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Commentary

The master energy sensor AMPK-1α regulates the expression of various autophagic and mitochondrial respiratory elements in T cell memory

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Abstract: AMPK-1α is a master energy sensor that phosphorylates more than 100 client proteins involved in almost all branches of cellular metabolism. We recently demonstrated that weak mTORC1 (mTORC1^{Weak}) signaling promotes the differentiation of pro-survival cytokine IL-7- or IL-15-stimulated CD8$^+$ memory T (IL-7/T$_M$ and IL-15/T$_M$) cells derived from ovalbumin (OVA)-specific T-cell receptor transgenic OTI mice by upregulating the expression of AMPK-1α and another twelve autophagic and metabolic regulators, including ULK1, ATG7, LC3II, SIRT1, PGC1α, CPT1α, AQP9, Complex I, LAL, OPA1, Bcl6, and TFAM. To investigate the potential role of AMPK-1α in controlling the abundance of these proteins, we genetically engineered AMPK knockout (KO)/OTI mice, and then prepared and subjected IL-7/T$_M$ or IL-15/T$_M$ cells from these animals to western blot analyses. Interestingly, we found that their steady-state levels were all significantly down-regulated in both IL-7/T$_M$ and IL-15/T$_M$ cells upon the loss of AMPK-1α expression. Thus, our data suggest that AMPK-1α indeed regulates these 12 downstream targets, a possibility that is further substantiated by the fact that a modern chemical genetic screen previously identified ULK1, ATG7, LC3II, SERT1, and PGC1α as AMPK-1α substrates. Taken together, our data establishes that the master energy sensor AMPK-1α controls the expression of seven additional regulatory markers, which are all critical to cellular

metabolism and whose identification may impact the development of AMPK-1α-targeted therapeutics for treating metabolic disorders and cancer diseases.
Keywords: AMPK-1α; autophagy; cell metabolism; T cell memory; western blotting

Abbreviations

ADP: adenosine diphosphate
AMPK-1α: adenosine monophosphate-activated protein kinase-1α
APC: antigen-presenting cells
AQP9: aquaporin-9
ATG7: autophagy-related gene-7
ATP: adenosine triphosphate
CaMKK2: Ca^{++}/calmodulin-activated protein kinase kinase-2
CPT1α: carnitine palmitoyl transferase-1α
DRP1: dynamin-related protein-1
FAO: fatty-acid oxidation
FOXO1: forkhead box-O-1
HIF-1α: hypoxia-inducible factor-1α
ID3: DNA binding-3
JAK3: Janus kinase-3
KLRG1: killer cell lectin-like receptor subfamily G member-1
LAL: lysosomal acid lipase
LC3II: microtubule-associated protein light chain-3 II
LKB1: liver kinase-B1
mTORC1: mammalian target of rapamycin complex-1
NF-κB: nuclear factor kappa B
OPA: optic atrophy-1
OVA: ovalbumin
PCG1α: PPARγ coactivator-1α
PKA: cyclic AMP-activated protein kinase A
PPARγ: peroxisome proliferator-activated receptor γ
SIRT: silent information regulator of transcription-1
SOD: superoxide dismutase
TAK-1: TGF-β-activated kinase-1
TCF1: T cell factor-1
TCR: T-cell receptor
T_E: effector T
T_M: memory T
T_n: naïve T
TSC2: tuberous aclerosis-2
UCP2: uncoupling protein-2
ULK1: Unc-51-like autophagy-activating kinase-1
WT: wild-type

