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Review article

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AMPK as a mediator of tissue preservation: time for a shift in dogma?

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Abstract

Ground-breaking discoveries have established 5′-AMP-activated protein kinase (AMPK) as a central sensor of metabolic stress in cells and tissues. AMPK is activated through cellular starvation, exercise and drugs by either directly or indirectly affecting the intracellular AMP (or ADP) to ATP ratio. In turn, AMPK regulates multiple processes of cell metabolism, such as the maintenance of cellular ATP levels, via the regulation of fatty acid oxidation, glucose uptake, glycolysis, autophagy, mitochondrial biogenesis and degradation, and insulin sensitivity. Moreover, AMPK inhibits anabolic processes, such as lipogenesis and protein synthesis. These findings support the notion that AMPK is a crucial regulator of cell catabolism. However, studies have revealed that AMPK's role in cell homeostasis might not be as unidirectional as originally thought. This Review explores emerging evidence for AMPK as a promoter of cell survival and an enhancer of anabolic capacity in skeletal muscle and adipose tissue during catabolic crises. We discuss AMPK-activating interventions for tissue preservation during tissue wasting in cancer-associated cachexia and explore the clinical potential of AMPK activation in wasting conditions. Overall, we provide arguments that call for a shift in the current dogma of AMPK as a mere regulator of cell catabolism, concluding that AMPK has an unexpected role in tissue preservation.

Sections

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Key points

- AMPK is traditionally viewed as a predominantly anti-anabolic enzyme that mitigates the inhibition of protein synthesis.
- Emerging evidence from preclinical models suggests that activating AMPK could be a viable strategy to improve muscle and adipose tissue maintenance during wasting conditions, such as cancer cachexia.
- AMPK's ability to ensure sufficient ATP levels by regulating mitochondrial function and insulin sensitivity supports cellular homeostasis and survival during cancer cachexia.
- Direct and indirect AMPK-activating strategies in preclinical cachexia models resulted in increased anabolism and attenuated muscle and adipose tissue atrophy.
- The benefits of AMPK are probably not limited to cancer cachexia but can be found in other metabolic conditions that also involve tissue wasting, such as sarcopenia or congenital muscular dystrophies.
- AMPK could be a target for the design of strategies that address the unmet clinical need for treatment of wasting conditions, such as cancer cachexia.

Introduction

5′-AMP-activated protein kinase (AMPK) has a fundamental role in tissue metabolism, predominantly by supporting the maintenance of cellular energy homeostasis via the generation of ATP through increased nutrient uptake and oxidation, and upregulation of mitochondrial capacity. Nutrient uptake is further augmented by AMPK via its insulin-sensitizing effects, which enable tissues to maintain ATP levels when internal energy stores are low. In addition, AMPK serves as a crucial regulator of protein turnover by providing essential signals to finely adjust the balance between catabolic and anabolic processes.

In this Review, we explore evidence suggesting that AMPK coordinates tissue preservation, rather than its loss, during times of energy crisis, such as cancer cachexia. Tissue preservation will be viewed from the perspective of energy-dense tissues, such as skeletal muscle and adipose tissue. These tissues have dynamic substrate fluxes in which nutrient uptake and utilization are intimately linked to tissue mass[1]. For example, it is well known that muscle and adipose tissue undergo atrophy during dietary nutrient restriction or fasting. The reduction in tissue mass includes losses of all major macromolecules, including protein. Proteostasis (that is, the dynamic regulation of a functional proteome) is an energy-demanding process that accounts for approximately 20–30% of mammalian ATP consumption[2]. Therefore, it is not surprising that cells would acquire a mechanism to link the balance between AMP or ADP and ATP levels to protein synthesis and growth[3]. AMPK is perfectly poised to uphold the high-energy turnover required for proteostasis.

Skeletal muscle comprises about 40% of body mass in healthy individuals and myofibrillar protein is the primary amino acid repository in the body[2,4]. Furthermore, protein turnover in skeletal muscle is dynamically regulated. In this tissue, AMPK activation enhances both insulin-dependent and insulin-independent glucose uptake and fatty acid turnover to ensure nutrient supply for the mitochondria to generate the ATP needed to uphold muscle mass and support locomotion. During times of metabolic cellular stress, AMPK is a crucial factor for tissue preservation. This pro-anabolic function of AMPK seems to be largely overlooked in the study of conditions of tissue wasting, such as cancer cachexia, in which AMPK has been suggested to be a pathogenic driver of the disease.

In this Review, we outline AMPK's role in generating ATP by regulating mitochondrial health and insulin sensitivity, eventually resulting in improved proteostasis. We particularly focus on the role of AMPK in cancer cachexia and metabolic dysfunction and how targeting AMPK might offer an avenue to aid in the preservation of muscle and adipose tissue mass.

AMPK signalling

The overarching premise of AMPK signalling is to support energy supply via preservation of the adenine nucleotide pool and, more broadly, to maintain cellular energy homeostasis. All eukaryotic cells express AMPK. The heterotrimeric AMPK complex comprises α-subunits (catalytic), β-subunits (regulators) and γ-subunits, which exist in different isoforms (α1 or α2, β1 or β2, and γ1, γ2 or γ3). The expression of these isoforms and composition of the AMPK holoenzyme are highly tissue-specific and species-specific.

AMPK is activated (meaning the protein activity increases and AMPK interacts with substrates) under conditions of low cellular energy caused by glucose or nutrient deprivation, and on exercise via increased levels of AMP and ADP. In addition to previous landmark articles on the molecular basis of AMPK activity[5,6], an excellent review of AMPK structure, activation and general functions was published a few years ago[7]. Thus, these subjects will only be briefly covered in the current Review. Activation via canonical mechanisms involves phosphorylation of Thr residue 172 within the activation loop, which is the primary mechanism for covalent activation. At least two principal upstream kinases phosphorylate AMPK at Thr172: the constitutively active tumour suppressor liver kinase B1 (LKB1)[8] and calcium/calmodulin-dependent kinase kinase 2 (CaMKK2)[9]. The canonical activation mechanism involves three effects of γ-AMP binding: allosteric activation, Thr172 phosphorylation, and minimal Thr172 dephosphorylation due to conformational changes, making Thr172 less accessible to phosphatases[10–12]. Moreover, AMPK activity is regulated at different subcellular locations for precise spatiotemporal control[13].

In cancer cachexia, there are various cytokines found in the circulation that are associated with disease progression[14] and are thought to be related to AMPK activity at the cellular level. For example, IL-6 increases AMPK activity in C2C12 cells and mice with cancer cachexia[15]. Similarly, growth differentiation factor 15 (GDF15) mediates AMPK activity in skeletal muscle in vitro and in vivo[16]. By contrast, TNF, another pro-inflammatory cytokine known to contribute to cancer cachexia, suppresses AMPK activity[10]. Whether cytokines directly activate AMPK or if the connections seen are indirect results of disease progression is uncertain. Nonetheless, these findings underscore AMPK's role at the centre of systemic disease regulation in cancer cachexia. Figure 1 summarizes some of the most common inputs known to activate AMPK and the physiological outputs of AMPK, with additional information in Box 1.

