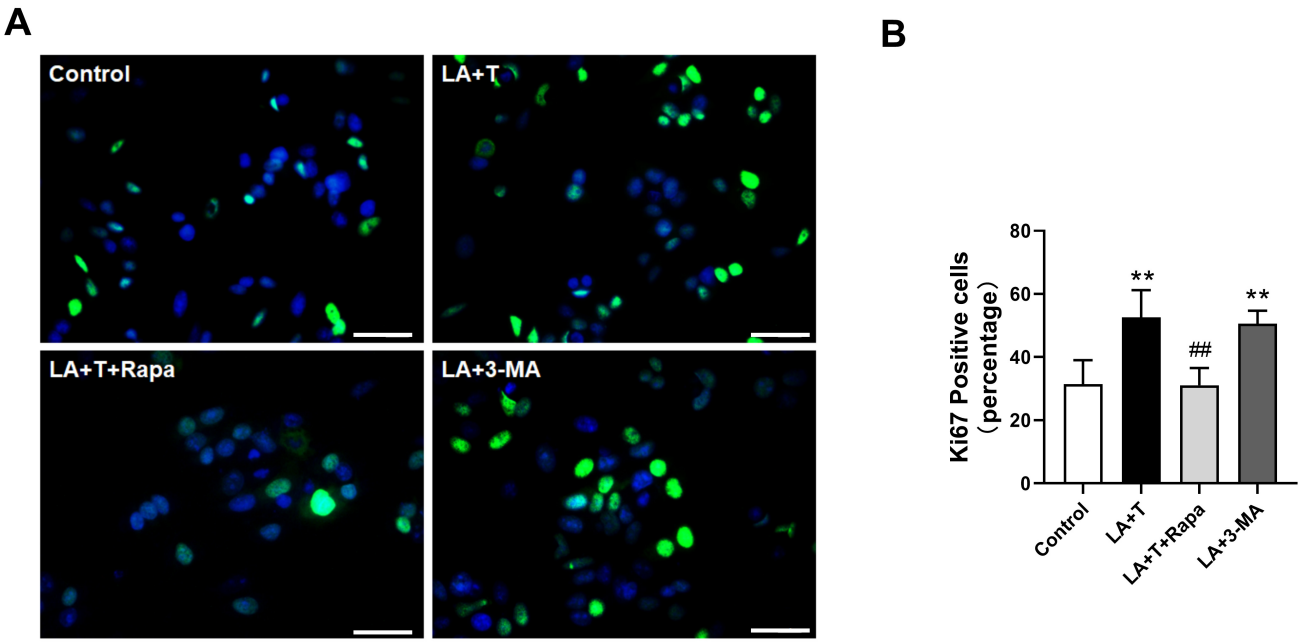

Fig. 6. Testosterone increases Ki67 expression in human SZ95 sebocytes. (A,B) Following a 24-hour treatment with testosterone as indicated, the cells were fixed and the expression of Ki67was identified using immunofluorescence detection, and then the relative number of Ki67-positive cells was quantified. Scale bar: 50 μm. $^{**}p < 0.01$, compared with the control group. $^{\#\#}p < 0.01$, compared with the LA+T group (n = 4).

Discussion

Androgen-induced dysregulated lipid accumulation is an important mechanism underlying the development of acne [27]. However, the mechanism by which androgens induce lipid increase is not fully elucidated. Several recent findings have found that suppressed autophagy significantly contributes to the amplified aggregation of lipids within sebaceous cells. The inactivation of autophagy within the sebaceous glands resulted in an oily and unkempt appearance of the coat in aged male mice, enlarged glands, increased proliferation in SG epithelia, and altered lipid class composition of sebum and fatty acyl chain length of wax esters [28]. The present study found that androgen exposure suppressed autophagy in sebocytes. These data suggest that androgen might act as a significant suppressor of autophagy, potentially representing a novel mechanism contributing to the development of acne.

It is widely accepted that androgen plays a crucial role in the progress of both benign prostatic hyperplasia and prostate carcinogenesis [29,30]. The mechanisms underlying the pathological activities of androgens in prostate carcinogenesis are complex, and suppressed autophagy by androgen has been regarded as a crucial mechanism involved in the progression of prostate cancer [31,32]. In addition to prostate cancer cells, the inhibitory effects of androgens on autophagy have been previously observed in skeletal muscle and Sertoli cells [33,34]. Scientists have examined the impact of autophagy on glucose utilization and insulin sensitivity in mice with a skeletal muscle-specific Atg7 gene knockout (absence of autophagy). These mice exhibited a reduction in lean body mass and fat mass, along with heightened glucose clearance and increased energy expenditure. Furthermore, the identification of muscle atrophy and decreased muscle strength in mutant mice suggests the function of autophagy in maintaining muscle mass [35]. Utilizing pharmacological approaches, including co-administration of an autophagy inducer and treatment with an autophagy inhibitor, the current investigation also revealed that the stimulatory effects of testosterone on sebocytes dependon its inhibitory activities on autophagy. Therefore, the modulation of autophagy may represent a common molecular mechanism responsible for both the physiological and pathophysiological effects of androgens.