1. Introduction

The hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) is the primary source of energy for all processes that occur in living cells. Maintenance of an adequate supply of ATP is therefore essential for cell survival and homeostatic function. Adenosine monophosphate-activated protein kinase-1α (AMPK-1α), a heterotrimeric complex composed of a catalytic α subunit and regulatory β and γ subunits, is an evolutionarily conserved serine/threonine kinase. AMPK-1α is a master energy sensor that plays a crucial role in the regulation of (i) protein synthesis, cell growth, and cell differentiation; (ii) redox balance; (iii) anti-inflammatory responses; (iv) autophagy; and (v) mitochondrial biogenesis (Figure 1A) [1,2]. First, activated AMPK-1α inhibits T cell protein synthesis, proliferation and differentiation by phosphorylating S_{1387} of tuberous sclerosis complex-2 (TSC2), which in turn leads to the phosphorylation of S_{792} of regulatory-associated protein of mTOR (raptor) and suppression of mammalian target of rapamycin complex 1 (mTORC1) (Figure 1A) [3]. Second, AMPK-1α regulates antioxidant defense during oxidative stress via upregulation of antioxidant genes coding for superoxide dismutase (SOD) and uncoupling protein-2 (UCP2) (Figure 1A) [3]. Third, AMPK-1α exerts anti-inflammatory effects by inhibiting nuclear factor kappa B (NF-κB), a key regulator of innate immunity and inflammation, through activation of silent information regulator of transcription-1 (SIRT1) and peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PCG1α) (Figure 1A) [1,2]. Last, AMPK-1α controls autophagy and mitochondrial biogenesis via activation of Unc-51-like autophagy-activating kinase-1 (ULK1)/autophagy-related gene-7 (ATG7) and SIRT1/PGC1α, respectively (Figure 1A) [3].

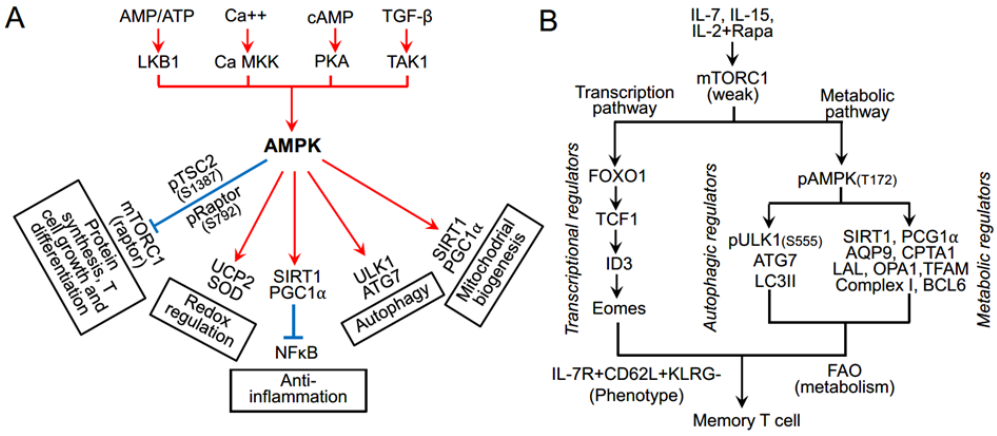

Figure 1. The master energy sensor AMPK-1α regulates the activity of various autophagic and mitochondrial respiratory markers in T cell memory. (A) A schematic illustrating the regulatory diversity of AMPK-1α function. Red arrows indicate AMPK-1α dependent activation while blue bar-headed lines reflect AMPK-1α driven inhibition (see text for details). (B) A schematic showing that the prosurvival cytokines IL-7 and IL-15 along with inflammatory IL-2+rapamycin (Rapa) stimulate weak mTORC1 signaling. Weak mTORC1 signaling in turn induces $CD8^+$ T cell memory via activation of the transcriptional FOXO1-TCF1-ID3-Eomes pathway for T_M cell differentiation and the metabolic AMPK-1α-controlled autophagic and mitochondrial biogenesis pathways in support of FAO metabolism.

Several regulatory nodes modulate AMPK-1α activity (Figure 1A) [1,2]. AMPK-1α is activated by its upstream liver kinase-B1 (LKB1) and Ca^{2+}/calmodulin-activated protein kinase kinase-2 (CaMKK2) in response to a stress of high adenosine monophosphate (AMP)/ATP levels and an increase in calcium, respectively (Figure 1A) [1,2]. AMPK-1α can also be activated by its upstream cyclic AMP (cAMP)-activated protein kinase A (PKA) and TGF-β-activated kinase-1 (TAK-1) in response to an increase in cAMP and TGF-β, respectively (Figure 1A) [1,2]. The primary mechanism of activation targeted by each of these regulatory nodes is phosphorylation of AMPKα1 at T_{172}. When active, AMPK-1α acts to switch off ATP-consuming anabolic processes, such as protein synthesis, and switch on ATP-producing catabolic processes, such as fatty-acid oxidation (FAO) [1,2].

