



## ORIGINAL ARTICLE

# Azidothymidine Downregulates Insulin-Like Growth Factor-1 Induced Lipogenesis by Suppressing Mitochondrial Biogenesis and Mitophagy in Immortalized Human Sebocytes

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**Background:** Increased sebum secretion is considered the main causative factor in the pathogenesis of acne. There is an unmet pharmacological need for a novel drug that can control sebum production with a favorable adverse effect profile.

**Objective:** To investigate the effect of azidothymidine on lipid synthesis in sebocytes and to identify the underlying mechanism of the inhibitory effect of azidothymidine on insulin-like growth factor (IGF)-1-induced lipid synthesis in sebocytes. **Methods:** Immortalized human sebocytes were used for the analysis. Thin-layer chromatography (TLC) and Oil Red O staining were performed to evaluate lipid synthesis in the sebocytes. The differentiation, lipid synthesis, mitochondrial biogenesis, and mitophagy in sebocytes were investigated. **Results:** TLC and Oil Red O staining revealed that azidothymidine reduced IGF-1 induced lipid synthesis

in the immortalized human sebocytes. Azidothymidine also reduced IGF-1-induced expression of transcriptional factors and enzymes involved in sebocyte differentiation and lipid synthesis, respectively. Moreover, we found that IGF-1 upregulated the levels of peroxisome proliferator-activated receptor-gamma coactivator-1  $\alpha$ , LC-3B, p62, and Parkin, major regulators of mitochondrial biogenesis and mitophagy in immortalized human sebocytes. In contrast, azidothymidine inhibited IGF-1 induced mitochondrial biogenesis and mitophagy in the sebocytes. **Conclusion:** These results suggest that azidothymidine downregulates IGF-1-induced lipogenesis by dysregulating the quality of mitochondria through suppression of mitochondrial biogenesis and mitophagy in immortalized human sebocytes. Our study provides early evidence that azidothymidine may be an effective candidate for a new pharmacological agent for controlling lipogenesis in sebocytes. (*Ann Dermatol* 33(5) 425 ~ 431, 2021)

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## -Keywords-

Acne, Azidothymidine, Lipids, Mitochondria, Sebocyte

## INTRODUCTION

Acne is a common and chronic inflammatory disorder of the pilosebaceous gland<sup>1</sup>. Since acne follows a prolonged relapsing and remitting course, and the associated lesions are mainly located on the face, it significantly impairs the patient's quality of life<sup>1</sup>. Although the exact mechanism of acne remains unclear, it is well established that an increase in sebum synthesis is a key pathogenic factor in the development of acne<sup>1,2</sup>. Although various topical and systemic

therapies have been introduced for the treatment of acne, only isotretinoin reduces the production of sebum<sup>1,3</sup>. However, the adverse effects of isotretinoin, including teratogenicity, mood change, and dysregulation of blood lipid profile has limited its wide use in the treatment of acne<sup>1,3</sup>. Therefore, there is a pressing need for finding novel agents that control sebum production with favorable adverse effect profiles.

Highly active antiretroviral therapy (HAART), based on the use of a combination of antiretroviral agents acting on different viral targets, is the current standard therapy for the treatment of human immunodeficiency virus (HIV) infection<sup>4,5</sup>. However, the use of HAART in HIV-infected patients has been associated with the development of abnormal lipid metabolism and lipodystrophy<sup>4,5</sup>. Peripheral fat loss is a clinical presentation of lipodystrophy following HAART and its relationship with the use of azidothymidine has been well established<sup>4,6</sup>. Previous studies suggest that abnormal adipogenesis induced by mitochondrial toxicity following HAART may be the mechanism for peripheral fat loss following HAART<sup>4,6</sup>.

In this study, we investigated the effect of azidothymidine on lipid production in immortalized human sebocytes and found that azidothymidine decreased lipid synthesis in immortalized human sebocytes by suppressing mitochondrial biogenesis and mitophagy.