Cancer cachexia: an untreated wasting condition

Patients with cancer often present with metabolic and endocrine dysfunction. For example, anorexia[17,18], insulin resistance[19–23], and perturbed metabolism of proteins[24–26], carbohydrates[27,28] and fatty acids[29–32], are common in patients with cancer. These alterations

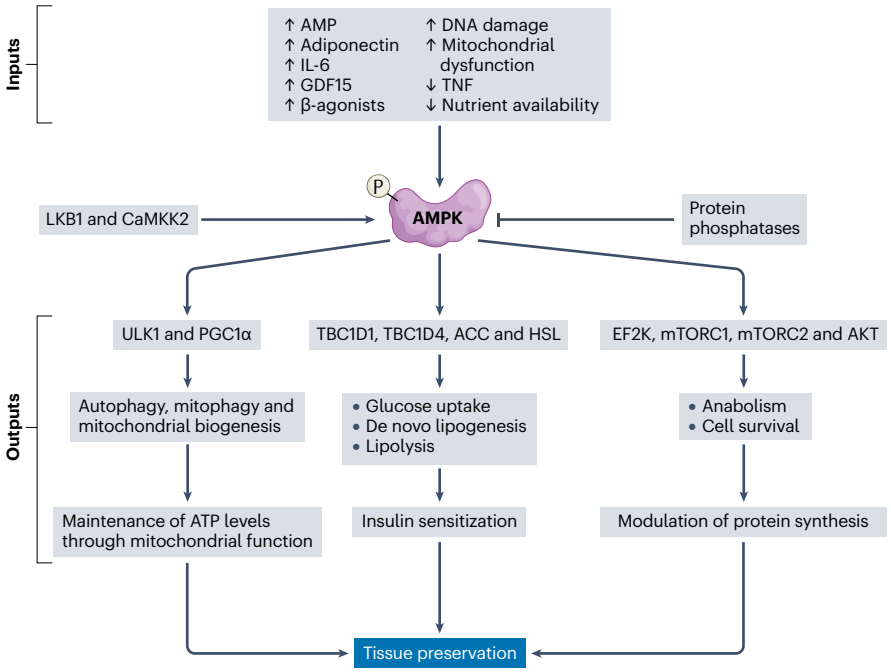

Fig. 1 | Activating and inhibitory signalling events. Schematic overview of examples for major signalling events that activate or inhibit 5′-AMP-activated protein kinase (AMPK) (inputs), specifically in cancer cachexia, and the downstream targets (outputs) by which AMPK affects tissue preservation through its role in generating ATP for the maintenance of energy levels, insulin sensitivity and proteostasis. ACC, acetyl-CoA carboxylase; CaMKK2, calcium/calmodulin-dependent kinase kinase 2; GDF15, growth differentiation factor 15; HSL, hormone-sensitive lipase; LKB1, liver kinase B1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; TBC1D1, TBC1 domain family member 1; TBC1D4, TBC1 domain family member 4; ULK1, unc51-like autophagy-activating kinase 1.

compromise cellular energy status in skeletal muscle and adipose tissue, leading to tissue atrophy. This wasting syndrome is often referred to as cancer cachexia, and is independently associated with decreased survival[33], worsened response to anticancer therapy[34,35], discontinuation of anticancer treatment and reduced quality of life[36]. Cancer cachexia is estimated to directly contribute to one in five cancer-related deaths[37]. Due to its clinical relevance and strong manifestations, cancer cachexia was assigned its own International Classification of Diseases code (ICD-10, R64) in 2016. Cancers of the lungs, pancreas and liver have the highest prevalence of cachexia, ranging from 37% to 50%[38]. With no effective pharmacological treatment available for cancer cachexia[39], new drug targets are urgently needed. AMPK might be one such target and this article focuses heavily on its role specifically in the context of cancer cachexia.

Mitochondrial dysfunction disrupts energy homeostasis in cancer cachexia

AMPK protein levels and signalling are reported to be upregulated in skeletal muscle in cancer cachexia mouse models[15,40–42] and in patients with cancer cachexia[40,43]. AMPK activity is probably induced in this setting by widespread mitochondrial dysfunction. For example, cancer cachexia is associated with decreased metabolic efficiency as a result of increased mitochondrial uncoupling[44,45], which causes pathological changes to mitochondrial morphology (such as swelling and altered cristae structure[46,47]) and leads to disrupted mitochondrial dynamics, increased production of reactive oxygen species, impaired mitophagy[48,49] and eventually a progressive loss of mitochondrial content[50,51], all of which contribute to deficits in energy production in animals[52] and humans with cancer cachexia[53,54], resulting in a rise of intracellular levels of AMP[55]. Therefore, transiently increased AMPK levels are probably a physiological response to this intramuscular energy shortage as a result of the deleterious effects of cancer cachexia on systemic metabolism and mitochondrial function. This view can be reconciled with the energy charge hypothesis first introduced in the late 1960s: the charge in the adenylate pool (ATP to ADP and AMP ratios) was suggested to be a metabolic regulatory parameter[56]. Additionally, this view corresponds with the concept that AMPK is an evolutionarily conserved energy sensor with the crucial role of maintaining cellular health and energy status in the face of crisis.

In tumour-bearing mice, the reduction in mitochondrial quality and function precedes the onset of muscle atrophy, which suggests that it might be a primary contributor to the cachectic phenotype of these mice[51]. Several studies with interventions to improve mitochondrial function also preserve skeletal muscle mass and function in cancer cachexia. For example, exercise is a powerful, physiological method to increase mitochondrial density and efficiency, in part via AMPK activation[57]. Indeed, exercise training preserves muscle mass and function in mice with cancer cachexia[46,58–60]. Similarly, pharmacological or nutritional interventions that restore mitochondrial function have been successful in delaying and treating body weight loss in mouse cancer cachexia models[61–63]. AMPK regulates mitochondrial homeostasis by orchestrating a myriad of signalling events through important modulators, such as PPARG coactivator 1α (PGC1α) and unc51-like autophagy-activating kinase 1 (ULK1). Mitochondrial modulators might be targets for cancer cachexia therapy and treatment of other muscle wasting conditions, such as age-related muscle loss (sarcopenia[64]) and neuromuscular disorders; in a review this approach has been fittingly termed ‘mitochondrial medicine’[65]. In agreement with this approach, another study found that increased AMPK signalling through the muscle-derived protein erythroferrone (also known as C1q/TNF-related protein 15 or myonectin) improves the maintenance of muscle mass in various atrophy models by restoring PGC1α activity and mitochondrial function[66]. Furthermore, muscle-specific deletion of the gene encoding AMPK β1/β2 leads to a decrease in mitochondria number and function, glucose uptake and exercise performance, eventually leading to a myopathy with reduced muscle fibre size[67,68].

The seeming contradiction between elevated AMPK activity during the onset and earlier stages of cancer cachexia, and the therapeutic

potential of AMPK-activating strategies in wasting conditions suggests a time-dependent and context-dependent role of AMPK[69]. During the onset of cancer cachexia, AMPK levels might transiently increase to compensate for the development of progressive mitochondrial dysfunction, rather than reflecting a pathological role of the molecule per se. By contrast, deliberately activating AMPK through pharmacological or exercise-induced means has indicated a beneficial effect of the molecule on energy maintenance and mitostasis across various tissues and wasting conditions, including cancer cachexia.

Insulin sensitivity and glucose tolerance in cancer

In addition to the decline in mitochondrial function with cancer cachexia, insulin resistance could contribute to the cellular energy crisis and disrupted tissue preservation during cachexia[23]. Insulin resistance was first identified in patients with cancer in the early 20th century owing to the disruption of glucose uptake and homeostasis[70]. These observations were later confirmed by studies showing decreased glucose tolerance and reduced insulin responsiveness in patients with various cancers, including lung, gastrointestinal and pancreatic cancers[19–23]. The development of insulin resistance in cancer might be severe, leading to hyperglycaemia and an increased risk of new-onset type 2 diabetes mellitus[71,72]. Although insulin-stimulated glucose uptake is not reduced in AMPK-knockout or kinase-inactive mice, AMPK activation is necessary for exercise to enhance insulin sensitivity[73,74]. Thus, AMPK activation might attenuate insulin resistance associated with cancer[43], optimize metabolic homeostasis and possibly stop muscle and adipose tissue wasting. The mechanisms involved in AMPK's insulin-sensitizing effects are beginning to emerge and probably involve TBC1 domain family member 1 (TBC1D1) and TBC1D4 (also known as AKT substrate of 160 kDa, AS160), which are Rab GTPase-activating proteins that inhibit translocation of the glucose transporter GLUT4 to the membrane[75,76]. Other insulin signals, such as the small Rho GTPase RAC1 (refs. 77–80), AKT, IRS1/2 and PI3K do not seem to be implicated in AMPK's insulin-sensitizing effect.

