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Fatty acid oxidation regulates cellular senescence by modulating the autophagy-SIRT1 axis

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Senescence, a cellular process through which damaged or dysfunctional cells suppress the cell cycle, contributes to aging or age-related functional decline. Cell metabolism has been closely correlated with aging processes, and it has been widely recognized that metabolic changes underlie the cellular alterations that occur with aging. Here, we report that fatty acid oxidation (FAO) serves as a critical regulator of cellular senescence and uncover the underlying mechanism by which FAO inhibition induces senescence. Pharmacological or genetic ablation of FAO results in a p53-dependent induction of cellular senescence in human fibroblasts, whereas enhancing FAO suppresses replicative senescence. We found that FAO inhibition promotes cellular senescence through acetyl-CoA, independent of energy depletion. Mechanistically, increased formation of autophagosomes following FAO inhibition leads to a reduction in SIRT1 protein levels, thereby contributing to senescence induction. Finally, we found that inhibition of autophagy or enforced expression of SIRT1 can rescue the induction of senescence as a result of FAO inhibition. Collectively, our study reveals a distinctive role for the FAO-autophagy-SIRT1 axis in the regulation of cellular senescence. [BMB Reports 2023; 56(12): 651-656]

INTRODUCTION

Aging is a progressive decline of functions of tissues or organs. Besides its harmful effects on healthy life, aging is one of the primary causes of many human diseases, such as metabolic diseases, neurodegenerative diseases, and cancers (1). Like organisms, cells also age, a progress called cellular senescence. Cellular senescence is primarily induced either by the p53-$p21^{WAF1/CIP1}$, $p16^{INK4A}$-pRb, or p27 pathway (2-4). Importantly, accumulating evidence has suggested that senescence is closely associated with organismal aging (5, 6). For example, it has been shown that more senescent cells are frequently observed in tissues or organs from older individuals compared to those from young ones (2). Senescent cells not only accumulate in tissues and organs with age but also contribute to their functional defects, resulting in aging-associated degenerations (5, 7). Moreover, eliminating senescent cells has been shown to improve tissue functions and lead to lifespan extension (7). Therefore, many efforts have been made to investigate how senescence occurs or to develop strategies to selectively remove senescent cells from old tissues or organs.

Cell metabolism is intimately associated with aging processes, and many key factors in cell metabolism function as crucial regulators in aging and senescence (8, 9). For example, AMP activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR), which regulate cell metabolism by sensing the cellular energy status, are intimately involved in senescence and aging (9, 10). Indeed, AMPK activation or mTOR inhibition has been proven to delay aging and increase the healthy life span in many organisms (8, 11). Lipid metabolism is also closely associated with aging. On the one hand, aging plays a causal role in driving dysregulations in lipid metabolism. For instance, lipid usage, such as fatty acid oxidation (FAO), decreases with age, which can lead to increased adiposity in old age (12, 13). On the other hand, alterations in lipid metabolism can contribute to aging. For example, excess fat accumulation accelerates cellular senescence, resulting in an increase in senescent cell populations in various organs, including adipose tissues, liver, and brain, which may promote or exacerbate age-related chronic diseases in obese patients (13, 14).

Lipids, derived from adipose tissue, are used by cells in the form of fatty acids. Free fatty acids are oxidized in the mitochondria, producing NADH, FADH2, and acetyl-CoA (15). Together with glucose and glutamine, fatty acids are important nutrients required for cell growth and survival. While FAO has been considered primarily as an energy source for cells, recent

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studies have suggested that FAO also plays crucial roles in cellular pathways, independent of energy production. For example, it has been shown that FAO can support the cellular redox balance by promoting NADPH production (16, 17). Additionally, FAO serves as a major source of cellular acetyl-CoA, which plays a crucial role in regulating protein activities and gene expression through acetylation (18, 19). It has been reported that FAO-derived acetyl-CoA increases global histone acetylation (19). Thus, considering the critical role of lipid metabolism in the aging process and the indispensability of FAO in maintaining cellular homeostasis, it is not surprising that FAO has been implicated in cellular senescence. However, despite accumulating evidence on the involvement of FAO in aging and senescence, our current understanding of the precise mechanisms by which FAO regulates senescence remains limited.