## MATERIALS AND METHODS

We obtained human scalp tissues under the written informed consent of donors under the Institutional Review Board of Chungnam National University Hospital (IRB No. 1011-135).

### Cell culture

Immortalized human sebocytes were used for the experiment. The cell line was established as previously described<sup>7</sup>. The immortalized human sebocytes were cultured in Sebomed Medium (Biochrom, Berlin, Germany) supplemented with 10% fetal bovine serum (Gibco BRL, Rockville, MD, USA) and 5 ng/ml of recombinant human epidermal growth factor (Invitrogen, Grand Island, NY, USA).

### Thin-layer chromatography

For quantitative analysis of intracellular lipids, we performed thin-layer chromatography (TLC) as described previously<sup>7</sup>. In brief, immortalized human sebocytes were incubated with medium containing 2  $\mu$ Ci of <sup>14</sup>C-acetate and sodium salt (PerkinElmer, Boston, MA, USA) and incubated for 4 hours. Intracellular lipids were extracted with chloro-

form and methanol (2:1). The solvents were evaporated, and the lipids were reconstituted in chloroform. TLC (TLC silica gel 60 F<sub>254</sub>, Merck KgaA) was performed to separate the intracellular lipids. After developing with hexane and ethyl acetate (6:1), an autoradiographic method was used to visualize the intracellular lipids.

### Oil Red O staining

To detect intracellular lipids in the immortalized human sebocytes, the cells were grown on a cover glass. At the end of the treatment, cells were washed with PBS and fixed with 10% formaldehyde at room temperature for 1 h. After washing with distilled water, the fixed cells were stained with filtered Oil Red O solution for 30~60 minutes. The cells were then washed with distilled water and counterstained with hematoxylin.

### Western blotting

After harvesting, the cells were lysed in protein extraction solution (Intron, Daejeon, Korea). Equal amounts of protein were then loaded and separated on a sodium dodecyl sulfate-polyacrylamide gels, and then the proteins were transferred onto nitrocellulose membranes (Pall Corp., Port Washington, NY, USA). After blocking with 5% skim milk, the membranes were incubated with various primary antibodies. The blots were then incubated with peroxidase-conjugated secondary antibody, and enhanced chemiluminescence (Biomax, Seoul, Korea) was used to visualize the specific proteins. The primary antibodies used in western blot analysis were as follows: actin, sterol regulatory element-binding protein-1 (SREBP-1) (Santa Cruz Biotechnology, Santa Cruz, CA, USA), SREBP-2, farnesyl-diphosphate farnesyltransferase-1 (FDFT-1), peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1  $\alpha$ , mitochondrial transcription factor A (mtTFA), p62, Parkin (Abcam, Cambridge, UK), fatty acid synthase (FASN), peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), insulin-like growth factor-1 receptor (IGF-1R), phospho-IGF-1R, Akt, phospho-Akt, mechanistic target of rapamycin (mTOR), phospho-mTOR, (Cell Signalling Technology, Danvers, MA, USA), stearoyl-coenzyme A desaturase (SCD) (Thermo Scientific, Rockford, IL, USA), and LC-3 (Sigma, St. Louis, MO, USA).

### Real-time polymerase chain reaction

Total ribonucleic acid (RNA) was isolated from the immortalized human sebocytes using an easy-BLUE RNA Extraction Kit (Intron, Daejeon, Korea). Total RNA (2  $\mu$ g) was reverse-transcribed to complementary DNA using M-MLV reverse transcriptase (ELPIS Biotech, Daejeon, Korea) according to the manufacturer's instructions. Real-time

