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REVIEW ARTICLE

LncRNAs are involved in regulating ageing and age-related disease through the adenosine monophosphate-activated protein kinase signalling pathway

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Abstract A long noncoding RNA (lncRNA) is longer than 200 bp. It regulates various biological processes mainly by interacting with DNA, RNA, or protein in multiple kinds of biological processes. Adenosine monophosphate-activated protein kinase (AMPK) is activated during nutrient starvation, especially glucose starvation and oxygen deficiency (hypoxia), and exposure to toxins that inhibit mitochondrial respiratory chain complex function. AMPK is an energy switch in organisms that controls cell growth and multiple cellular processes, including lipid and glucose metabolism, thereby maintaining intracellular energy homeostasis by activating catabolism and inhibiting anabolism. The AMPK signalling pathway consists of AMPK and its upstream and downstream targets. AMPK upstream targets include proteins such as the transforming growth factor β-activated kinase 1 (TAK1), liver kinase B1 (LKB1), and calcium/calmodulin-dependent protein kinase β (CaMKKβ), and its downstream targets include proteins such as the mechanistic/mammalian target of rapamycin (mTOR) complex 1 (mTORC1), hepatocyte nuclear factor 4α (HNF4α), and silencing information regulatory 1 (SIRT1). In general, proteins function relatively independently and cooperate. In this article, a review of the currently

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known lncRNAs involved in the AMPK signalling pathway is presented and insights into the regulatory mechanisms involved in human ageing and age-related diseases are provided.

Introduction

Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is the centre of the AMPK signalling pathway. AMPK plays an important role in regulating cellular energy balance and is activated by changes in the adenine nucleotide (AMP)/adenosine diphosphate (ADP) ratio or directly by changes in adenosine triphosphate (ATP) levels. The activation of AMPK increases the catabolic rate and reduces the anabolic rate in cells.[1] Because it controls energy homeostasis, AMPK has attracted widespread attention as a potential therapeutic target in metabolic diseases (including type 2 diabetes, obesity, and cancer).[1] AMPK is involved in energy metabolism in multiple ways, including the direct binding of its subunits to environmental factors and synergistic effects mediated through its upstream/downstream target proteins, which are cofactors that increase the phosphorylation and expression levels of pathway components.[2] The AMPK signalling pathway components communicate with other important signalling pathway components, such as constituents of the mTOR signalling pathway, jointly regulating the molecular mechanism of an organism and maintaining its health.

Long noncoding RNAs (lncRNAs) are longer than 200 bp and show limited protein-coding potential. LncRNAs are involved in various physiological and pathological processes, such as apoptosis, cell differentiation, and immune responses.[3] Previous studies have shown that lncRNAs are key regulators of the occurrence and development of various diseases, including cancer,[4] cardiovascular disease,[5] and diabetic vascular complications.[6] With the deepening of research, the important roles of lncRNAs in tumorigenesis and development have been gradually revealed through their effects on tumour cell proliferation, migration, invasion, and metastasis, especially in lung cancer,[7] breast cancer,[8] and gastric cancer[9] cells. Hence, lncRNAs are biomarkers for the clinical diagnosis, prognosis, and clinical treatment of cancer.

Ageing is a natural multifactorial process characterized by the accumulation of degeneration that is accompanied by alterations and damage to multiple important molecular pathways that ultimately impair cell and tissue function.[10] Ageing mediates major age-related diseases by regulating the physiological activities of organisms mediated through various common ageing signalling pathways. Previous studies have reported that AMPK signalling pathways are involved in regulating ageing and age-related diseases.[11] In this article, a summary of lncRNAs involved in the regulation of AMPK signalling pathways is presented and a foundation to explain the occurrence and development of ageing and age-related diseases is provided.