In mice with cancer cachexia, insulin resistance correlates with reduced AMPK activity and the loss of skeletal muscle and adipose tissue[28,41]. For example, in mice implanted with Lewis lung carcinoma (LLC) cells, the lack of AMPKα2 activity in the muscle caused whole-body glucose intolerance and insulin resistance[43]. Insulin-stimulated TBC1D4 Thr649 levels (the human orthologue of Thr642) in muscle increased more in tumour-bearing mice than in non-tumour-bearing controls. This upregulation was dependent on AMPK activity, as tumour-bearing mice with muscle-specific AMPK kinase did not exhibit upregulated TBC1D4 Thr649. Numerous AMPK-dependent molecular changes in skeletal muscle occur in LLC tumour-bearing mice compared with non-tumour-bearing control mice, including increased muscle protein content of pyruvate dehydrogenase (PDH), PDH kinase 2 (PDK2), PDK4, rS6 and glycogen synthase. The PDH–PDK axis is involved in glucose metabolism, and pharmacological PDH activation increases glucose oxidation in muscle[81], which would be expected to increase muscle glucose uptake. Moreover, interventions that directly or indirectly activate AMPK, such as AICAR and thiazolidinediones, reverse cancer-associated insulin resistance (according to findings published in a preprint article)[82].

The role of AMPK in maintaining insulin sensitivity might be specific to the type of stress, such as cancer, as there are mixed reports on AMPK's part in other conditions (for example, diet-induced metabolic dysfunction)[83–85]. The lack of AMPKα2 activity in skeletal muscle exacerbated[84] or did not alter[83] the insulin resistance caused by high-fat diet feeding, whereas in another study, AMPKα1 and AMPKα2 deficiency blocked obesity-induced insulin resistance[85]. Together, the current evidence suggests that AMPK helps maintain insulin sensitivity under specific stress conditions such as cancer; however, further research is needed to fully understand the role of AMPK in cancer-induced metabolic dysfunction.

AMPK and preservation of skeletal muscle mass

The contribution of AMPK to the maintenance of energy levels and cellular homeostasis are undisputed; however, AMPK is still often viewed as a pro-catabolic and anti-anabolic factor in proteostasis. This concept developed because AMPK phosphorylates and activates eEF2K[86], raptor[87] and TSC2 (ref. 88), resulting in reduced mTORC1 activity and reduced rates of protein synthesis. For example, the activation of AMPK with AICAR in healthy rats leads to reduced mTORC1 signalling and rates of protein synthesis in skeletal muscle[89], whereas deleting the gene encoding AMPKα1 and AMPKα2 in mice increases mTOR activity and enlarges the myofibre cross-sectional area[90]. Based on this link between AMPK and

Box 1

Upstream signals that activate or inhibit AMPK

AMPK is activated by an increase in the AMP (or ADP) to ATP ratio that occurs with metabolic stress, such as cellular starvation[221], exercise[222] and mitochondrial dysfunction[223]. AMPK can be activated via direct phosphorylation of the α subunit by LKB1 or CaMKK2. In most tissues, LKB1 controls the activation of AMPK[224]. CaMKK2 is activated by calcium influx[225], which can be triggered by exercise or induced by various DNA-damaging agents[226]. Interestingly, however, CaMKK2 is not involved in contraction-stimulated AMPK activation[227]. The role of CaMKK2 in skeletal muscle is therefore questionable. Inflammation, which is commonly documented in conditions of tissue wasting and insulin resistance, reduces AMPK activity by increasing protein phosphatase activity and ubiquitinating LKB1 (refs. 10–12,228).

Circulating factors also activate AMPK. The adipokine adiponectin increases AMPK phosphorylation via AdipoR1 or AdipoR2, which recruit the adaptor protein phosphotyrosine that interacts with the PH domain and leucine zipper 1 (APPL1)[214]. In muscle, this pathway could be coupled to calcium influx[229]. Leptin, another adipokine, stimulates fatty acid oxidation in muscles through AMPK[230]. Adrenaline and noradrenaline, which are secreted by the adrenal gland and sympathetic nervous system, can also activate AMPK in various tissues, including adipose tissue and liver, promoting glucose uptake and fatty acid oxidation[127]. In the context of cancer cachexia, circulating levels of IL-6 modulate AMPK[231]. Cytokines related to cancer cachexia, such as GDF15 and TNF, increase and suppress AMPK activity in healthy mice, respectively[10,16]. Thus, AMPK receives input from intracellular metabolic and enzymatic events as well as circulating factors, orchestrating AMPK activity in a coordinated and tightly controlled manner.

mTORC1 inhibition, it has been hypothesized that tissue loss during cancer cachexia could also be driven by AMPK[15,40]. Interestingly, the catabolic effects of AMPK in muscle could have a subunit-specific component. Unlike the results in mice lacking AMPKα1 and AMPKα2, deletion of the gene encoding for AMPKβ1 and AMPKβ2 in muscle led to a decrease in fibre size[67], and hampered type 2 fibre hypertrophy in response to functional overload[91].

Indeed, activation of AMPK does not always seem to result in increased net catabolism and blunted cell growth. For example, the presence of AMPK is required for the growth and survival of certain cancers[92,93], and activation of AMPK has been associated with the promotion of anabolism through nutrient scavenging in prostate cancer and breast cancer cells[94,95]. Furthermore, the loss of *Prkaa1* and *Prkaa2* (that encode AMPKα1 and AMPKα2, respectively) seems to reduce tumour growth in non-small-cell lung cancer in mice[96]; however, other studies found the opposite[97,98]. These data suggest that AMPK activity is not unilaterally connected with net catabolism and suggest a more complex involvement in the regulation of cell size, survival and growth. For a more detailed overview of the seemingly contradictory role of AMPK in cancer, the reader is referred to the excellent work of our colleagues[99–103].

Therefore, in a chronically catabolic milieu such as cancer cachexia, AMPK could be more than just a sensor of energy status; in line with the energy charge theory, it could be a first line of defence in the response to cellular energy crises and restoration of homeostasis. Supporting this hypothesis, crucial mechanistic evidence for the role of AMPK in tissue preservation in cancer cachexia has been obtained using drug interventions and exercise interventions to activate AMPK directly or indirectly. For example, stimulating AMPK activity systemically with A769662, resveratrol or exercise delays cancer cachexia-related muscle wasting in mice with colon carcinoma (C26)[69,104]. In addition, we and others have found that thiazolidinediones (such as rosiglitazone) can increase circulating levels of adiponectin, which indirectly enhances the activity of AMPK in skeletal muscle, resulting in preserved body weight, muscle mass and adipose tissue during cancer cachexia in mice and rats with lung, colon, breast or liver cancer[82,105–108]. Similar results were found in vitro when adiponectin was used to activate AMPK in C2C12 cells treated with cachexia-promoting conditioned medium[109]. In addition, muscle-specific expression of a dominant-negative mutation in the gene encoding AMPK resulted in decreased mass of the tibialis anterior muscle and adipose tissue in mice with lung cancer[43]. Interestingly, muscle-specific overexpression of PGC1α alone does not improve cancer cachexia in mice implanted with LLC, despite improving markers of mitochondrial biogenesis and proteolysis[110,111]. This finding could indicate that the positive effects of AMPK in other scenarios are either not exclusively mediated by PGC1α or that any benefits of increased levels of PGC1α in the LLC model were offset by the fact that the overexpression group had a 30–50% increase in tumour size[110,111]. This finding also highlights how chronic pathway activation via drugs and/or genetic manipulation can fundamentally alter the role of molecules, making comparisons to the physiological state difficult.