polymerase chain reaction (RT-PCR) was performed using SYBR Green Real-time PCR Master Mix (Applied Biosystems, Waltham, MA, USA). The expression level of each gene was presented as fold-change normalized to the level of glyceraldehyde 3-phosphate dehydrogenase (GAPDH). The primers used in RT-PCR are listed below: FDFT-1 (5'-CATTGGGATGGCAGAGTTTT-3' and 5'-TGGTGCAGTGCATTGGTTAT-3'); FASN (forward: 5'-CCCACCTACGTACTGGCCTA-3' and reverse: 5'-CTTGGCCTTGGGTGTGTACT-3'); SCD (forward: 5'-CGACGTGGCTTTTCTTCTC-3' and reverse: 5'-GGGGCTAATGTTCTTGTCA-3'); and GAPDH (forward: 5'-CGACCACTTTGTCAAGCTCA-3' and reverse: 5'-AGGGGTCTACATGGCAACTG-3').

### Statistical analysis

The results are presented as mean  $\pm$  standard deviation. Student's t-test was used to analyze the difference between the sets of data using IBM SPSS (version 24.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at  $p < 0.05$ .

## RESULTS

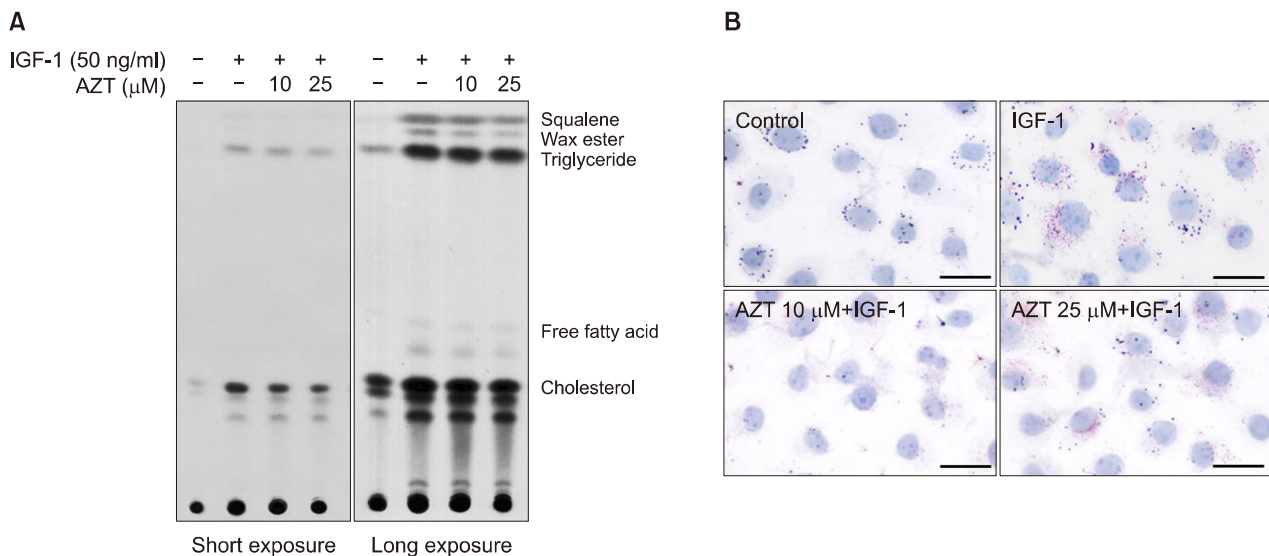
### Azidothymidine decreased intracellular lipid levels in immortalized human sebocytes

Using an immortalized human sebocyte cell line that was established previously<sup>7</sup>, we first investigated the effect of