Here, we aimed to understand the role of FAO in cellular senescence. We found that FAO inhibition induced senescence via acetyl-CoA. Mechanistically, increased autophagy formation caused by FAO inhibition led to SIRT1 degradation, which contributed to senescence induction. Collectively, our study sheds light on the importance of FAO in cellular senescence and elucidates the mechanism by which FAO regulates cellular senescence.

RESULTS

FAO inhibition induces cellular senescence

Although it has been shown that FAO is closely associated with aging and senescence, the specific mechanism by which FAO regulates cellular senescence is not clear. First, to examine the role of FAO in cellular senescence, we suppressed FAO in human diploid fibroblasts by inhibiting carnitine palmitoyltransferase 1A (CPT1A), the first required enzyme for mitochondrial FAO. We observed that FAO inhibition had a growth-suppressive effect on cells (Fig. 1A) and led to cell cycle arrest at the G1 phase (Supplementary Fig. 1A). However, CPT1A knockdown did not induce cell death (Fig. 1B), indicating that the reduced cell growth might be caused by senescence induction. Indeed, CPT1A knockdown markedly promoted an increase in fibroblasts exhibiting senescence-associated β-galactosidase (SA-β-Gal) activity (Fig. 1C). Comparable results were observed in cells treated with etomoxir (ETO), an inhibitor of CPT1A (Supplementary Fig. 1B). Moreover, we observed that GW6471 treatment, which can suppress FAO via PPARα inhibition, markedly elicited cellular senescence (Supplementary Fig. 1C). Additionally, as senescent cells had been reported to maintain a state of permanent DNA damage response (20), we next examined the levels of phosphorylation of H2AX at serine 139 (γH2AX). In line with our results, CPT1A knockdown increased the number of γH2AX foci in human fibroblasts (Fig. 1D). To further confirm the significance of FAO in senescence, we tested whether enhancing FAO could delay the onset of replicative senescence. Our results demonstrated that CPT1A-overexpressing cells exhibited a decreased number of SA-β-Gal positive cells during replicative senescence when compared to control cells (Fig. 1E). Collectively, these findings indicate that FAO plays a crucial role in senescence regulation.

FAO inhibition elicits p53-mediated senescence

Our data indicated that FAO inhibition promoted cellular senescence in human fibroblasts. To determine which pathway is responsible for the FAO inhibition-mediated senescence, we first examined the change in mRNA levels of these genes upon CPT1A knockdown. The expression of p21 was robustly induced in CPT1A knockdown cells, whereas we did not observe a change in the p16 or p27 mRNA level (Fig. 2A). We also found that p21 protein levels were markedly increased after CPT1A knockdown (Fig. 2B), indicating that FAO inhibition activates the p53-p21 pathway.

Next, to directly test whether FAO inhibition elicits senescence via the p53-p21$^{WAF1/CIP1}$ pathway, we reduced p53 expression by using a siRNA against p53. Interestingly, CPT1A

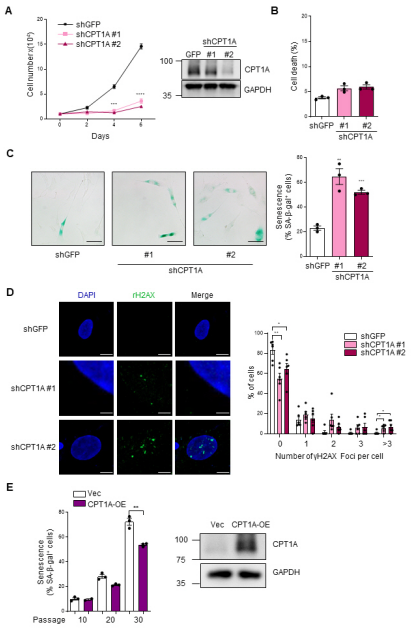

Fig. 1. Fatty acid oxidation (FAO) inhibition promotes cellular senescence. (A, B) Growth Curves (A) and cell death (B) of human fibroblast cells expressing a control shRNA (shGFP) or two independent shRNAs against CPT1A. (C) Representative images of SA-β-gal staining (left). The scale bar represents 200 μm. Percentage of SA-β-gal positive cells in control and CPT1A knockdown cells (right). (D) Representative images of immunofluorescence staining γH2AX foci (left). The scale bar represents 10 μm. Percentage of γH2AX foci positive cells in control and CPT1A knockdown cells (right). (E) Senescence induction of human fibroblasts expressing empty vector (Vec) or CPT1A (CPT1A-OE) at different passages. All error bars ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001.