Pointing further in the same direction and suggesting that signalling molecules rarely have a unilateral purpose, blunting traditional growth signals can promote tissue preservation as well. Although mTOR activity is indispensable for load-induced muscle growth[112,113], chronically increased mTORC1 activity contributes to age-related muscle atrophy[114]. Accordingly, age-related[115,116] and cancer-related muscle wasting can be attenuated in rodents by suppressing mTOR hyperactivity through rapamycin[104]. Additionally, inducible deletion of the gene encoding raptor, a protein known to regulate mTORC1 activity[117], did not exacerbate lean mass loss or adipose tissue mass loss and did not change the decrease in fibre cross-sectional area or force that is seen in mice with cancer cachexia[118]. Interestingly, the same study found that stimulating muscle anabolism at the level of AKT almost completely protected the mice from tissue wasting[118]. Although a negative relationship between AKT and AMPK has been found previously[119], studies from the past few years have found conditions in which AKT and AMPK activity positively depend on each other[120,121], possibly mediated through a relationship between AMPK and mTORC2 (ref. 122). Overall, these findings put a twist on the dogma of AMPK as a mere mediator of cell catabolism in muscle, and support the idea of a more nuanced role for AMPK in tissue preservation, including one as a pro-anabolic factor that ensures adequate ATP production and cell survival under certain states of chronic metabolic stress, such as cancer cachexia. These positive effects on protein turnover and tissue preservation are probably connected to the aforementioned role of AMPK in mitostasis and 'recharging' the cell. The role of AMPK in orchestrating signalling events that lead to the preservation of skeletal muscle in wasting conditions such as cancer cachexia is summarized in Fig. 2.

Stabilizing AMPK reverses white adipose tissue wasting

Lipid metabolism is altered in patients with cancer[123,124], possibly because of insulin resistance and β-adrenergic stimulation, which induce lipolysis in white adipose tissue (WAT). β-Adrenergic stimulation activates AMPK in rodent and human adipocytes and is involved in catabolic tissue remodelling[125,126]. β-Adrenergic receptor signalling also regulates AMPK activity in adipose tissue of rodents in vivo[127,128], which is thought to be an indirect effect of accelerated lipolysis and increased AMP to ATP ratios[129–131]. Mice deficient in AMPKβ1 and AMPKβ2 in mature adipocytes have impaired mitochondrial integrity and function due to diminished mitophagy[126]. Additionally, AMPK modifies regulators of adipogenesis, such as PPARγ, C/EBPs and genes that encode proteins involved in lipid metabolism (such as *ACC* and *FASN*[132]). Interestingly, in brown adipocytes, AMPK–mTORC1 crosstalk seems to facilitate adipocyte differentiation, including increased accumulation of brown adipocytes in mouse WAT[133].

Adipose tissue lipolysis and oxidation of liberated fatty acids are increased in many cancer types[28,134]. For example, the release of fatty acids and glycerol is increased by 30–40% in WAT explants from mice bearing cachexia-promoting tumour allografts[135] and gonadal WAT isolated from mice with endogenous lung tumours[136]. Increased lipolysis also occurs in primary or 3T3-L1 adipocytes treated with tumour cell-conditioned medium, demonstrating that tumour-derived factors directly affect lipid metabolism in adipocytes[30]. Whole-body insulin action is restored by blocking fatty acid oxidation via etomoxir administration in tumour-bearing mice, supporting an association between fatty acid metabolism and insulin resistance[28]. Similarly, inhibition of lipid oxidation rescues glucose intolerance[28] and helps prevent muscle atrophy in tumour-bearing mice[135,137].

AMPK regulates lipolysis through phosphorylation of the key enzymes adipocyte triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). Specifically, AMPK phosphorylates Ser565 of HSL, which inhibits its function. Defective AMPK-mediated phosphorylation at Ser565 of HSL results in increased phosphorylation at the activating protein kinase A target sites Ser563 and Ser660 of HSL. Thus, mice with low adipocyte levels of AMPKα1 or AMPKα2 have increased lipolysis and higher energy expenditure than wild-type mice[138].