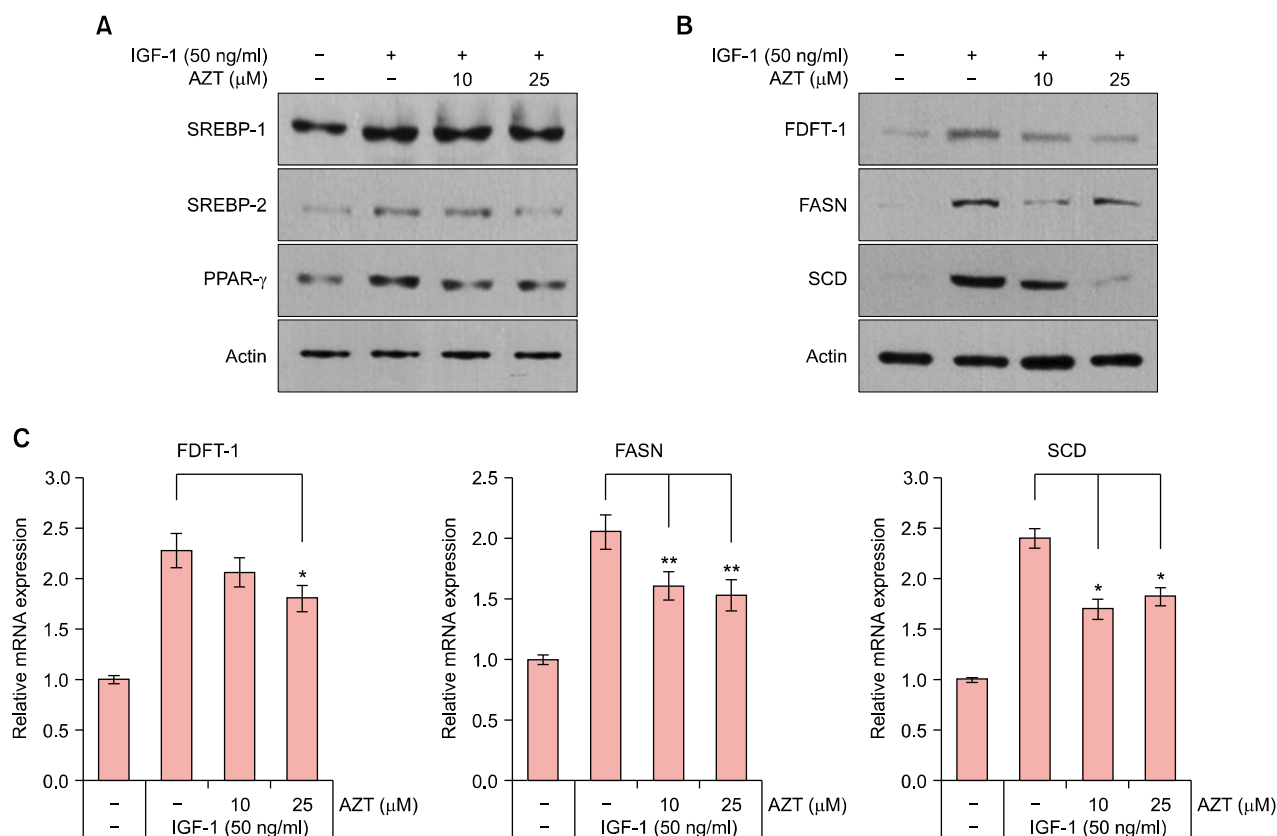
azidothymidine on IGF-1-induced lipogenesis. The immortalized human sebocytes were treated with 10 or 25  $\mu$ M of azidothymidine. Following azidothymidine treatment for 1 hour, the sebocytes were treated with 50 ng/ml of IGF-1 to induce differentiation and lipid production. The results of TLC performed after 48 hours of IGF-1 treatment showed that IGF-1 treatment increased intracellular lipid accumulation in the immortalized human sebocytes, while treatment with azidothymidine decreased intracellular lipid accumulation in a dose-dependent manner (Fig. 1A). IGF-1 induced increased synthesis of intracellular lipids such as cholesterol, triglycerides, wax esters, and squalene in the immortalized human sebocytes. In contrast, treatment with azidothymidine decreased IGF-1 induced lipid synthesis. Among the various lipids, the synthesis of squalene and wax ester was markedly reduced by azidothymidine. Oil Red O staining after 48 hours of IGF-1 treatment also revealed that IGF-1 increased the number of lipid droplets in the immortalized human sebocytes, whereas treatment with azidothymidine decreased the number of lipid droplets in the immortalized human sebocytes (Fig. 1B).