Autophagy and mitochondrial biogenesis are two major cellular processes specifically regulated by AMPK-1α. Autophagy is a cytosolic self-recycling process beginning with generation of autophagosomes and recognition of cargo, followed by maturation of autophagosomes, fusion with lysosomes, and formation of the lysosomal system. Proteins and organelles are degraded by lysosomes to provide essential metabolic intermediates and building blocks to support metabolism and homeostasis under stress conditions [1,2]. AMPK-1α directly activates ULK1 by phosphorylation of ULK1 at S_{555}, which goes on to form a protein complex to initiate autophagy [1,2]. AMPK indirectly activates ULK1 by inhibiting mTORC1 (Figure 1A), thus releasing mTORC1's suppressive effect on ULK1 and subsequently strengthening the ULK1 autophagy complex [1,2]. Using shRNA and RNA array techniques [4], researchers have determined AMPK-1α also promotes mitochondrial biogenesis through the regulation of PGC1α [1,2], a cofactor that promotes mitochondrial biogenesis by enhancing the expression of numerous mitochondrial genes (Figure 1A). Additionally, AMPK-1α activity leads to an increase in intracellular NAD^+, which indirectly enhances the activity of SIRT1, an NAD^+-dependent deacetylase. SIRT1 in turn deacetylates PGC1α, leading to PGC1α activation (Figure 1A) [5]. SIRT1 and PGC1α are both critical regulators of mitochondrial biogenesis and FAO metabolism.

$CD8^+$ cytotoxic T lymphocytes play a critical role in immunity against infectious and neoplastic diseases. Naïve $CD8^+$ T (Tn) cells under quiescent conditions generate most of their ATP through mitochondrial oxidative phosphorylation of glucose-derived pyruvate [6]. In response to a pathogenic stimulus, antigen-presenting cells (APCs) stimulate Tn cells by delivering three signals (T-cell receptor [TCR], co-stimulation, and cytokines) leading to their entry into a developmental program characterized by proliferation and differentiation into two T cell subsets with distinct expression of the IL-7 (IL-7R), CD62L (memory T [T_M] cell markers), and killer cell lectin-like receptor subfamily G member-1 (KLRG1) (a senescent effector T [T_E] cell marker) receptors [6,7]. Roughly 95% of the expanded T cell pool become short-lived IL-$7R^-CD62L^-KLRG1^+$ effector cells that show an increase in glucose uptake and aerobic glycolysis and die of activation-induced cell apoptosis during the T cell contraction phase [6,7]. The remaining 5% of the expanded T cell pool are IL-$7R^+KLRG1^-$ memory precursor effector cells, which ultimately differentiate into quiescent IL-$7R^+CD62L^+KLRG1^-$ memory T (T_M) cells during the T_M cell formation phase. T_M cells depend on FAO for energy to ensure long-term survival and functional recall responses upon secondary pathogenic challenge [6,7]. As the ultimate goal of vaccination is to generate a large pool of T_M cells, understanding the molecular mechanism that governs T cell memory is of great importance to vaccine and immunotherapy design, such as anti-tumor chimeric antigen receptor T (CAR-T) cell preparation [8,9].

mTORC1 is an evolutionarily conserved serine/threonine kinase and a master regulator that senses three major immune signals (antigen, co-stimulation, and cytokines); modulates protein

synthesis; and regulates T cell growth, differentiation, and metabolism [7]. Triggering mTORC1 signaling has been found to induce $CD8^+$ T_E cell formation via activation of transcriptional T-bet and metabolic master regulator hypoxia-inducible factor (HIF)-1α pathways [7]. Ahmed's group first reported that inhibition of mTORC1 by rapamycin (Rapa) promotes $CD8^+$ T_M cell formation in 2009 [10]; however, the underlying molecular mechanisms are largely unknown.