In addition to lipolytic enzyme-dependent lipid catabolism, an increasing amount of research suggests that autophagy is involved in the regulation of lipid breakdown as well [36,37]. Autophagy and lipolysis participate in lipid catabolism, with crosstalk and regulatory interactions [38]. A recent study revealed that the absence of autophagy in Atg7 mutant mice led to increased sebogenesis in the skin [28]. This study demonstrated that autophagy is implicated in acne development. Furthermore, when comparing the transcriptome expression of patients who did not respond to isotretinoin treatment with those who did, it was observed that the autophagy pathway was significantly upregulated in patients who positively responded to isotretinoin treatment [39]. *Pseudomonas acnes* can evade the autophagy process

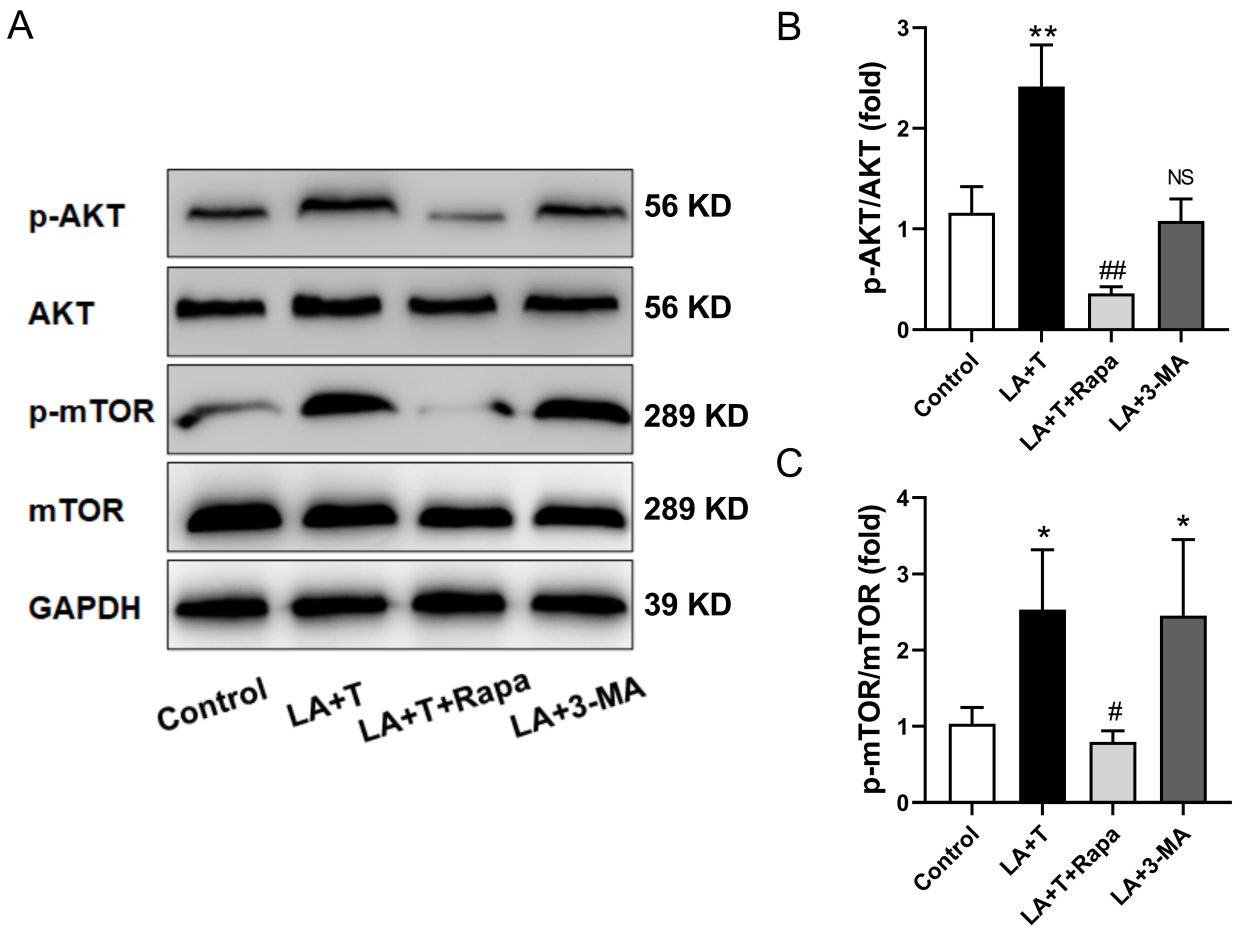

Fig. 7. Testosterone activates the v-akt murine thymoma viral oncogene homolog (AKT)-mammalian target of rapamycin (mTOR) signal pathway in human SZ95 sebocytes. (A) Following a 24-hour treatment with testosterone, cells were harvested to evaluate the levels of phosphorylated AKT, total AKT, phosphorylated mTOR, and total mTOR using western blotting, with GAPDH as the loading control. (B,C) The blots were then semi-quantitatively analyzed, and the results were presented as relative intensity levels. $^{*}p < 0.05$, $^{**}p < 0.01$, compared with the control group. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, compared with the LA+T group. NS (not significant) indicated no significant differences from the control group (n = 4).

and induce the skin's inflammatory response, resulting in acne rash [40]. Local administration of an autophagy inducer mitigated sebaceous lipogenesis, enhanced the skin's barrier function, and alleviated acne manifestations [17]. Therefore, the modulation of autophagy in sebocytes might be responsible for the pathological effects of testosterone in patients with acne.

Androgen stimulation not only modulates lipid accumulation but also contributes to the development of acne by promoting sebocyte proliferation [41]. Interestingly, growing evidence suggests that autophagy may play a role in regulating proliferation. For example, activation of the autophagy pathway has been shown to suppress the proliferation of A549 cells [14]. Similarly, in sebocytes, the rate of proliferation was increased in mice lacking Atg7, a critical autophagy-related protein [28]. Therefore, the inhibition of autophagy by testosterone may also lead to enhanced proliferation of sebocytes, ultimately resulting in the development of acne.