The AMPK signalling pathway

Characteristics of AMPK composition

AMPK is the centre of the AMPK signalling pathway and a sensor of cellular energy status. AMPK is expressed in almost all eukaryotic cells, including protists, fungi, plants, and animals.[12] AMPK often forms heterotrimers that include a catalytic subunit (α subunit) and two regulatory subunits (β and γ subunits)[13] (Fig. 1). In invertebrates such as *Drosophila*, each subunit is encoded by a single orthologous gene, while in humans, each subunit is encoded by different genes. Specifically, the α subunit is composed of the α1 and α2 subunits, which are encoded by protein kinase AMP-activated catalytic subunit alpha 1 and protein kinase AMP-activated catalytic subunit alpha 2, respectively.[14] The β subunit is composed of β1 and β2 subunits that are encoded by protein kinase AMP-activated non-catalytic subunit beta 1 and protein kinase AMP-activated non-catalytic subunit beta 2, respectively.[15] In addition, the γ subunit is composed of the subunits γ1, γ2, and γ3, which are encoded by protein kinase AMP-activated non-catalytic subunit gamma 1, protein kinase AMP-activated non-catalytic subunit gamma 2, and protein kinase AMP-activated non-catalytic subunit gamma 3, respectively.[16] Because each AMPK complex is composed of an α subunit, a β subunit, and a γ subunit, 12 different AMPK complexes may be generated[17] that are expressed in mammals, and in bacteria, at least 6 AMPK different complexes are produced.[18] Previous studies have shown that the various combinations appear to represent different modes of action, with β1 complexes (α1β1γ and α2β1γ) being more abundant in the liver than β2 complexes; specifically, most active AMPK subunits can be immunoprecipitated by specific anti-β1 antibodies.[15] In contrast, in skeletal muscle, β2 complexes are more abundant than β1 complexes.[15]

Each subunit of AMPK exhibits a specific function. The α subunit includes a kinase domain and a key residue, Thr172, which is phosphorylated by upstream kinases (Fig. 1), and phosphorylation of this residue also indicated phosphorylation of AMPK. In mammals, calcium/calmodulin-dependent protein kinase β (CaMKKβ) and liver kinase B1 (LKB1) have been identified as two upstream kinases in the AMPK cascade.[19] The β subunit consists of a carbohydrate-binding module that allows AMPK to bind to glycogen.[20] The γ subunit is composed of four tandem cystathionine-beta synthase domains that enable AMPK to respond to changes in the ATP-to-AMP ratio.[21] Under energy-depletion conditions, cellular ATP levels decrease and bound AMP levels increase.[21] AMP can directly bind to the regulatory γ subunit of the AMPK complex, resulting in allosteric activation