2. $mTORC1^{Weak}$ signaling promotes T cell memory by activating AMPKα1-dependent autophagic and metabolic pathways

The pro-inflammatory IL-2 and pro-survival IL-7 belonging to the common γ-chain (γc)- cytokine family both trigger Janus kinase-3 (JAK3) that activates mTORC1 signaling; however, IL-2 induces $CD8^+$ T_E cell formation while IL-7 stimulates $CD8^+$ T_M cell differentiation [11]. To reveal why activation of the same JAK3-mTORC1 pathway results in distinct effects on T cell biology, we systematically characterized in vitro prepared IL-2- and IL-7-cultivated T (IL-2/T_E and IL-7/T_M) cells derived from naïve $CD8^+$ T cells purified from splenocytes of wild-type (WT) OVA-specific TCR transgenic OTI mice [11]. We found IL-2 stimulates strong mTORC1 signaling (IL-2/$mTORC1^{strong}$) due to persistent expression of CD25 (a T cell-surface IL-2 receptor) leading to $IL\text{-}7R^-CD62L^-KLRG1^+$ IL-2/T_E cell formation via activation of transcriptional T-bet and metabolic HIF-1α pathways for T_E cell phenotype and glycolytic metabolism, respectively [11]. Interestingly, we observed IL-7 stimulates weak mTORC1 signaling (IL-7/$mTORC1^{weak}$) due to transient expression of CD127 (a T cell-surface IL-7 receptor) leading to $IL\text{-}7R^+CD62L^+KLRG1^-$ IL-7/T_M cell formation [11]. We then demonstrated the IL-7/$mTORC1^{weak}$ signaling upregulates transcription factors, including forkhead box-O-1 (FOXO1), T cell factor-1 (TCF1), inhibitor of DNA binding-3 (ID3), and Eomes, all of which are required for the T_M cell phenotype (Figure 1B), as we previously described [11]. In addition, the IL-7/$mTORC1^{weak}$ signaling also activates the master energy sensor AMPK-1α and another 12 autophagic and metabolic regulators, including autophagic regulator ULK1, ATG7, and an autophagosome maturation marker microtubule-associated protein light chain-3 II (LC3II) that induces a shift from dynamin-related protein-1 (DRP1)-regulated fission to optic atrophy-1 (OPA1)-controlled mitochondrial fusion events and mitochondrial FAO (Figure 1B), as we previously reported [11]. Furthermore, the IL-7/$mTORC1^{weak}$ signal also triggers several metabolic regulators (SIRT1, PGC1α, carnitine palmitoyl transferase-1α [CPT1α, a key regulator for FAO], glycerol channel aquaporin-9 [AQP9, a metabolic factor importing glycerol for fatty acid esterification and triacylglycerol synthesis], Complex-I of the electron transport chain, lysosomal acid lipase [LAL], metabolic suppressor Bcl6 for the inhibition of glycolysis, and mitochondrial transcription factor-A [TFAM]) critical to mitochondrial biogenesis and FAO (Figure 1B) [11]. Collectively, our data indicates distinct strengths of mTORC1 signaling control T cell differentiation [12]. IL-7/$mTORC1^{Weak}$ signaling induces $CD8^+$ T cell memory via the transcriptional FOXO1 and metabolic AMPKα1 pathways, whereas IL-2/$mTORC1^{Strong}$ signaling induces $CD8^+$ T_E cell formation via the transcriptional mTORC1-T-bet and metabolic mTORC1-HIF-1α pathways (Figure 1B), as we previously described [11,13,14]. This signaling model is also supported by our further findings that Rapa-promoted IL-2(Rapa+)/T_M [13] and pro-survival IL-15-stimulated IL-15/T_M cells [14] all show $mTORC1^{Weak}$ signaling, FOXO1-regulated $CD8^+$ T_M cell phenotype, and AMPK-1α-controlled FAO metabolism leading to long-term survival of $CD8^+$ T_M cells after their adoptive transfer into C57BL/6 mice (Figure 1B), as we previously

shown [11,13,14]. In fact, CAR-T cells have been shown to expand with pro-survival IL-7/IL-15 mediating superior anti-tumor effects [8,9].

In addition to cytokines, nutrient glucose also stimulates $CD8^+$ T_E cell responses via triggering strong mTORC1 (glucose/$mTROC1^{strong}$) signaling. In support of our observation that IL-7/$mTORC1^{weak}$ and IL-15/$mTORC1^{weak}$ signaling [11,14], as well as Rapa-treated IL-2/$mTORC1^{weak}$ and low concentration IL-2-stimulated weak mTORC1 ($IL\text{-}2^{low}$/$mTORC1^{weak}$) signaling, induce T_M cell formation via activation of AMPK-1α [11,13,15]. The glucose starving or limitation triggering weak mTORC1 ($glucose^{low}$/$mTORC1^{weak}$) signaling also activates the master energy sensor AMPK-1α, leading to induction of T_M cell differentiation [16–18] and thus strongly supporting our new insight that distinct strengthens of mTORC1 signaling controls T cell memory in linear differentiation and asymmetric cell division models [12].