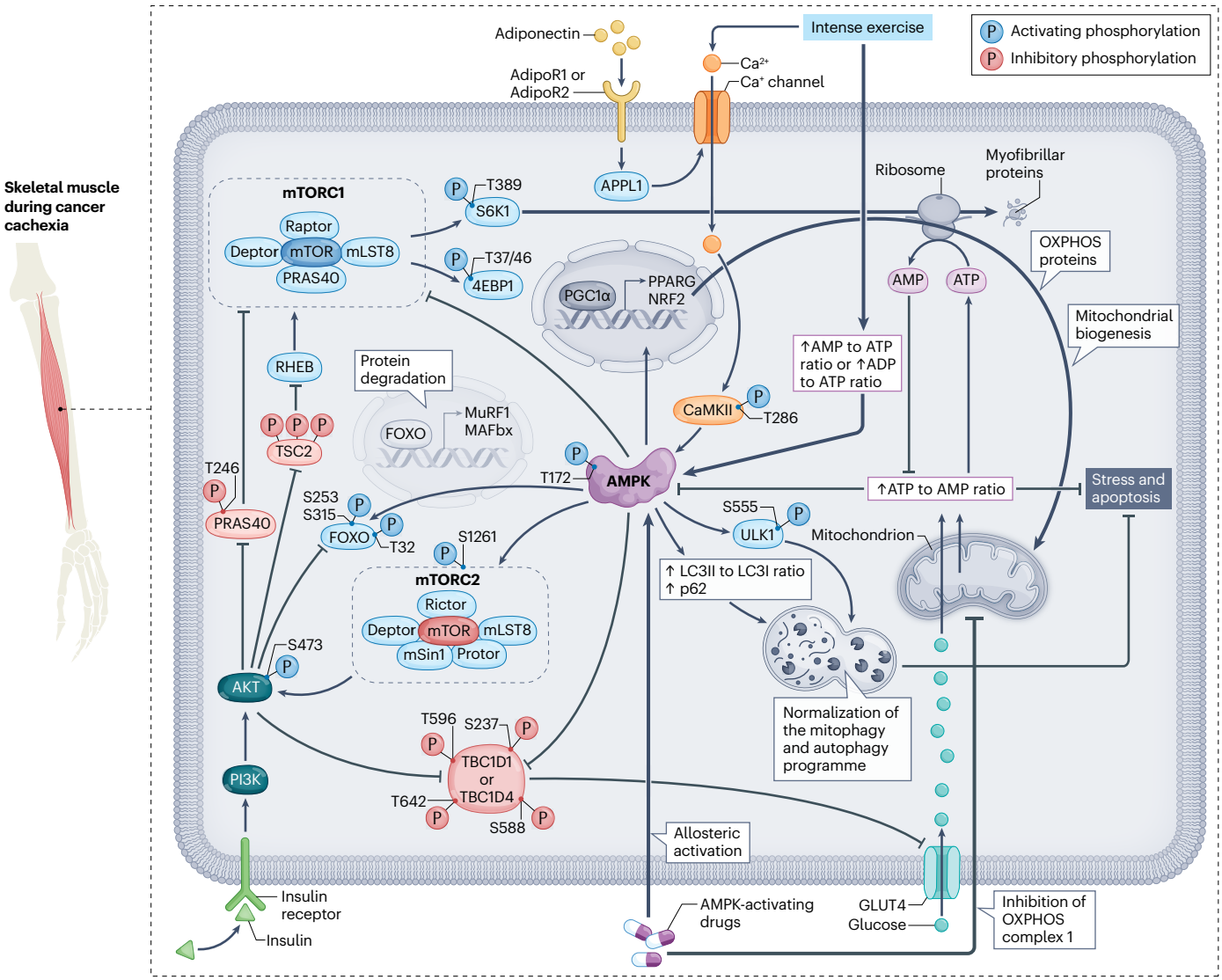

Fig. 2 | Skeletal muscle during cancer cachexia. During times of metabolic stress, 5′-AMP-activated protein kinase (AMPK) is a crucial mediator of tissue maintenance. The figure highlights some of the external factors that activate AMPK, such as exercise, pharmacological agents and circulating levels of adiponectin, as well as the potential mechanisms by which AMPK signalling could aid the preservation of skeletal muscle during wasting conditions such as cancer cachexia. Firstly, the maintenance of energy levels is upheld through improved mitochondrial function via pathways involving PPARG coactivator 1α and unc51-like autophagy-activating kinase 1. Secondly, AMPK enhances insulin sensitivity via TBC1 domain family member 4 (TBC1D4) and other unknown mechanisms. Thirdly, through the maintenance of cellular energy levels and insulin signalling, AMPK helps to sustain functional protein synthesis via pathways involving AKT, mTORC1 (or mTORC2) and S6K1. APPL1, adaptor protein phosphotyrosine that interacts with the PH domain and leucine zipper 1; OXPHOS, oxidative phosphorylation.

Deletion of the genes encoding ATGL or HSL partially protects mice from tumour-induced adipose tissue loss and wasting[135]. In rodents, increased tumour-induced lipolysis is partly mediated by AMPK[30,139], as a reduction (associated with cancer cachexia) in AMPK activity in adipocytes leads to reduced phosphorylation of Ser565 on HSL, causing overactivation of the enzyme. Under normal conditions, roughly 30% of the fatty acids produced during lipolysis of rat adipocytes are recycled intracellularly[140]. This process with a high energy cost depletes ATP and increases AMP levels, thus activating AMPK-mediated feedback inhibition of mouse adipocyte lipolysis under physiological conditions[125]. Reduced AMPK activity in cachectic adipocytes from mice not only prevents this feedback inhibition at the level of HSL, but also leads to reduced phosphorylation (inhibition) of acetyl-CoA carboxylase (ACC), enabling fatty acid re-esterification. Therefore, increased lipolysis re-esterification cycling might explain the paradoxical simultaneous increase in triglyceride degradation and triglyceride build-up, which represents an energy-costly process that contributes to WAT wasting in cachexia. Accordingly, the levels of ATP in cachectic adipocytes are up to 50% lower than in healthy mouse adipocytes[30]. In addition to the direct regulation of key proteins involved in adipocyte lipid metabolism, AMPK further affects lipid turnover by its modulation of autophagy and mitophagy, the latter of which is critical for maintaining

mitochondrial integrity and subsequently cellular energy homeostasis[141]. AMPK involvement in WAT autophagy, mitophagy and mitochondrial function has not yet been studied in the context of cancer cachexia; however, it is likely that cancer cachexia also affects these processes.

The AMPK–PGC1α pathway promotes the activation of the thermogenic gene programme in brown adipose tissue (BAT)[142]. Brown and brite (or beige) adipocytes typically express DFFA-like effector A (CIDEA), which induces cell death, and it is considered a marker of adipocytes capable of thermogenesis[143]. Under normal physiological conditions, CIDEA expression in WAT is very low, but increases markedly in cachectic mouse models and in patients with cancer cachexia[30]. High CIDEA expression is associated with reduced AMPK protein levels and activity[30], and CIDEA-mediated ubiquitination and degradation of AMPK, as previously described in brown adipocytes, also occurs in cachectic WAT in mice[144]. In line with reduced AMPK activity in cachectic WAT, the AMPK targets ACC and HSL are phosphorylated less in the WAT of mice with cachexia than in those without cachexia, causing impaired lipid metabolism, mitochondrial respiration and energy homeostasis. The reduced AMPK activity is, at least in part, dependent on CIDEA, because knockdown of the gene encoding CIDEA prevents tumour-induced lipolysis in mice[30]. A peptide that stabilizes AMPK by interfering with the interaction between CIDEA and AMPK restores adipose tissue function and energy homeostasis, which counters adipose tissue loss, but also partly prevents lean mass loss and extends cachexia-free survival in tumour-bearing mice[30,145].

As touched on in the previous section, muscle-specific PGC1α overexpression does not protect mice from LLC-induced cachexia[110,111], but adipose-specific overexpression has not been assessed in the context of cachexia. PGC1α mRNA levels are slightly elevated in WAT and BAT of cachectic mice[136,146]. However, the decreased oxidative metabolism and impaired mitochondrial function observed in adipocytes treated with tumour cell-conditioned medium[30] and reduced mitochondrial biogenesis in adipose tissue of cachectic animals[147] are in contrast to this finding and would argue for reduced PGC1α activity, in line with reduced AMPK levels. In agreement with this observation, rosiglitazone and imidazole partly prevent adipose tissue wasting in rodents[82,106], as does pioglitazone[108]. AMPK signalling in WAT during cancer cachexia is summarized in Fig. 3.

Physiological activation of AMPK

The most well-described physiological methods of activating AMPK are cellular starvation[148] and exercise[149]. Activation of AMPK through cellular starvation is an impracticable strategy in cancer cachexia because of the reduced food intake that would be required[150], which hampers the maintenance of energy levels. Accordingly, decreased energy availability exacerbates atrophy of skeletal muscle and adipose tissue in cancer cachexia[151]. Additionally, unlike in adipose tissue, where fasting rapidly induces AMPK activity[152], this effect seems to be largely absent in skeletal muscle of humans, and its effect on AMPK activity in rodents remains uncertain[153,154]. By contrast, use of ATP during exercise potently elevates intramyocellular levels of AMP, thereby robustly activating AMPK[155]. Exercise-induced AMPK activation can restore substrate flux (for example, diversion of substrates from the tumour to the working muscle as discussed in Box 2), promote mitochondrial biogenesis and improve insulin sensitivity, and is also accompanied by the stimulation of mTOR-dependent and mTOR-independent growth signals. For example, in healthy rodents and humans, resistance exercise acutely activates AMPK[156,157] without suppressing a concomitant increase in mTORC1 activity and muscle protein synthesis[113,157,158]. In line with this finding, chronic resistance exercise in humans results in increased AMPK activity while also improving muscle mass and strength[157,159,160]. This finding highlights that exercise-induced, anabolic signals and muscle growth can occur in the presence of elevated AMPK activity. Another example is AMPK activation through high-intensity interval training, which does not suppress anabolic signalling and protein synthesis in human skeletal muscles[161,162]. Similarly, aerobic exercise activates AMPK, mTOR and muscle protein synthesis concurrently in human skeletal muscle[157,163]. In agreement with AMPK's central role in the maintenance of energy levels, insulin sensitization and modulation of protein synthesis, exercise-dependent AMPK activation potently induces all of these benefits[164–166]. Altogether, these effects of exercise promote tissue health and cell survival, which would be particularly beneficial during cancer cachexia.

In mice with colorectal or lung cancer, voluntary daily exercise delays the development of cancer cachexia and maintains muscle mass and function. If an exercise intervention is initiated before tumour inoculation, exercise improves survival[46,167]. In humans, across various cancer types and stages, during and after treatment, aerobic and resistance exercise improve muscle mass, muscle strength and aerobic fitness[168–171]. Work in preclinical cancer cachexia models suggests that the beneficial effects of exercise are, at least partially, mediated through adiponectin and AMPK[104,109]. However, this finding remains to be translated to humans and proven mechanistically in transgenic AMPK-deficient models.