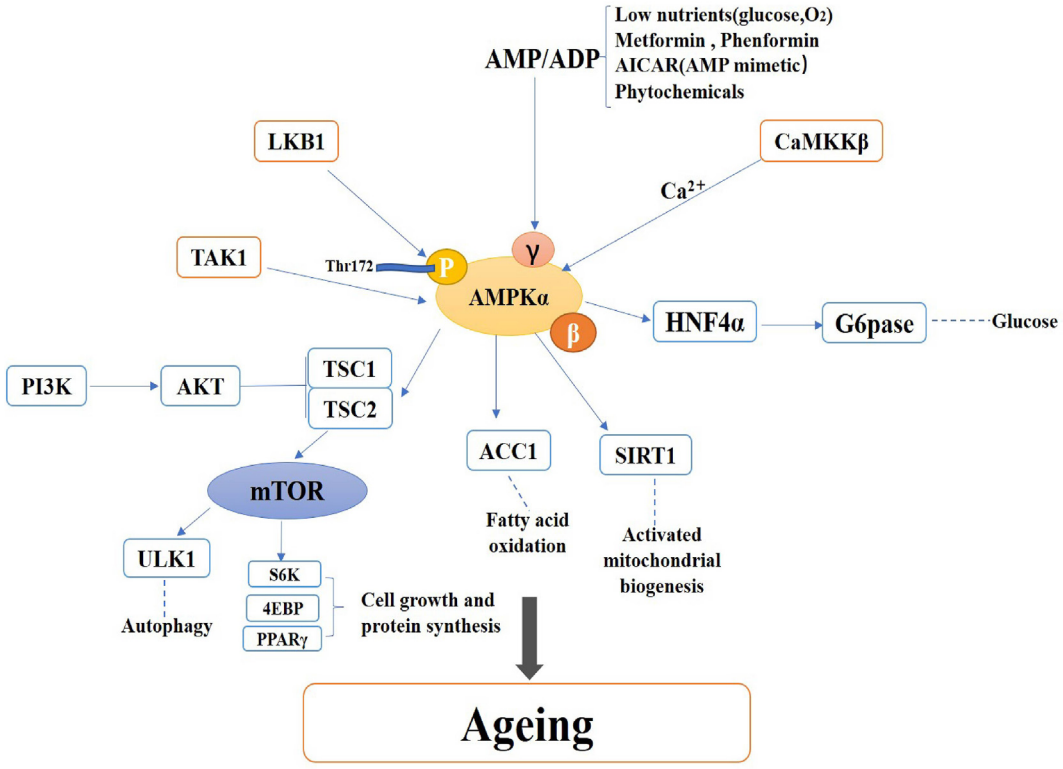

Figure 1 The structure, major upstream, and downstream targets of AMPK and the relationship between AMPK and ageing. ACC1, acetyl coenzyme A carboxylase 1; AKT, protein kinase B; AMP/ADP, adenine nucleotide (AMP)/adenosine diphosphate (ADP); CaMKKβ, calcium/calmodulin-dependent protein kinase β; 4EBP, eukaryotic translation initiation factor 4 E (eIF4E)-binding protein; G6pase, glucose-6-phosphatase; HNF4A, hepatocyte nuclear factor 4 A; LKB1, liver kinase B1; mTOR, mechanistic/mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferator-activated receptor γ; S6K, ribosomal protein S6 kinase; SIRT1, silencing information regulatory 1; TAK1, transforming growth factor β-activated kinase 1; TSC1, TSC complex subunit 1; TSC2, TSC complex subunit 2; ULK1, Unc-51 like autophagy activating kinase 1.

of AMPK. Due to the favourable physiological consequences of AMPK activation on metabolism, AMPK is considered an important therapeutic target for the control of human diseases, including metabolic syndrome and cancer.

The role played by AMPK in ageing

AMPK is involved in the regulation of cellular energy homeostasis and is a key sensor of nutrients and energy[2] (Fig. 1). Metabolic levels in animals are closely related to health status. Metabolic disorders are the main causes of obesity and diabetes and are also important markers of ageing[22] (Fig. 2). Studies have shown that AMPK activation capacity and expression levels generally decrease with age.[11] AMPK phosphorylation levels are significantly reduced in aged mice compared with young mice.[23] A previous study reported that long-term feeding of metformin (AMPK activator) to female transgenic human epidermal growth factor receptor 2/neu mice (breast cancer model) increased average and maximum life spans by 8% and 13%, respectively.[24,25] When another normal short-lived mouse was treated with metformin over a long period, its average and maximum life spans increased by 38%and 21%, respectively.[26] As a master regulator of ageing and caloric restriction, AMPK has been increasingly recognized as a potential longevity factor in model organisms. Notably, AMPK plays a very important role in the occurrence and development of many cardiovascular diseases, such as atherosclerosis and ischaemia/reperfusion (I/R) injury, hypertension, diabetes, cardiac hypertrophy, and heart failure, which are caused by mitochondrial dysfunction. AMPK plays specific regulatory roles in various aspects of mitochondrial homeostasis. The control of early mitochondrial dysfunction by AMPK is a promising step in the prevention and treatment of cardiovascular disease[27] (Fig. 2). The central role it plays in maintaining energy homeostasis makes AMPK an attractive drug target for the prevention and/or treatment of metabolic diseases and cancer. For example, metformin activates AMPK to attenuate type 2 diabetes.[28] Several studies have demonstrated that activation of the AMPK pathway promotes autophagy by inhibiting the phosphorylation of the downstream protein mTORC1. This evidence suggests that activating AMPK may be a potential strategy to delay ageing.

AMPK regulates energy metabolism

With the continuous evolution of biological systems, both unicellular organisms and multicellular organisms have evolved a complete energy metabolic system, the core of