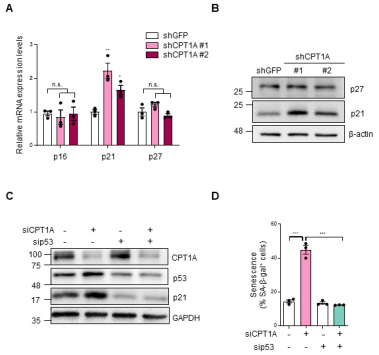

Fig. 2. FAO inhibition induces p53-dependent cellular senescence. (A, B) Relative mRNA levels (A) and western blot (B) of indicated genes in human fibroblasts expressing a control shRNA (shGFP) or two independent shRNAs against CPT1A. (C, D) Western blot (C) and senescence induction (D) of human fibroblasts transfected with siRNAs against CPT1A and/or p53. All error bars ± SEM. n.s., nonsignificant, *P < 0.05, **P < 0.01, ***P < 0.001.

knockdown increased the expression levels of p53 and p21 and promoted senescence induction, whereas p53 knockdown reversed the effects of FAO inhibition (Fig. 2C, D). Collectively, these results demonstrate that FAO inhibition induces cellular senescence through the p53-p21$^{WAF1/CIP1}$ pathway.

FAO regulates cellular senescence through acetyl-CoA

We next sought to elucidate the underlying mechanism through which FAO inhibition promotes cellular senescence. Given that FAO is an important source of cellular energy production (15, 21), we first examined whether the depletion of cellular energy production caused by FAO inhibition plays a role in this process. However, we did not observe a decrease in cellular ATP levels in cells following CPT1A knockdown (Fig. 3A). Consistent with these results, the phosphorylation of AMPK on Thr172, an indicator of cellular energy depletion, remained unaffected upon CPT1A knockdown (Fig. 3B). Next, we examined whether the FAO inhibition-induced senescence is linked to alterations in the cellular reactive oxygen species (ROS) levels. However, knockdown of CPT1A did not have a significant impact on cellular ROS production (Fig. 3C). Moreover, when we treated the cells with the antioxidant N-acetylcysteine (NAC) to assess the role of ROS, NAC treatment did not rescue senescence induction following CPT1A knockdown (Fig. 3D). Thus, these results demonstrate that FAO inhibition induces senescence in an energy- or ROS-independent manner.

Besides energy or ROS production, FAO functions as a critical source of cellular acetyl-CoA. Recently, we demonstrated that FAO modulates autophagosome formation through acetyl-CoA in pancreatic cancer cells (22). Thus, we hypothesized that a reduction in acetyl-CoA production by FAO inhibition might elicit senescence in human fibroblasts. To investigate this idea, we examined whether acetyl-CoA supplement was

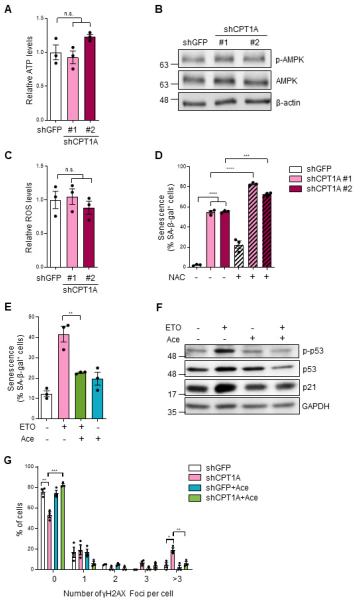

Fig. 3. FAO regulates cellular senescence through acetyl-CoA. (A, B) Relative ATP levels (A) and western blot (B) of human fibroblasts expressing a control shRNA (shGFP) or two independent shRNAs against CPT1A. (C) Relative ROS levels in control and CPT1A knockdown cells. (D) Percentage of SA-β-gal positive cells in control and CPT1A knockdown human fibroblasts treated with or without 4 mM NAC for 48 h. (E, F) Senescence induction (E) and western blot (F) of human fibroblasts treated with 200 μM ETO or 20 mM acetate for 72 h, as indicated. (G) Percentage of γH2AX foci positive cells in control and CPT1A knockdown human fibroblasts treated with or without acetate. All error bars ± SEM. n.s., nonsignificant, *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001.