Challenges in implementing exercise in many patients with cancer are probably the reason why few researchers have confronted this question and why there is a profound lack of data on exercise in people with cancer cachexia[172]. Notably, although AMPK stimulation might account for several exercise-induced metabolic and mitochondrial adaptations, other signalling molecules activated by exercise probably contribute to improving tissue preservation in an AMPK-independent manner. For example, directly targeting muscle-specific AKT and mTORC1 activity have both resulted in improvements in muscle anabolism and tissue preservation in cancer models[118,173,174]. Moreover, exercise-induced glucose and fatty acid uptake into skeletal muscle does not seem to require AMPK[175]. Therefore, it would be inaccurate to attribute the success of exercise interventions in preclinical models exclusively to AMPK. Nevertheless, while AMPK alone might not be sufficient to drive all adaptations related to exercise and tissue preservation, AMPK does orchestrate a large number of them through its effect on PPARδ, PPARγ and PGC1α[165]. Even though exercise would be the most comprehensive solution, pharmacological activation of AMPK (Table 1) could be an attractive means to help preserve tissues under conditions of chronic cellular stress where exercise capacity is limited, such as in cancer cachexia, and is discussed in the next section.

Drugs targeting AMPK

The primary therapeutic challenge in cancer cachexia is reversing catabolic processes while meeting the need for ATP in skeletal muscles and adipose tissues without simultaneously promoting tumour growth. Numerous drugs activate AMPK, and many are already in clinical use and are well tolerated by humans[176]. The most well-known and widely used drug that targets AMPK is metformin[177]. Metformin effectively improves glucose homeostasis, which could be useful for cancer-associated metabolic dysfunction. Several epidemiological studies have correlated the use of antihyperglycaemic medications with the risk of cancer and cancer outcomes. A general finding is that patients with type 2 diabetes mellitus treated with insulin and sulfonylureas,

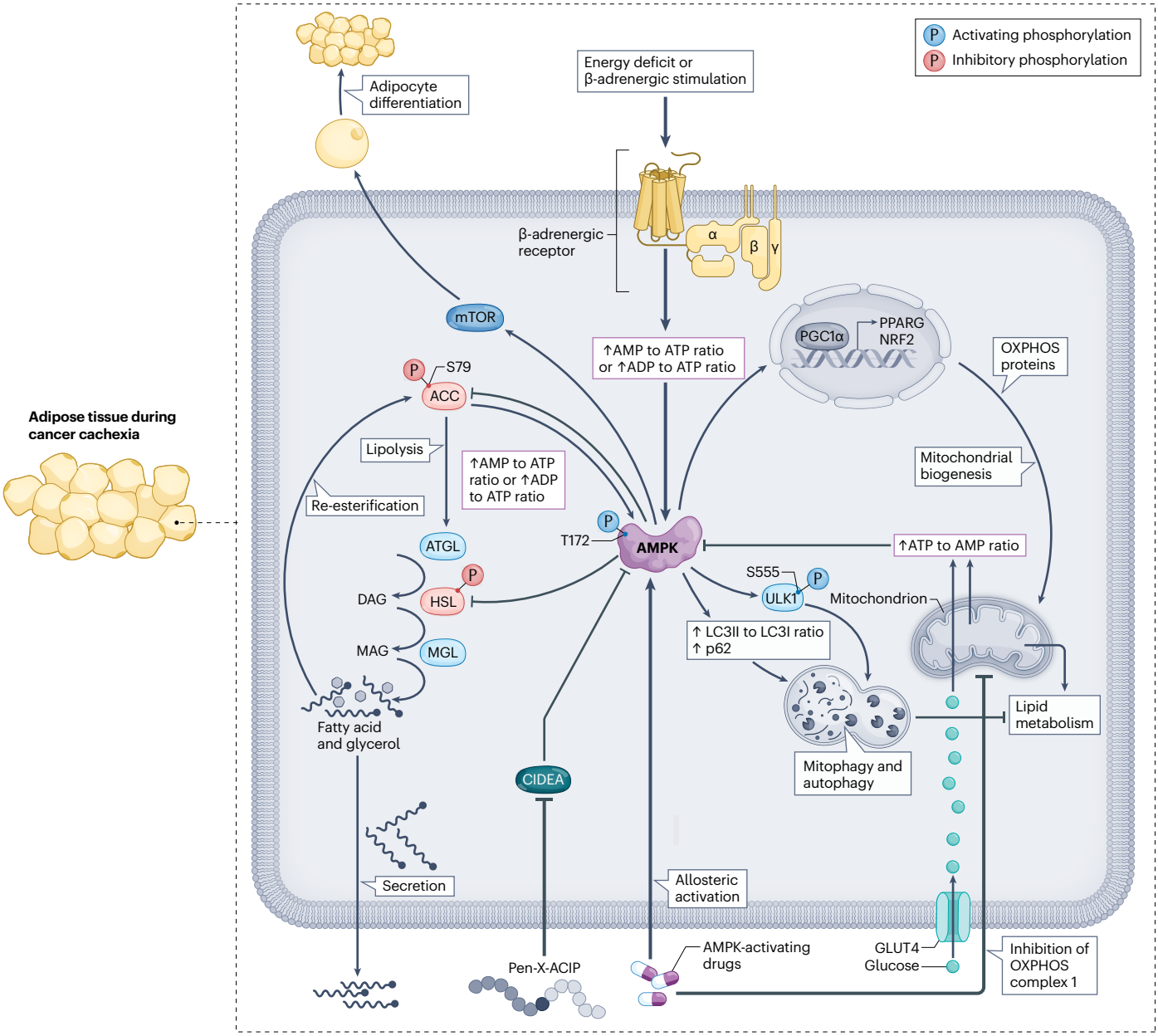

Fig. 3 | Proposed AMPK signalling network in white adipose tissue during cancer cachexia. 5′-AMP-activated protein kinase (AMPK) mediates mitochondrial health through PPARG coactivator 1α (PGC1α) and unc51-like autophagy-activating kinase 1 (ULK1), while also modulating adipocyte differentiation and fatty acid secretion. Stabilizing AMPK by interfering with the interaction between DFFA-like effector A (CIDEA) and AMPK through a prototypic peptide (Pen-X-ACIP) helps maintain AMPK activity and aids in the preservation of white adipose tissue during cancer cachexia. ACC, acetyl-CoA carboxylase; ATGL, adipocyte triglyceride lipase; HSL, hormone-sensitive lipase; OXPHOS, oxidative phosphorylation.

which stimulate insulin secretion, have a higher cancer incidence and mortality than those treated with metformin[178,179]. However, the addition of metformin to chemotherapy for lung cancer reduced hyperinsulinaemia, which is indicative of metabolic benefits, but did not improve survival[180]. Moreover, metformin mainly activates AMPK in the liver[181], and its applicability in muscle and adipose tissue preservation needs to be determined (according to findings published in a preprint article)[182]. For example, metformin had an AMPK-independent function in preventing adipose tissue wasting in a mouse model of burns[183]. In addition, metformin had adverse effects on exercise adaptations in older patients (62 ± 1 years of age) owing to mitochondrial complex I blockade[184]. Thus, metformin-induced blockade of mitochondrial complex I is probably not an optimal way to activate AMPK in cancer cachexia because mitochondria are already dysfunctional[52]. Here, allosteric activation (such as through AICAR, MK-8722 or PXL770) might prove more beneficial. Accordingly, AICAR, but not metformin,

ameliorated cancer cachexia in preclinical mouse models[43,69,104]; however, not all studies support this finding[185].