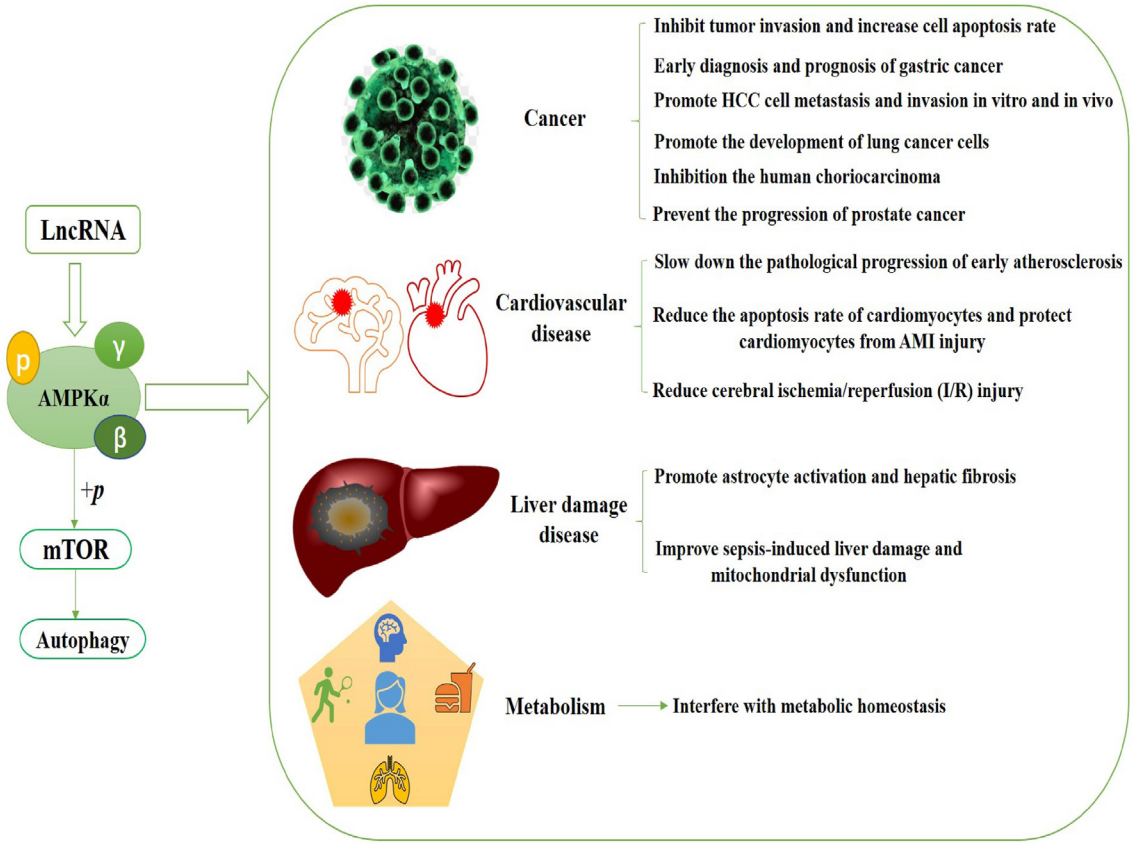

Figure 2 The relationship between AMPK and age-related diseases. AMI, acute myelocytic leukaemia; AMPK, adenosine monophosphate-activated protein kinase; HCC, hepatic cell carcinoma; lncRNA, long noncoding RNA; mTOR, mechanistic/mammalian target of rapamycin.

which is AMPK (Fig. 1). In unicellular eukaryotes, the AMPK's homologous gene sucrose non-fermenting 1 not only switches fermentative metabolism to oxidative metabolism during glucose starvation but also enables yeast to consume alternative carbon sources to survive the crisis by inhibiting the other carbon source pathways.[29] In multicellular eukaryotes, AMPK senses the amount of ATP in cells by directly binding to adenine nucleotides. When the amount of available energy changes directly, the AMP/ADP ratio changes. AMP promotes allosteric activation of AMPK by inhibiting the dephosphorylation of Th172 in the α subunit through direct binding to the γ subunit[30,31] (Fig. 1). After activation, AMPK regulates key protein functions in multiple signalling pathways through phosphorylation, such as the mTORC1 in the TOR pathway,[32] 6-phosphofructokinase-2 in the glycolytic pathway,[33] and the main regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma coactivator-1α (PGC1α), which in turn maintains cellular energy homeostasis by increasing the catabolic rate and reducing the anabolic rate.[34]

AMPK and mitochondrial biogenesis

The physiological activity of AMPK is important for maintaining mitochondrial function (Fig. 1). During cellular energy imbalance, AMPK contributes to mitochondrial biosynthesis to increase ATP production. Biogenesis of new mitochondria is realized through the growth and division of mitochondria.[35] During exercise and other causes of limited energy, changes in AMP and calcium ion (Ca^{2+}) levels can directly or indirectly activate AMPK, which in turn activates mitochondrial energy metabolism and mitochondrial energy metabolism through the positive regulation of the intermediate target PGC1α.[36–38] Moreover, chronic activation of AMPK has been observed to lead to increased mitochondrial biosynthesis.[39] Overexpression of the AMPK γ3 subunit induced mitochondrial biogenesis in mice.[37] In contrast, AMPK mutations failed to induce mitochondrial production. In addition, mice lacking the AMPK β1/β2 subunits or the upstream kinase LKB1 showed reduced muscle mitochondrial content, and muscle-specific LKB1-knockout mice failed to show increased mitochondrial biosynthesis after exercise.[40,41]