### Azidothymidine suppressed insulin-like growth factor-1 induced lipid synthesis in the immortalized human sebocytes

To examine the effect of azidothymidine on IGF-1-in-



**Fig. 1.** Azidothymidine (AZT) decreased the intracellular lipid in insulin-like growth factor (IGF)-1 treated immortalized human sebocytes. (A) Intracellular lipids were analyzed using thin-layer chromatography. The intracellular lipids increased following IGF-1 treatment for 48 hours, however, AZT decreased the intracellular lipids in IGF-1 treated immortalized human sebocytes. (B) Intracellular lipids were stained with Oil Red O stain. IGF-1 treatment for 48 hours increased the number of lipid droplets in the immortalized human sebocytes, whereas treatment with AZT decreased the number of lipid droplets in the immortalized human sebocytes. Scale bar = 20  $\mu$ m ( $\times 400$ ).



**Fig. 2.** Azidothymidine (AZT) suppressed insulin-like growth factor (IGF)-1 induced lipid synthesis in immortalized human sebocytes. (A) Analysis of sebocyte differentiation-associated transcription factors in immortalized human sebocytes after 12 hours of IGF-1 treatment. (B) Analysis of lipid synthesis-associated enzymes in immortalized human sebocytes after 24 hours of IGF-1 treatment. (C) Analysis of mRNA expression of lipid synthesis-associated enzymes in IGF-1 treated immortalized human sebocytes after 24 hours of IGF-1 treatment (\* $p < 0.05$ , \*\* $p < 0.01$ ). SREBP: sterol regulatory element-binding protein, PPAR: peroxisome proliferator-activated receptor, FDFT: farnesyl-diphosphate farnesyltransferase, FASN: fatty acid synthase, SCD: stearoyl-coenzyme A desaturase.

duced lipid synthesis in immortalized human sebocytes, we investigated the transcription factors and enzymes involved in sebocyte differentiation and lipid synthesis. Treatment of the immortalized human sebocytes with IGF-1 for 12 hours increased the levels of various transcription factors associated with sebocyte differentiation, such as SREBP-1, SREBP-2, and PPAR- $\gamma$ , but azidothymidine decreased their levels in a dose-dependent manner (Fig. 2A).

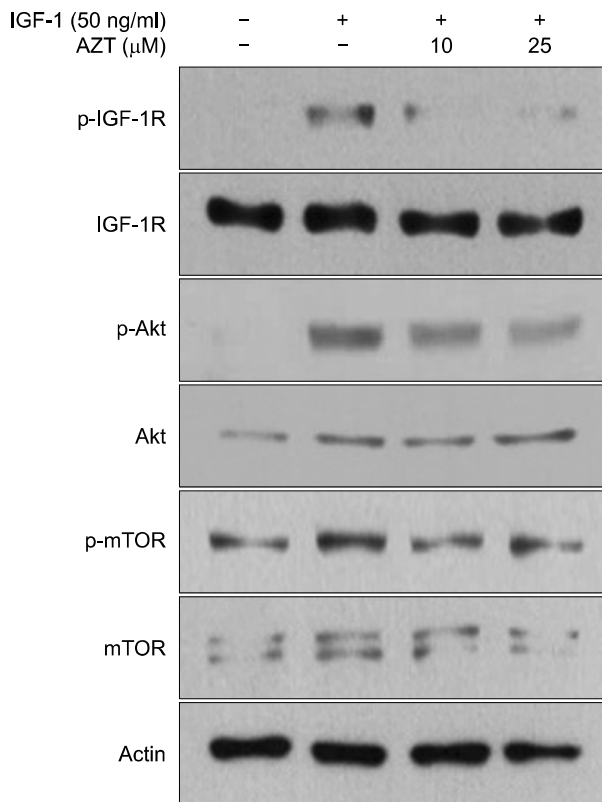
As these transcription factors control the expression of enzymes involved in lipid synthesis, we investigated the expression of these enzymes involved, including FDFT-1 for squalene synthesis, and FASN and SCD for fatty acid synthesis. As expected, the results showed that azidothymidine downregulated FDFT-1, FASN, and SCD in a dose-dependent manner, whose expressions were increased by 24-hour IGF-1 treatment (Fig. 2B). Moreover, the mRNA expression of these enzymes that was upregulated by the treatment of IGF-1 for 24 hours was downregulated fol-