able to rescue the FAO inhibition-induced senescence. Cells were cultured with exogenous acetate, which is converted into acetyl-CoA by acetyl-CoA synthetase 2 (ACSS2) to replenish the cytosolic acetyl-CoA pool. Notably, the percentage of SA-β-Gal-positive senescent cells following FAO inhibition was robustly decreased in the presence of acetate (Fig. 3E). Moreover, we found that acetate treatment rescued the elevation of phosphorylated p53 and p21 protein levels upon ETO treatment (Fig. 3F). We observed comparable results in CPT1A knockdown cells (Supplementary Fig. 2A). Lastly, acetate treatment reversed the increased number of γH2AX foci in ETO treated or CPT1A knockdown cells, restoring the number of foci to that in control cells (Fig. 3G and Supplementary Fig. 2B, C). We also obtained similar results when examining the expression of γH2AX (Supplementary Fig. 2D, E). Collectively, these results indicate that FAO regulates cellular senescence through acetyl-CoA.

SIRT1 downregulation by FAO inhibition-induced autophagy promotes senescence

Recently, it has been shown that the downregulation of SIRT1 by autophagy is an important contributor to senescence induction in human fibroblasts (23). Considering the established role of the autophagy-SIRT1 axis in senescence and our previous finding that FAO inhibition increases autophagosome formation via acetyl-CoA (22, 23), we hypothesized that FAO might regulate the induction of cellular senescence by modulating the autophagy-SIRT1 axis. To test this idea, we first examined whether FAO inhibition induced autophagosome formation in human fibroblasts. As shown previously, FAO inhibition increased the levels of the lipidated LC3 (LC3-II) and decreased p62 expression (Fig. 4A). Importantly, we found that the levels of SIRT1 protein were reduced in the FAO inhibited cells (Fig. 4A, B), implying that the autophagy-SIRT1 axis might play a role in the FAO inhibition-mediated senescence.

To explore the involvement of this pathway in senescence induction, we suppressed autophagosome formation by reducing the expression of ATG5, which is essential for autophagosome formation. Notably, the inhibition of autophagy by ATG5 knockdown markedly impaired senescence induction after ETO treatment (Fig. 4C and Supplementary Fig. 3A). Moreover, we observed that the induction of p21 upon FAO inhibition was also blunted by ATG5 knockdown (Fig. 4D), demonstrating that FAO inhibition induces senescence by promoting autophagosome formation. Given that the downregulation of SIRT1 by autophagy is responsible for senescence induction, we next investigated whether SIRT1 overexpression could reverse senescence induction following FAO inhibition. Consistent with this pathway, SIRT1 overexpression markedly reduced the number of SA-β-Gal-positive cells following ETO treatment (Fig. 4E and Supplementary Fig. 3B). Together, these results indicate that FAO inhibition elicits senescence in part by regulating the autophagy-SIRT1 axis.

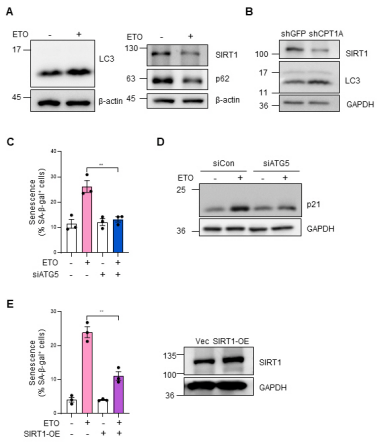

Fig. 4. Autophagy-SIRT1 axis mediates FAO inhibition-induced senescence. (A) Western blot of human fibroblasts treated with or without ETO for 72 h. (B) Western blot of human fibroblasts expressing a control shRNA (shGFP) or a shRNA against CPT1A. (C, D) Senescence induction (C) and western blot (D) of human fibroblasts transfected with a control siRNA or a siRNA against ATG5 in the presence or absence of ETO for 72 h. (E) Percentage of SA-β-gal positive cells in human fibroblasts expressing empty vector (Vec) or SIRT1 (SIRT1-OE) in the presence or absence of ETO. All error bars ± SEM. **P < 0.01.