AMPK and autophagy

AMPK not only regulates cellular energy metabolism but also participates in autophagy (Fig. 2). Autophagy is an important catabolic pathway conserved in all known nucleated cells. The functions of autophagy include the removal of defective proteins and organelles, the prevention of abnormal protein aggregation, and the removal of pathogens in cells. These functions may be critical for

autophagy-mediated protection against ageing, cancer, neurodegenerative diseases, and infections.[42] The initiation of physiological autophagy is induced by nutrient deprivation or energy deprivation. This intrinsic feature of cells has been conserved in organisms from yeast to humans.[43] In the autophagy degradation pathway, macromolecular substances are degraded and recycled to maintain necessary cellular functions, enabling cells to survive when energy is limited.[44] Although the regulation of autophagy is complex and requires the participation of multiple signalling cascades and regulatory mechanisms, AMPK may be the most evolutionarily conserved autophagy inducer.[45] Activation of AMPK positively regulates the autophagy pathway and promotes its catabolic function. In contrast, AMPK enables antagonize the TOR signalling pathway, and inhibition of mTORC1 activity is one of the main mechanisms by which AMPK increases autophagic degradation.[45] The reciprocal antagonism between AMPK and mTORC1 is also reflected in transcriptionally affecting autophagy activity. Under stressful conditions, AMPK and mTOR can regulate autophagy by increasing and decreasing the phosphorylation of FOX (forkhead box) family members and TFEB/TFE transcription factors.[46–48]

LncRNAs involved in the regulation of ageing and age-related diseases

Long noncoding RNA (lncRNA) is a unique noncoding RNA with a large molecular weight and limited protein-coding capacity. LncRNAs are involved in the regulation of various biological processes, and the roles they play in ageing have received extensive attention in recent years. LncRNAs can affect not only the expression of age-related genes by mediating telomere length, heterochromatin formation, protein translation arrest, stem cell differentiation, the cell cycle, and other processes but also the acquisition of age-related phenotypes by regulating multiple levels of gene expression, such as transcriptional, post-transcriptional, translational and posttranslational.[49,50] Previous studies have indicated that low expression of the lncRNA metastasis-associated lung adenocarcinoma transcript 1 can lead to G1 or G1/S phase arrest, inhibiting cell growth and proliferation and increasing senescence phenotype acquisition.[51–54] A variety of lncRNAs have been shown to target genes for the prevention and treatment of age-related diseases, such as *linc00857*, which regulates cell proliferation, migration, and invasion and, thus, tumour growth in lung cancer.[55] The lncRNA antisense noncoding RNA in the INK4 locus (*ANRIL*) is abnormally expressed in patients with acute myelocytic leukaemia (AML), and its specific expression pattern makes it to be a potentially promising target for the diagnosis and treatment of AML.[56]

Although recent research on the AMPK signalling pathway has been relatively comprehensive, lncRNAs are emerging as a hot research hotspot. Therefore, identifying the relationship between AMPK, lncRNAs, and ageing is a key step in antiaging research.

LncRNAs directly interact with AMPK subunits

LncRNAs can interact with AMPK in several ways. Some lncRNAs affect AMPK activity by directly binding to components of the AMPK complex, while others regulate AMPK signalling pathways by directly or indirectly regulating proteins upstream or downstream of AMPK (Fig. 3). All lncRNAs described in this review are listed in Table 1. Altered AMPK expression or activity can modulate the acquisition of age-related phenotypes or the course of certain diseases.

LncRNAs interact with the AMPK α subunit

LncRNA *NBR2*

LncRNA neighbour of *BRCA1* gene 2 (*NBR2*) is one of the glucose deprivation-induced lncRNAs and promotes AMPK-activated energy stress.[57] The transcript of *NBR2* is expressed in most tissues and ranges in size from 1 to 3 kb, and the gene neighbours the tumour suppressor gene breast cancer susceptibility gene 1 (*BRCA1*).[58] For many years, *NBR2* was considered a "junk gene" because its underlying function was not clear. Recently, however, *NBR2* was found to interact directly with the α catalytic subunit complex of AMPK, promoting AMPK signalling under energy stress by regulating its kinase activity.[59] Glucose starvation not only up-regulated the expression of *NBR2* but also induced its interaction with the AMPK α subunit.[58] AMPK promoted *NBR2* expression in response to energy stress through an unknown mechanism. *NBR2* in turn interacted with AMPK to promote AMPK activation under energy stress, forming a feedforward loop that enhanced AMPK activation during prolonged energy stress.[57] During prolonged energy stress, *NBR2* deletion led to the inactivation of AMPK, which promoted mTORC1 activation, cell proliferation, and tumour development.[59] *NBR2* was the first lncRNA found to be induced by AMPK, and the forward loop between *NBR2* and AMPK was identified as promoting tumour growth.