It has been confirmed that the AKT-mTOR signaling pathway plays a crucial role in regulating autophagy [42]. The activation of AKT-mTOR leads to the phosphorylation of serval autophagy-related proteins, resulting in the suppression of autophagy [43]. Evidence indicates that mTOR is upregulated in acne vulgaris lesions [44]. The present study found that treatment with testosterone enhanced the phosphorylation of AKT-mTOR, suggesting that AKT-mTOR is activated by testosterone. Consistent with our findings, treatment with testosterone activated mTOR and reduced autophagy in cultured C2C12 myotubes [19]. In addition to drug therapy, a diet with no hyperglycemic carbohydrates and dairy products can be beneficial in treating acne by decreasing the activity of the mTOR pathway [3]. Moreover, the present study showed that inhibiting mTOR with rapamycin can reverse the effects of testosterone on autophagy. Consequently, the activation of mTOR may play a crucial role in mediating the effects of testosterone on sebocytes.

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Recent studies have revealed that several hormone receptors, such as androgen receptor (AR), are expressed in the sebaceous gland, indicating direct hormonal regulation of this gland [8,45]. Among these receptors, androgens emerge as the most effective regulators influencing the biology and function of sebaceous glands in both males and females [46]. Testosterone and dihydrotestosterone are the most active androgens that exert their effects through AR [47]. Treatment with anti-androgens, such as AR antagonists, has been shown to significantly reduce sebum secretion, decrease hyperkeratosis, and mitigate subsequent inflammatory responses, offering a key approach in acne treatment [46]. Therefore, anti-androgen therapy may promote autophagy-mediated lipid catabolism, presenting a crucial strategy in acne treatment.

Conclusions

The present study uncovered that androgens might promote the formation of sebum through the repression of autophagy-induced lipid degradation in sebocytes, which would be prevented by the treatment with the autophagy activator rapamycin. While the precise mechanisms underlying the suppressive effects of androgens on autophagy require further investigation, the present study has revealed a novel pathway through which androgens may promote the progression of acne.

Availability of Data and Materials

Information will be available on reasonable request from the corresponding authors.

Author Contributions

Conceptualization, YX and LS; Methodology, YX; Validation, YX, BW, and TC; Formal analysis and investigation, YX, BW and LS; Resources, TC; Data curation, YX, BW; Writing—original draft preparation, YX; Writing—review and editing, TC, WS; Visualization, JY, WS, YX and LS; Supervision, YX and LS; Funding acquisition, BW and LS. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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