Unfortunately, AICAR is poorly tolerated in humans and therefore other drugs activating AMPK directly or indirectly, such as canagliflozin[186], thiazolidinediones[187,188], salicylate[189], PXL770 (ref. 190), O304 (ref. 191) and MK-8722 (refs. 192,193), are clinically more attractive. MK-8722 reduces adipocyte lipolysis[145], and in a study published in 2023, MK-8722-induced AMPK activation stimulated mitophagy (via ULK1) in dystrophic muscle from a mouse model of Duchenne muscular dystrophy[194]. Thiazolidinediones, including pioglitazone and rosiglitazone, activate AMPK in skeletal muscle[188] and adipose[195] tissue via two independent pathways. One pathway involves the accumulation of AMP due to inhibition of the mitochondrial complex I, similar to metformin[187]. The other involves the release of adiponectin from adipocytes[188], which in turn activates AMPK in mammalian tissues. Adiponectin is not just a potent activator of AMPK, but can also positively affect anabolic signalling and skeletal muscle[82,109], as well as cardiac muscle, in mice[196,197]. There are mixed data from clinical studies on thiazolidinediones influencing tissue preservation, with studies showing increased[198] or unchanged[199] lean mass following thiazolidinedione treatment in people with prediabetes. Ongoing clinical studies, such as the TRACE-1 trial (NCT05919147), aim to explore the effect of pioglitazone on insulin sensitivity in patients with advanced non-small-cell lung cancer and cachexia.

A challenge with drugs targeting AMPK systemically, such as MK-8722, is that AMPK activation in the heart can promote cardiac hypertrophy, which has deterred clinical development[192,200]. Nevertheless, the direct AMPK activator PXL770 has advanced to phase II clinical trials, in which it was shown to reduce HbA_{1c} levels and insulin resistance in people with non-alcoholic fatty liver disease (also known as metabolic dysfunction-associated steatotic liver disease)[190]. The clinical success of PXL770 might be related to its moderate potency, allowing a more physiological activation of AMPK compared with highly potent compounds, such as MK-8722, for which clinical concerns have been reported[192]. Interestingly, while the high subunit specificity of PXL770 for AMPKβ1 offers a compelling explanation for its efficacy in rodent models of metabolic dysfunction-associated steatohepatitis (also known as non-alcoholic steatohepatitis) or kidney disease[201,202], the same cannot be said for human liver tissue, where AMPKβ2 predominates[203]. Similarly, WAT has a fairly even distribution between AMPKβ1 and AMPKβ2 (refs. 204,205) but skeletal muscle has a much higher expression of AMPKβ2 than of AMPKβ1 (ref. 206). This finding raises doubt over a potential role for PXL770 in the maintenance of muscle mass during cancer cachexia.

In a study published in 2018, the pan-AMPK activator O304 was found to improve insulin resistance and exercise performance in models of ageing and diet-induced obesity, while also being well tolerated in humans[191]. In a separate preclinical trial, O304 substantially increased glucose uptake into skeletal muscle[207]. Unlike long-acting AMPK activators, such as MK-8722, treatment with the short-acting O304 did not result in increased glycogen deposition or gross hypertrophy of the heart, but rather improved cardiac function[207]. The idea that the length of exposure in addition to the potency of the compound could be key to optimizing interventions is supported by a study that showed that chronically elevated AMPK signalling results in hyperphagia and obesity in mice[208].

Box 2

Redirection of glucose from the tumour to muscle during cancer cachexia

The acute generation of ATP required during exercise is enabled by a remarkable increase in glucose uptake by the working muscles[232]. In cancer, insulin resistance in muscle and adipose tissue might develop to impart a selective growth advantage for tumours as it redistributes nutrients away from healthy tissue and towards the cancer cells. Cancer cells rely heavily on glucose, even in the presence of sufficient oxygen[233]. The constitutively high uptake of glucose supports the continuous proliferation and growth of cells in the tumour[234]. This process might be exacerbated by insulin resistance, and impaired glucose uptake into skeletal muscle and adipose tissue increases the release of mitogenic stimuli such as insulin. These effects might explain why disrupted glucose metabolism[72,235–237] and hyperinsulinaemia[238–241] are strong risk factors for cancer, cancer recurrence and death from cancer[242]. Activation of AMPK might be highly desirable in patients with cancer as it increases insulin sensitivity and promotes glucose disposal into organs in an insulin-independent fashion.

The concept of redirecting glucose away from the tumour is supported by a study in which BAT was stimulated to take up glucose through cold treatment[243]. The results showed reduced glucose uptake in the tumour and a reduced growth rate. However, a major caveat of that study was the concomitant accelerated loss of body mass, with potential detrimental effects in patients. As unintentional loss of body weight is the primary symptom of cancer cachexia, BAT activation through cold treatment does not seem to be a clinically suitable strategy for glucose redistribution in cancers that tend to cause cancer cachexia. Furthermore, cold treatment increases glucose uptake into BAT fivefold to 12-fold in humans[244,245], whereas exercise can increase glucose uptake into skeletal muscle by 25-fold to 100-fold[232]. Moreover, skeletal muscle is about 500 times more abundant than BAT in the human body[246]. Therefore, exercise might be a more appealing strategy for the redirection of fuel during cancer. In the context of cancer-associated insulin resistance, exercise offers a powerful alternative to drugs, as it promotes glucose uptake into muscle without requiring insulin[247]. In addition to these acute, insulin-independent effects, after each exercise bout insulin sensitivity in muscle transiently increases for up to 48 h in humans[248] via a mechanism involving AMPK. However, to our knowledge, no study has determined the effect of an acute exercise bout on insulin sensitivity or the efficacy of exercise in stimulating glucose uptake in the muscle of patients with cancer cachexia.

Table 1 | Transgenic and pharmacological manipulation of AMPK in cancer cachexia

Cancer and model	Number of animals (sex)	Tissue examined	AMPK model	Finding	Ref.
Transgenic models of modulated AMPK activity					
Mouse, LLC	9–38 (male)	Skeletal muscle, adipose tissue	Loss of function, skeletal and cardiac muscle-α2 kinase dead mutant	Insulin resistance, glucose intolerance, accelerated muscle and adipose tissue wasting	43
Mouse, *Apc*$^{Min/+}$	6–10 (male)	Skeletal muscle	Tamoxifen-inducible skeletal muscle knockout of AMPKα1 and AMPKα2 (crossed with Apc$^{Min/+}$)	Reduced muscle atrophy, reduced autophagy markers	58
Pharmacological AMPK activity modulation					
Mouse, C26, SW480	8–12 (male)	Adipose tissue	CIDEA or ACIP (AMPK stabilization in adipose tissue)	Reduced white adipose tissue wasting, improved cachexia-free survival	30
Mouse, C26	7–8 (male)	Adipose tissue	CIDEA or ACIP peptide compound	Reduced white adipose tissue wasting	145
Mouse, C26	12–26 (female)	Skeletal muscle	AICAR	Preserved skeletal muscle mass and fibre size	104
Mouse, C26	4–8 (male)	Skeletal muscle, adipose tissue	AICAR and metformin	AICAR, but not metformin preserved skeletal muscle mass and fibre size	69
Mouse, LLC	10 (male)	Skeletal muscle, adipose tissue	AICAR	Improved glucose tolerance	43
Mouse, C26	9–15 (male)	Skeletal muscle, adipose tissue	Rosiglitazone	Improved insulin sensitivity, attenuated weight loss, preserved muscle and adipose tissue, decreased catabolic signalling	105
Rat, hepatoma	10–49 (male)	Adipose tissue	Rosiglitazone	Improved survival, attenuated weight loss, preserved adipose tissue	107
Mice, KL	17 (male)	Skeletal muscle, adipose tissue	Rosiglitazone	Attenuated weight loss, preserved muscle and adipose tissue, maintained anabolic signalling	82

CIDEA, DFFA-like effector A; KL, *Kras*$^{G12D/+}$;*Lkb1*$^{f/f}$; LLC, Lewis lung carcinoma.