LncRNA *H19*

H19 gene is one of the first genes that have been proven to be capable of being imprinted.[60] It is located on chromosome 11 p 15.5 and lies within 200 kb downstream of the insulin-like growth factor 2 (*IGF2*) gene.[61] *H19* is an important oncogenic factor and is considered a marker of tumour development.[62] It regulates *IGF-2* expression by affecting the transcription and translation of the oncogene *IGF-2*.[63,64] *H19* expression is up-regulated in many types of cancer, including liver cancer, stomach cancer, colorectal cancer, and breast cancer, and its abnormal up-regulation is associated with the proliferation and invasion of cancer cells and poor prognosis.[60,65–67]

H19 has been shown to affect DNA methylation in a genome-wide manner by interacting with s-adenosyl homocysteine hydrolase.[68,69] *H19* was abundantly expressed in the fetal liver and *H19* is highly expressed in the fetal liver and gradually decreases after birth.[60] *H19* has been found to be closely related to hepatic fibrosis and to

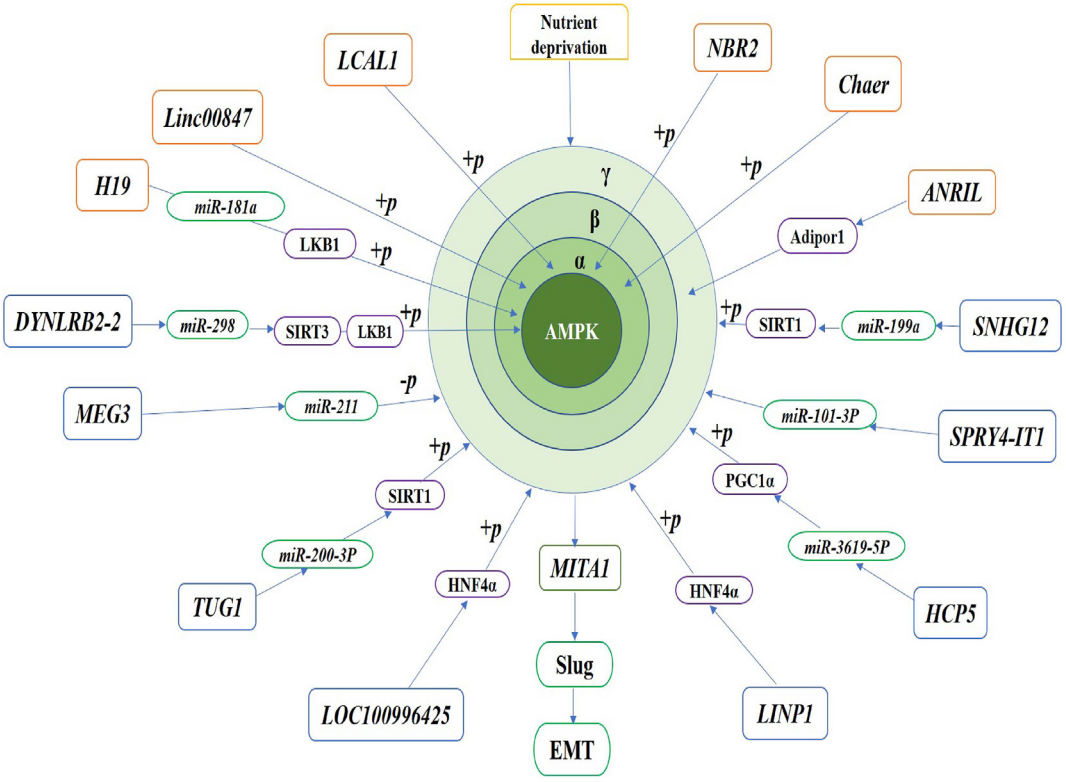

Figure 3 LncRNAs involved in the regulation of AMPK and its subunits. ACC1, acetyl coenzyme A carboxylase 1; AdipoR1, adiponectin receptor1; AKT, protein kinase B; AMP/ADP, adenine nucleotide (AMP)/adenosine diphosphate (ADP); CaMKKβ, calcium/calmodulin-dependent protein kinase β; Chaer, the lncRNA cardiac hypertrophy-associated epigenetic regulator; DYNLRB2, intergenic lncRNA dynein light chain roadblock-type 2; EMT, epithelial—mesenchymal transition; 4EBP, eukaryotic translation initiation factor 4 E (eIF4E)-binding protein; G6pase, glucose-6-phosphatase; HCP5, lncRNA human histocompatibility leukocyte antigen complex P5; HNF4α, hepatocyte nuclear factor 4α; LCAL1, lung cancer-associated lncRNA; LKB1, liver kinase B1; LINP1, lncRNA in nonhomologous end joining pathway 1; MEG3, maternally expressed gene 3; MITA1, the lncRNA metabolism-induced tumour activator 1; mTOR, mechanistic/mammalian target of rapamycin; NBR2, lncRNA neighbour of BRCA1 gene 2; PI3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferator-activated receptor; S6K, ribosomal protein S6 kinase; SIRT1, silencing information regulatory 1; Slug, snail family zinc finger 2; SNHG12, the lncRNA small nucleolar RNA host gene 12; TAK1, transforming growth factor β-activated kinase 1; TSC1, TSC complex subunit 1; TSC2, TSC complex subunit 2; *SPRY4-IT1*, the lncRNA sprouty4-intron 1; *TUG1*, the lncRNA taurine up-regulated gene 1; ULK1, Unc-51 like autophagy activating kinase 1.