lowing azidothymidine treatment (Fig. 2C). These results suggest that azidothymidine suppresses IGF-1-induced lipid synthesis in sebocytes by inhibiting sebocyte differentiation and lipid synthesis.

As we previously reported a role of the Akt/mTOR signaling pathway in IGF-1-induced lipid synthesis in sebocytes<sup>2</sup>, we further examined whether azidothymidine modulates the Akt/mTOR signaling pathway. Our analysis revealed that the IGF-1 treatment for 30 minutes increased the phosphorylation of IGF-1R and downstream effectors including Akt and mTOR (Fig. 3). In contrast, azidothymidine markedly decreased the phosphorylation of IGF-1R, Akt, and mTOR in a dose-dependent manner.

**Azidothymidine suppresses insulin-like growth factor-1-induced mitochondrial biogenesis and mitophagy**

Previous studies reported the role of IGF-1 in maintaining mitochondrial function<sup>8</sup>. Lyons et al.<sup>8</sup> reported that IGF-1 maintains mitochondrial homeostasis by inducing mito-



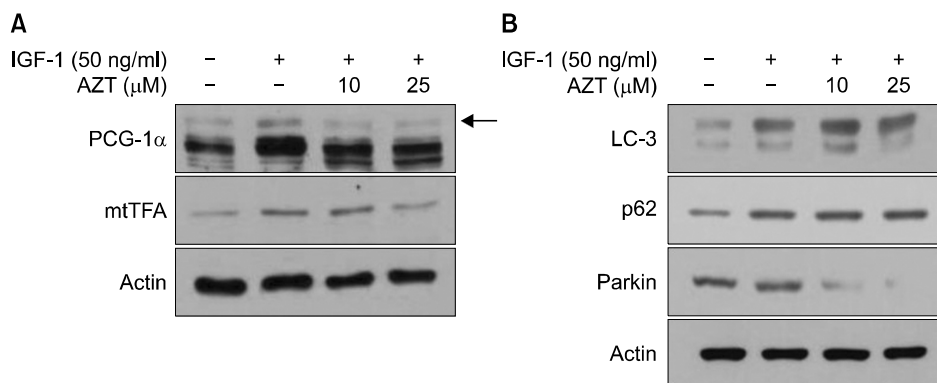
**Fig. 3.** Azidothymidine (AZT) suppresses the insulin-like growth factor (IGF)-1-induced Akt/mechanistic target of rapamycin (mTOR) signaling in immortalized human sebocytes. IGF-1 treatment for 30 minutes increased the phosphorylation of IGF-1 receptor (IGF-1R) and the downstream effectors, Akt and mTOR. In contrast, AZT decreased the IGF-1-induced phosphorylation of IGF-1R, Akt, and mTOR.

chondrial biogenesis and mitophagy. In contrast, azidothymidine was reported to induce mitochondrial dysfunction and suppress autophagy in adipocytes<sup>4</sup>. Therefore, we investigated the role of IGF-1 and azidothymidine in mitochondrial biogenesis and mitophagy in the immortalized human sebocytes.