The examples of PXL770 and O304 highlight that it is possible to design drugs that capitalize on the powerful metabolic benefits of AMPK activation without creating an unfavourable risk profile. However, tissue specificity, subunit specificity, avoidance of supraphysiological potency and duration of activation must be considered when designing such drugs. Nevertheless, despite the longstanding interest in AMPK as a druggable target and the progress in translation into clinics, no pharmacological intervention that activates AMPK has yet been tested in humans with cachexia. These are exciting avenues to be explored in the context of cancer, cancer cachexia and other tissue-wasting conditions.

Finding AMPK-activating drugs could be highly desirable in patients with cancer cachexia, especially given the fact that many patients might be unable to engage in the intense exercise needed to activate AMPK. Thus, people with cancer are likely to benefit from pharmacological AMPK activation to treat cancer-related pathologies, such as mitochondrial dysfunction, insulin resistance and tissue wasting. Repurposing drugs is appealing because pharmacological and toxicological data are available. Consequently, failure risk and costs are reduced compared with novel drugs[209]. We propose that pharmacological and physiological tissue-specific AMPK activation can be a safe, effective and practical therapeutic approach to aid the maintenance of energy levels, prevent insulin resistance and preserve tissue mass in conditions such as cancer cachexia.

Future directions

To successfully translate the results from preclinical models to clinics, it is important to acknowledge several gaps in our understanding of AMPK's role in tissue preservation, particularly with regard to the mode of action and specificity of certain AMPK-targeting strategies and the quality of evidence for their clinical applicability. For example, AICAR is a widely used AMPK activator in preclinical studies. It is a nucleotide analogue that is taken up by skeletal muscle and phosphorylated to form ZMP, an AMP mimetic, thereby increasing AMPK activity[210]. While showing promise in several preclinical studies (discussed in previous sections), the high doses required to successfully stimulate AMPK activity in patients are unfortunately associated with severe adverse effects[211]. Additionally, AICAR has AMPK-independent effects (for example, increased fatty acid oxidation in skeletal muscle[212]). Therefore, in addition to its limited clinical applicability, the AMPK specificity of the results observed in preclinical studies needs to be evaluated carefully.

Similarly, thiazolidinediones affect AMPK indirectly on multiple levels; for example, by increasing intracellular levels of AMP through inhibition of mitochondrial complex I or II[187], and through activating PPARγ in adipose tissue, which in turn leads to increased adiponectin synthesis and release into the circulation. Adiponectin then binds to AdipoR1 or AdipoR2 in skeletal muscle and other tissues, where it causes Ca^{+} influx into the cell through an interaction between the ligand and APPL1, eventually leading to increased AMPK activity[213,214]. Interestingly, in a preprint paper published in 2023, the AdipoR1 and AdipoR2 agonist AdipoRon was reported to show great promise not only in stimulating AMPK activity and protein synthesis in muscle cells[82], but also in improving muscle metabolism and function in obese, aged and dystrophic mice[215–217]. Attributing the benefits that were observed for thiazolidinediones in cachexia exclusively to AMPK would be naive

given the pleiotropic effects of the drugs. Likewise, exercise is known to have a plethora of health benefits for the human body and skeletal muscle specifically, many of which do not require or directly involve AMPK. Therefore, some of the preclinical observations regarding the positive effect of exercise on cancer cachexia might correlate with AMPK activity rather than being caused by it.

Nevertheless, there is also strong preclinical and clinical evidence for a direct role of AMPK in the modulation of systemic metabolism and tissue preservation. For example, MK-8722 is a potent and specific AMPK pan-β activator[218] that has shown robust effects on systemic and muscle-specific glucose uptake in rodent and primate models of type 2 diabetes mellitus[192]. In line with this finding, another pan-β activator of AMPK, PF-739, showed acute improvements in glucose disposal in mice and cynomolgus monkeys[193]. These benefits to glucose homeostasis were specific to the drug's effect on skeletal muscle and were accompanied by increased expression of the gene encoding PGC1α and increased levels of PGC1α in mitochondria. Furthermore, mice with diet-induced obesity in this study showed a reduction in adipose tissue mass and a tendency towards lean mass retention when treated with PF-739 compared with the control group and in the absence of changes to food intake[193]. Like MK-8722 and A769662, PF-739 binds to the allosteric drug and metabolite site of AMPK, which bridges the regulatory β subunits and the catalytic α subunits of AMPK[219]. However, unlike compounds such as A769662 or PF-249, which have a greater preference for the β1 than the β2 subunit of AMPK, the muscle-specific effects of PF-739 can probably be explained by its higher relative potency towards binding to the β2 subunit of AMPK, which is the primary subunit expressed in skeletal muscle of humans.

Although concerns have been raised for most of these drugs regarding safety or indication-specific efficacy, and therefore they have not yet transitioned into clinical trials, positive examples such as PXL770 and O304 highlight the pharmacological potential of direct AMPK activators to treat systemic metabolic diseases. The benefits of these drugs are predominantly modulated through increased glucose uptake into tissues and by upregulated expression of mitochondrial genes and proteins. All of which are highly desirable characteristics of strategies to improve tissue preservation during cancer cachexia. Future efforts in drug development in the cachexia space need to focus on improving the delivery of AMPK-activating compounds to skeletal muscle and adipocytes, while avoiding off-target effects on the heart and other tissues. Such strategies will have to finely balance the potency and pharmacokinetic profile of such compounds, as supraphysiological activity and duration of AMPK activity seem to have detrimental effects that might be exacerbated in off-target issues.

Conclusions

AMPK activation increases insulin sensitivity, glucose uptake and fatty acid oxidation, and promotes optimal mitochondrial function; as such, AMPK supplies tissues with the necessary energy to facilitate the maintenance or accrual of biomass under conditions of cellular stress. The unilateral role of AMPK as a pro-catabolic molecule must be revisited, and the potential of AMPK as a promoter of cell survival should be further explored for its clinical potential, especially in wasting disorders such as cancer cachexia, sarcopenia and muscular dystrophies. Preclinical studies in these conditions have shown that AMPK activation can benefit tissue preservation through the restoration of anabolic signalling and protein synthesis; however, current clinical trials using AMPK-activating drugs in a variety of tumour types have yielded mixed results[220]. Degradation of the AMPK complex (for example, in cancer or cancer cachexia, as seen in adipose tissue[30]) might explain why AMPK-directed therapies do not always work. Targeting AMPK in a tissue-specific and context-specific manner will be crucial for maximal benefit with minimal adverse effects, as exemplified by the adipose tissue-specific action of AMPK-stabilizing peptides[30,145]. Intriguingly, exercise-induced AMPK stimulation in skeletal muscle translates to mitochondrial, anabolic and metabolic benefits in skeletal muscle, which illustrates the potential of AMPK in tissue preservation. The complicated relationship between AMPK and mTOR also highlights that ubiquitously preserved signalling cascades are neither 'good' nor 'bad', nor are they unambiguously 'growth-promoting' or 'growth-suppressing'. Therefore, molecular signals work in concert to orchestrate a fine balance between the synthesis and degradation of biomass, fuelled by mitochondrial ATP production, which ultimately ensures adaptability and cell survival across a wide range of external and internal stimuli. Thus, AMPK has an unexpected role in tissue preservation, which calls for a shift in the current dogma.

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Competing interests

During revision of the manuscript H.T.L. started to work for Boehringer Ingelheim GmbH & Co. KG. The other authors declare no competing interests.

Additional information

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