regulate stellate hepatocyte activation and proliferation.[70] Knocking down *H19* expression significantly inhibited stellate cell activation and alleviated liver fibrosis, suggesting that *H19* may be a potential target for antifibrotic therapy.[71] It was found that H19 regulates lipid metabolism through the AMPKα pathway. *H19* formed a scaffold between AMPK and LKB1, and the phosphorylation of AMPK was dependent on this AMPK/LKB1 complex.[71] *H19* links the AMPK α subunit and LKB1 and promotes the phosphorylation of AMPK by LKB1.[71] However, only the correlation between *H19* and the AMPK/LKB1 complex was observed, and the specific binding site has not yet been explored.

Moreover, *H19* has been demonstrated to contribute to the cancer treatment drug metformin in inhibiting the invasion of gastric cancer cells.[72] The mechanism of metformin activity involves inhibiting the migration and invasion of gastric cancer cells by reducing *H19* expression to activate the AMPK α subunit and inhibit the expression of *MMP9* (matrix metalloprotease 9).[72] Although the AMPK α subunit and *MMP9* were found to be potential target genes of *H19* in this study, more in-depth studies are needed to determine whether the interaction between *H19* and these target genes is direct or indirect.[72]

Studies have found that *miR-181a* is highly expressed in atherosclerotic plaques.[73] The overexpression of *H19* inhibited the expression of *miR-181a*, while the overexpression of *miR-181a* inhibited the activity of *H19*, and its silencing enhanced the influence of *H19*.[74] It was found that c-Jun N-terminal kinase (JNK) and AMPK signalling pathways were activated by *H19* overexpression, while the overexpression of *miR-181a* eliminated this activation, suggesting that *H19* activates JNK and AMPK in a *miR-181a*-dependent manner.[74] Previous studies have reported that JNK and AMPK signalling pathways have become promising molecular targets for the treatment of cardiovascular diseases, and miR-181a can regulate the activation of JNK pathways.[75—77] It is speculated that *H19* overexpression down-regulates the expression of *miR-181a*, thus activating JNK and AMPK signals, and finally promoting the formation of neovascularization.[74] These findings provide

Table 1 Information about the lncRNAs described in this review.

LncRNAs	Targets	Disease	References
NBR2	AMPKα	Tumour	59
H19	LKB1/AMPKα	Stomach cancer	71
	miR-181a	Atherosclerosis	75
Linc00857	*p*-AMPKα	Lung cancer	83
LCAL1	AMPKα	Lung cancer	86
Chaer	*p*-AMPKα	Myocardial ischaemia	91
ANRIL	AMPK-γ	Atherosclerosis	98
	AdipoR1	Acute myeloid leukaemia	56
SPRY4-IT1	*miR-101-3P*	Stomach cancer	105
DYNLRB2-2	*miR-298*	Atherosclerosis	108
MEG3	*miR-211*	Human choriocarcinoma	114
LINP1	HNF4α	Acute myeloid leukaemia	119
LOC100996425	HNF4α	Prostate cancer	127
SNHG12	*miR-199a*	Ischaemic stroke	128
TUG1	*miR-200a-3p*	Sepsis	133
HCP5	*miR3619-5p*	Stomach cancer	149
MITAl	Slug	Liver cancer	152

in vitro evidence that *H19* may be one of the potential targets for the treatment of atherosclerotic-related diseases.

LncRNA *linc00857*

LncRNA *linc00857* is abnormally and highly expressed in lung cancer and is associated with poor patient survival. *Linc00857* has been found to regulate cell proliferation, migration, and invasion and, thus, tumour growth in lung cancer,[55] and has been identified to be oncogenic in gastric, bladder, and hepatocellular carcinoma (HCC), and oesophagal adenocarcinoma.[78–81] This suggests that *linc00857* can be used as a novel biomarker and therapeutic target for multiple cancers. However, the molecular mechanisms underlying the role played by *linc00857* in cancer biology remain poorly understood.