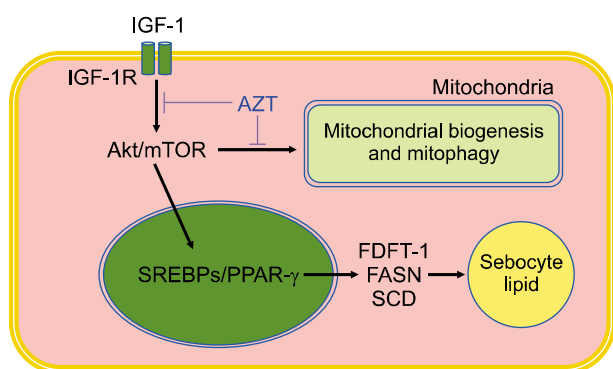
As expected, IGF-1 treatment for 24 hours increased the level of PGC-1  $\alpha$ , a major regulator of mitochondrial biogenesis (Fig. 4A)<sup>9</sup>. In addition, the expression of mtTFA, a key regulator of mitochondrial DNA transcription<sup>10</sup>, was also up-regulated following IGF-1 treatment. In contrast, azidothymidine suppressed the expression of PGC-1  $\alpha$  and mtTFA in the immortalized human sebocytes. To evaluate mitophagy in the immortalized human sebocytes, we investigated the levels of mitophagy-related proteins and found that IGF-1 treatment for 24 hours increased the levels of LC-3, p62, and Parkin, which implies activation of PINK1/Parkin-mediated mitophagy by IGF-1 in the immortalized human sebocytes (Fig. 4B)<sup>11-13</sup>. However, azidothymidine decreased the level of Parkin, while increasing the level of LC-3 and p62, which implies dysregulation of mitophagy by azidothymine in IGF-1 treated immortalized human sebocytes. These results suggested that azidothymidine suppressed IGF-1-induced mitochondrial biogenesis and mitophagy in sebocytes.

## DISCUSSION

Our study presents an in-depth analysis of the mechanism underlying the effects of IGF-1 and azidothymidine on sebocytes (Fig. 5). We found that azidothymidine decreased



**Fig. 4.** Azidothymidine (AZT) suppresses the insulin-like growth factor (IGF)-1-induced mitochondrial biogenesis and mitophagy. (A) IGF-1 treatment for 24 hours increased the levels of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1  $\alpha$  and mitochondrial transcription factor A (mtTFA) in the immortalized human sebocytes, which implies that IGF-1 induces mitochondrial biogenesis. In contrast, AZT decreased the levels of PGC-1  $\alpha$  and mtTFA in IGF-1-treated sebocytes, suggesting the suppressive effect of AZT on the IGF-1-induced mitochondrial biogenesis. An arrow indicates the exact protein size of PGC-1  $\alpha$ . (B) IGF-1 treatment for 24 hours increased the levels of mitophagy-related proteins (LC-3, p62, and Parkin), suggesting that IGF-1 induces mitophagy in immortalized human sebocytes. However, AZT treatment decreased the level of Parkin, and increased the level of LC-3 and p62, which suggests the suppressive effect of AZT on IGF-1-induced PINK1/Parkin-mediated mitophagy in the immortalized human sebocytes.



**Fig. 5.** Azidothymidine (AZT) downregulates insulin-like growth factor (IGF)-1 induced lipogenesis by suppressing mitochondrial biogenesis and mitophagy in immortalized human sebocytes. Schematic diagram of effect of azidothymidine on lipid synthesis in sebocytes. mTOR: mechanistic target of rapamycin, SREBP: sterol regulatory element-binding protein, PPAR: peroxisome proliferator-activated receptor, FDFT: farnesyl-diphosphate farnesyl-transferase, FASN: fatty acid synthase, SCD: stearyl-coenzyme A desaturase.

the intracellular lipids in IGF-1-treated immortalized human sebocytes. In addition, azidothymidine suppressed the expression of various transcription factors and enzymes involved in sebocyte differentiation and lipid synthesis in immortalized human sebocytes. Lastly, azidothymidine suppressed IGF-1-induced mitochondrial biogenesis and mitophagy, which are important mechanisms for mitochondrial quality control.