3. AMPK-1α may directly or indirectly activate the metabolic regulators CPT1α, AQP9, Complex I, LAL, OPA1, Bcl6, and TFAM in $CD8^+$ T_M cells

By using a chemical genetics screen coupled with a peptide capture approach to provide an AMPK-1α motif matrix and a pipeline to predict AMPK-1α substrates from quantitative phosphor-proteomics datasets, AMPK has been determined to be a master energy sensor that phosphorylates more than 100 proteins involved in almost all branches of cellular metabolism [1,2]. These include five critical regulators (three autophagic [ULK1, ATG7, and LC3II] and two metabolic [SIRT1 and PGC1α]), as previously reported by others [1,2]. However, whether AMPK-1α controls the expression of the remaining seven candidates (CPT1α, AQP9, Complex-I, LAL, OPA1, Bcl6, and TFAM) remains elusive.

State-of-the-art genetic tools, such as genetically engineered gene knockout (KO) mice, are commonly used to more precisely and definitely determine relationships between the KO gene and its downstream substrate genes than pharmaceutic tools using gene inhibitors or activators still with possibility to affect other gene pathways [19]. Michelini et al. demonstrated FOXO1 controls its substrates TCF1 and Eomes using FOXO1 KO mice [20] while Zhang et al. determined Rictor regulates AKT and FOXO1 using Rictor KO mice [21]. To evaluate AMPK-1α-controlled substrates, we recently prepared WT IL-7/T_M and IL-15/T_M cells derived from WT OTI mice, as well as (AMPK KO)IL-7/T_M and (AMPK KO)IL-15/T_M cells derived from AMPK KO/OTI mice we previously generated using state-of-the-art genetic tools. We then performed western blotting analyses using the above cell lysates and antibodies against autophagic pULK1 (S_{555}) and LC3II and found the AMPK-1α controls the expression of ULK1 and LC3II [11,13], consistent with previous reports [1,2]. To further measure whether AMPK-1α regulates the expression of the other seven regulators (CPT1α, AQP9, Complex-I, LAL, OPA1, Bcl6, and TFAM), we recently repeated western blotting analyses using the above cell lysates and antibodies against the seven molecules. Interestingly, we demonstrated the expression of the seven metabolic regulators was significantly down-regulated in (AMPK KO)IL-7/T_M and (AMPK KO)IL-15/T_M cells compared to WT IL-7/T_M and IL-15/T_M cells, respectively (Figure 2). Thus, our data demonstrates that the powerful master energy regulator AMPK-1α directly or indirectly controls expression of an additional seven important metabolic regulators CPT1α, AQP9, Complex-I, LAL, OPA1, Bcl6, and TFAM at the protein level in $CD8^+$ T_M cells (Figure 2), though AMPK-1α-controlled down-regulation of TFAM by AMPK inhibitor dorsomorphin, as well as up-

regulation of AQP9 and Bcl6 by AMPK activators (i.e., AICAR and glucose deprivation), were also previously reported by the others [22–24].