DISCUSSION

In this study, we reveal a crucial role of FAO in cellular senescence. Our findings demonstrated that inhibiting FAO promotes senescence in a p53-dependent manner. Notably, the induction of senescence following FAO inhibition is not attributed to energy depletion or ROS production but rather to a reduction in acetyl-CoA production. We found that acetyl-CoA supplement almost completely rescued the induction of senescence resulting from FAO inhibition. Mechanistically, we have elucidated that the induction of autophagy following FAO inhibition is responsible for cellular senescence by reducing SIRT1 expression. Collectively, our findings indicate that the FAO-autophagy-SIRT1 axis is an important modulator of cellular senescence.

Our results are in line with those of previous studies highlighting the multifaceted involvement of FAO in various cellular pathways by regulating acetyl-CoA levels. In a previous study, we demonstrated that FAO inhibition results in a decrease in the cellular acetyl-CoA levels, which increases autophagosome formation in pancreatic cancer cells via the reduction of LC3 acetylation (22). Our current study demonstrated that the induction of autophagy following FAO inhibition elicits cellular senescence by downregulating SIRT1 expression. Importantly, acetate supplement rescues this phenotype, underscoring the potential importance of acetyl-CoA in the regulation of cellular senescence. Interestingly, a recent study has demonstrated that acetate can ameliorate age-related defects in the mesenchymal stem cells (24). Thus, we propose that acetyl-CoA supplement might hold promise as a strategy to mitigate senescence induction and reverse age-related impairments.

Our study sheds light on the prominent role of FAO in cellular senescence. It is worth noting that various factors, including fasting, calorie restriction, exercise, and obesity, which are known to impact aging and longevity, can modulate FAO as well (25-27). Thus, it is plausible that these factors may influence the aging processes, at least in part, by regulating FAO. Furthermore, previous reports have indicated that the capacity of tissues to oxidize fatty acids is reduced in aged cells compared to young cells (13, 28), suggesting that the decline in FAO with aging could contribute to the accumulation of senescent cells in aged tissues and organs.

In conclusion, we discovered the role of FAO in cellular senescence, in part by modulating the autophagy-SIRT1 axis through acetyl-CoA. Moreover, we demonstrated that acetyl-CoA supplement can lessen senescence induction. Therefore, these

findings establish FAO as a crucial regulator of senescence and emphasize the potential therapeutic implications of modulating cellular acetyl-CoA for the treatment and prevention of age-related diseases.

MATERIALS AND METHODS

Cell culture

Human fibroblast and HEK293T cells were cultured in Dulbecco's Eagle's medium (Welgene, LM001-07) supplemented with 10% fetal bovine serum (Gibco, Grans Island, NY, USA, 1600-044) and penicillin streptomycin (Biowest, Nuaille, France, L0022-100).

Senescence associated β-gal assay (SA-β-gal assay)

SA β-gal staining was performed as previously described (29). Briefly, cells were washed twice with PBS and fixed with 4% paraformaldehyde for 5 min. Cells were incubated with β-gal staining solution for 18 h at 37°C. The stained cells were fixed with 20% glycerol and analyzed under the microscope (Olympus, Center Valley, PA, USA). The percentage of β-gal positive cells were calculated randomly for at least 300 cells.

Cell cycle

Cells were trypsinized and fixed with 100% cold ethanol for 20 min. Fixed cells were incubated with propidium iodide (10 μg/ml) and RNase A (100 μg/ml) at 37°C for 20 min and then analyzed by flow cytometry using a FACS-Canto (BD Biosciences, San Jose, CA, USA).

Immunofluorescence

Cells were grown on 18 mm coverslips in 60 mm dish and were fixed with 4% paraformaldehyde at room temperature (RT) for 5 min. After washing, cells were permeabilized with 0.5% Triton X-100 in PBS (PBST) at RT for 20 min. The permeabilized cells were washed twice with PBS and blocked in 0.1% PBST with 10% normal goat serum (NGS) for 1 h. Then cells were incubated with γH2AX antibody in 0.1% PBST with 10% NGS overnight at 4°C. Next day, cells were washed three times with 0.1% PBS for 5 min and then stained with FITC-conjugated secondary antibody for 1 h at RT. Cells were washed three times in 0.1% PBST and mounted with Vectashield mounting solution with DAPI (Vector Laboratories, Burlingame, CA, USA). The fluorescence was detected using confocal microscopy (Carl Zeiss Oberkochen, Germany, LSM800). The percentage of γH2AX foci positive cells were calculated for at least 100 cells.