Although IGF-1's role in lipid production in sebocytes is well documented<sup>7,14</sup>, the role of IGF-1 in mitochondrial homeostasis in sebocytes has not been sufficiently investigated. In this study, we investigated the effect of IGF-1 on the mitochondria of sebocytes and found that IGF-1 increased the levels of PGC-1 $\alpha$  and mtTFA in the immortalized human sebocytes. These results suggest that IGF-1 induces mitochondrial biogenesis in the immortalized human sebocytes. Moreover, the increased level of LC-3, p62, and Parkin in IGF-1-treated sebocytes also imply that IGF-1 activates PINK1/Parkin-mediated mitophagy in human sebocytes. Since mitochondria can be damaged during energy production or metabolism<sup>8,12</sup>, it is important to maintain the quality of mitochondria. Previous studies reported that the mitochondrial quality is controlled by mitochondrial biogenesis and mitophagy, and that IGF-1 plays an important role in regulating mitochondrial biogenesis and mitophagy in various cells and tissues<sup>8,9,12</sup>. Our results suggest that IGF-1 maintains mitochondrial homeostasis by inducing mitochondrial biogenesis and mitophagy for the differentiation and lipid synthesis in human sebocytes.

The association between HAART and the development of

lipodystrophy syndrome has been well established<sup>4</sup>. Previous studies revealed that azidothymidine dysregulated adipogenesis in adipose tissue and increased apoptosis in adipocytes<sup>4,15</sup>. Moreover, adipocytes treated with azidothymidine showed increased mitochondrial mass and disrupted mitochondrial membrane potential, which imply mitochondrial dysfunction<sup>15</sup>. In addition, Stankov et al.<sup>4</sup> suggested a role of azidothymidine in suppressing autophagy in cultured adipocytes. Lastly, other study revealed that adipocyte differentiation was negatively regulated by mitochondrial dysfunction and suggested that mitochondria were essential for adipocyte differentiation and lipid synthesis<sup>16,17</sup>. In this study, we found that azidothymidine treatment suppressed the mitochondrial biogenesis in the immortalized human sebocytes. Moreover, azidothymidine also inhibits IGF-1-induced mitophagy as evidenced by the decreased level of Parkin and increased level of LC-3B and p62 which imply suppression of PINK1/Parkin-mediated mitophagy<sup>13</sup>. Based on the results of our study and previous studies, we conclude that azidothymidine dysregulates the quality of mitochondria by suppressing mitochondrial biogenesis and mitophagy in human sebocytes. The mitochondrial dysfunction induced by azidothymidine may cause the reduced lipid production in human sebocytes.

There are some limitations in our study. First, we could not reveal the mechanisms how azidothymidine induced mitochondrial dysfunction and suppressed mitochondrial biogenesis and mitophagy in sebocytes. Moreover, considering the lipodystrophy by azidothymidine, further studies investigating the appropriate concentration or drug delivery systems which can minimize the effects on adipocytes are needed. Lastly, since we only investigated the effect of azidothymidine in immortalized human sebocytes cell line, investigation on the effect of azidothymidine in sebum production in human are also necessary.

There is an unmet need for novel medications that can safely control sebum production in acne patients. In this study, we found that azidothymidine decreased lipid synthesis in IGF-1-treated immortalized human sebocytes through dysregulation of mitochondrial function. Our results suggest the possibility that azidothymidine may be a new candidate for acne treatment by controlling sebum production.

## CONFLICTS OF INTEREST

The contents of this study have been used to apply for a patent application to the Korean Intellectual Property Office (Application number: 10-2019-0149751).



## FUNDING SOURCE

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None.

## DATA SHARING STATEMENT

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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