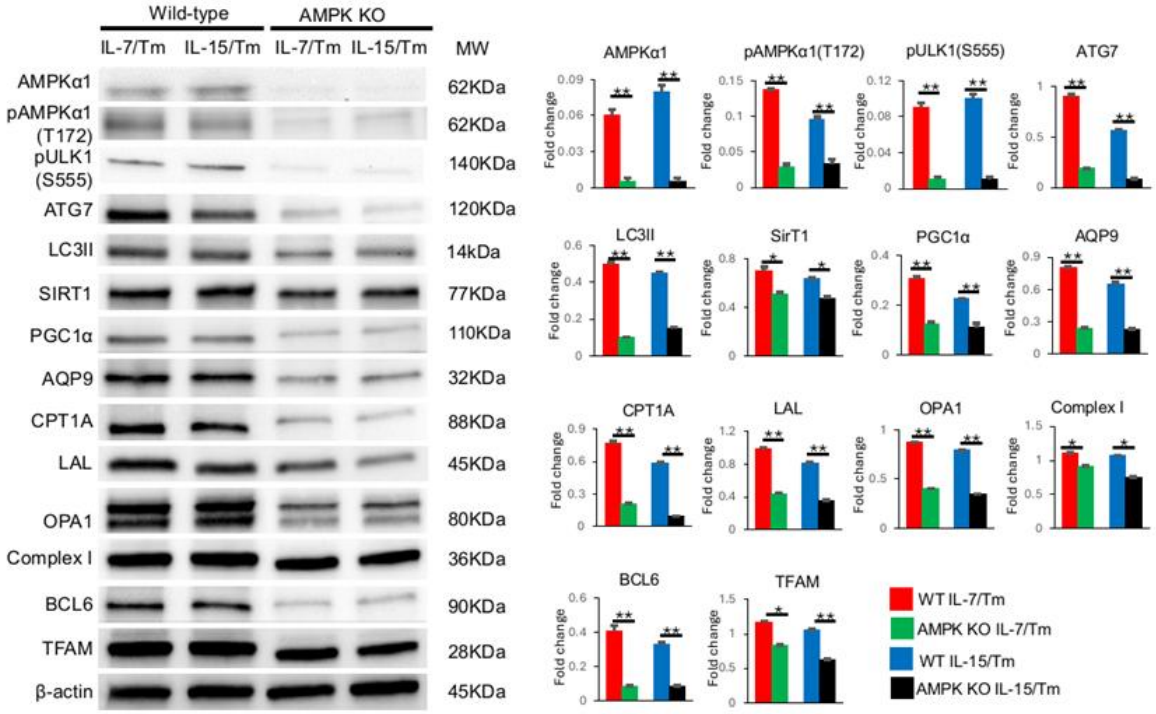

Figure 2. AMPK-1α controls the expression of various autophagic and mitochondrial respiratory markers. Lysates (20 μg/well) derived from WT and AMPK KO IL-7/T_M and IL-15/T_M cells were loaded onto SDS-PAGE gels and subjected to western blot analysis. β-actin served as an internal, loading control and was used to normalize the fold change in protein abundance in IL-7/T_M and IL-15/T_M cells from both WT and AMPK KO backgrounds. Data represent the mean ± SD. *$p < 0.05$, ** $p < 0.01$ versus different groups by two-tailed Student's *t*-test.

4. AMPK-1α is a potential therapeutic target for treating metabolic disorders and cancer diseases

Given its key role in controlling energy homeostasis, any perturbation in AMPK-1α function can result in dysregulation of autophagy, mitochondrial biogenesis and the metabolism of glucose and lipids [1]. Therefore, AMPK-1α has attracted wide interest as a potential therapeutic target for treating some diseases such as metabolic (diabetes and cardiovascular) diseases and cancer [25,26]. For example, type-2 diabetes is a metabolic disorder with elevated blood glucose levels and the metformin administration activating AMPK-1α, leading to up-regulation of GLUT4, facilitating insulin-mediated glucose uptake by muscle cells and subsequently reducing the elevated glucose levels in blood [27,28]. In cardiovascular diseases, dysregulation of cardio homeostasis results in cardiomyocyte loss [29]. Since autophagy plays an important role in cardiac tissue development and cardiomyocyte homeostasis [30], activation of AMPK-1α preserves cellular homeostasis and maintains cardiac function by promoting

autophagy [31]. The metformin has also been reported to reduce glycolytic flux in tumor cells by blocking glycolytic enzymes [32], leading to slowing tumor growth while supporting $CD8^+$ T cell survival in tumor microenvironment (TME) [33,34]. Thus, the administration of metformin has shown its significantly decreased tumor burden in both mouse tumor models and clinical cancer patients [35–37].

5. Conclusions

Taken together, the master energy sensor AMPK-1α modulates the expression of numerous regulators involved in autophagy, mitochondrial biogenesis, and energy metabolism. Our data establishes that AMPK-1α directly or indirectly controls the expression of CPT1α, AQP9, Complex-I, LAL, OPA1, Bcl6, and TFAM, seven previously unrecognized substrates that are all critical to cellular metabolism and whose modulation may have an impact on the development of AMPK-1α-targeted therapeutics for treating metabolic disorders and cancer diseases.

Author contributions

JX: Conceived the project. JX and MY: Manuscript writing. MY and ZW: Performing experiments and preparation of Figures 1 and 2. SCL: Manuscript reviewing and editing.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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