Antibodies and reagents

Antibody: CPT1A (Abcam, Cambridge, UK, ab128568), γH2AX (Merck Millipore, Bedford, MA, USA, 05-636), p53 (Santacruz, Biotechnology, California, USA, SC-126), p21 (abcam, ab109199), GAPDH (CUSABIO, CSB-PA00025A0Rb), β-actin (Genetex, Irvine, CA, USA, GTX109639), p27 (BD BIO, 610242), p-AMPK (Cell signaling technology, Danvers, MA, USA, 2535s), AMPK (Cell signaling technology, 5831s), p-p53 (ser15) (Cell signaling technology, 9284s), LC3 (MBL, Tokyo, Japan, PM036), SIRT1 (Cell signaling technology, 2310s), p62 (Cell signaling technology, 5114s), FITC (Santacruz, sc-516140), Rabbit IgG-HRP (Genetex, GTX213110-01) and Mouse IgG-HRP (Genetex, GTX 213111-01). ETO (E1905), GW6471 (G5045), sodium acetate (S5636), NAC (A9165) were purchased from Sigma Aldrich.

Constructs

SIRT1, CPT1A (M593S) were cloned into retroviral pBabe vector. CPT1A (M593S) was using with Quick change Kit (200523, Agilent Technologies, CA, USA) according to the manufacturer's protocol. CPT1A (M593S) primer sequences were: CTCACATA CGAGGCCTCCAGGACCCGGCTCTTCCGAGAG and CTCTC GGAAGAGCCGGGTCCTGGAGGCCTCGTATGTGAG. The sequences for shRNAs are as follows. shCPT1A #1 5′-CCGGGGA TGGGTATGGTCAAGATCTCTCGAGAGATCTTGACCATACC CATCCTTTTT-3′; shCPT1A #2 5′-CCGGGGTGGTTTGACAAGTC GTTCACTCGAGTGAACGACTTGTCAAACCACCTTTTT-3′. shGFP used as a control was purchased form Addgene (#30323).

Western blotting

Western blotting was performed as previously described (22). Briefly, proteins lysates were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to nitrocellulose (GE Healthcare, Buckinghamshire, UK, 10600001) or polyvinylidene difluoride membrane. The Membranes were probed with primary antibodies overnight at 4°C , followed by incubation with secondary antibodies for 1 h at RT. Protein specific bands were detected by ECL (W1015, Promega, Madison, WI, USA) and observed using LAS4000 (Fuji film, Tokyo, Japan).

Quantitative RT-PCR

Total RNA preparation and real-time RT-PCR were performed as previously described (22). Primer sequences were: GTGGACC TGGCTGAGGAG and CTTTCA ATC GGGGATGTCTG for p16, GGCAGACCAGCATGACAGATTT and GGCGGATTAGGGCTT CCTCT for p21, GCCCTCCCCAGTCTCTCTTA and TCAAAAC TCCCAAGCACCTC for p27, CTACGTCGCCCTGGACTTCGAGC and GATGGAGCCGCCGATCCACACGG for β-actin.

siRNA transfection

Transfections were performed as previously described (22). siRNAs for CPT1a (hs.Ri. CPT1A,13.1), Custom siRNA sequences were: 5′-GACUCCAGUGGUAAUCUAC-3′ for p53, 5′-GGAA UAUCCUGCAGAAGAAUU-3′ for ATG5 and 5′-UUCUCCG AACGUGUCACGUUU-3′ for negative control.

ATP measurement

ATP levels were detected using Cell Titer GLO (Promega, Fitchburg, WI, USA, G7571) as previously described (22). ATP levels were analyzed by synergy H1 microplate reader (Bio-Tek, Winooski, VT, USA) and normalized by the number of cells.

ROS measurement

The cellular ROS levels were measured by using CM-H2 DCFDA (C6827, Invitrogen) as previously described (22). Briefly, cells were incubated at 37°C for 30 min in 5 μM DCFDA with Hank' Balanced Salt Solution (Gibco, 14025092). ROS levels were measured by flow cytometry (BD Bio Science, San Jose, CA, USA, FACS-Canto).

Statistical analysis

Sample numbers are indicated by a dot. Unpaired two-tailed Student's t-test was used to compare the two groups. One-way ANOVA with Tukey's multiple comparisons test was performed to compare more than two groups. Two-way ANOVA was used to compare two independent variables, followed by Tukey's multiple comparisons tests. All experiments were performed three times.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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