Recent studies have confirmed that *linc00857* regulates the proliferation of lung cancer cells through different genomic alterations, thereby affecting cell death signalling (including apoptosis and autophagy signalling).[82] Mechanistically, *linc00857* interacts with Y-box-binding protein 1 (YBX1) and protects it from proteasomal degradation.[82] Some lncRNAs have been reported to exert oncogenic effects by interacting with YBX1, which are protected from proteasomal degradation.[83,84] YBX1 can also promote mesenchymal–epithelial transition factor (MET) expression by binding to the MET promoter, thereby regulating apoptosis and autophagy.[82] Experiments have shown that the phosphorylated AMPK (*p*-AMPK) α subunit is required for *linc00857* regulation of autophagy in lung cancer cells, but the specific mechanism remains unclear.[82] In conclusion, the *linc00847*-YBX1-met/*p*-AMPKα signalling pathway plays an important role in regulating cell proliferation, apoptosis, and autophagy and may become a potential target for the clinical treatment of lung cancer.[82] However, whether *linc00857* regulates *p*-AMPK remains to be determined.

LncRNA *LCAL1*

Lung cancer-associated lncRNA (*LCAL1*) has been found to be overexpressed in lung cancer tissues, and inhibition of *LCAL1* expression has shown the potential to inhibit the growth of lung cancer.[85] However, the molecular mechanisms of *LCAL1* in lung cancer cell survival remain poorly understood. Subsequent studies revealed that *LCAL1* may support lung cancer survival by inactivating the tumour suppressor AMPK.[85] Specifically, *LCAL1* may physically interact with AMPKα, the catalytic subunit of AMPK, and prevent LKB1-induced AMPKα phosphorylation and activation. Inactive AMPK may interfere with metabolic homeostasis by activating HIF1α function and reprogramming energy metabolism, switching it from oxidative respiration to aerobic glycolysis.[85] Notably, impaired AMPK activity enhanced protein synthesis by activating the mTOR signalling cascade and inhibited autophagic cell death by inactivating unc-51-like autophagy-activating kinase.[86–88] Together, these changes may promote rapid cell proliferation and support lung cancer survival in the presence of *LCAL1* overexpression. Therefore, knocking out *LCAL1* expression may reverse these oncogenic changes induced by AMPK loss and inhibit the rapid growth of lung cancer cells, which may become a potential new therapeutic strategy for the treatment of lung cancer.[85]

LncRNA *Chaer*

The lncRNA cardiac hypertrophy-associated epigenetic regulator (*Chaer*) was first discovered through a study of cardiac hypertrophy. It was found to be necessary for the development of cardiac hypertrophy, and inhibition of *Chaer* in intact hearts significantly reduces cardiac hypertrophy and dysfunction.[89] *Chaer* binds to the polycomb repressive complex 2 (PRC2) in a mTORC1-dependent manner, inhibiting the acetylation of H3K27, a downstream target of PRC2, and promoting cardiac hypertrophy.[89] It is speculated that *Chaer*-PRC2 interaction can be used as a potential therapeutic target for the treatment of cardiac hypertrophy and pathological remodelling of diseased hearts.[90] Studies have reported that lncRNA *Chaer* is downregulated in myocardial infarction tissue and cardiomyocytes under oxygen-glucose deprivation.[90] Overexpression of *Chaer* enhanced cardiomyocyte viability after oxygen-glucose deprivation, while knockdown of *Chaer* led to the opposite effect. This may be achieved by *Chaer* enhancing phosphorylation of AMPK and reducing phosphorylation of mTOR, thus reducing apoptosis of cardiomyocytes.[90] These effects reduced the cardiomyocyte apoptosis rate and conferred cardioprotection against AMI injury.[90] Although *Chaer* protected cardiomyocytes from AMI injury by stimulating the AMPK/mTOR cascade, the identification of a direct relationship between *Chaer* and specific subunits of AMPK remains to be investigated.[90] Taken together, the studies indicated that *Chaer* may be a candidate target for overcoming and treating ischaemic myocardial disease.

AMPK γ subunit interactions with lncRNAs

ANRIL is a 3.8-kb lncRNA encoded by chromosome 9p21 that consists of 19 exons and is stably expressed in vascular cells.[91] The increased expression of *ANRIL* mediates the risk of atherosclerosis through transcriptional regulation of gene networks to promote atherosclerosis.[91] According to a previous study, the expression level of *ANRIL* is decreased in coronary artery specimens,[92–94] and it regulates the function of endothelial cells and vascular smooth muscle cells through transcriptional up-regulation.[95,96] The above results suggest that *ANRIL* plays a key role in controlling vascular function. The lncRNA *ANRIL* has been shown to regulate the function of endothelial cells and vascular smooth muscle cells by transcriptionally up-regulating the expression of genes including CAP-Gly domain-containing linker protein 1, ezrin (EZR), and LYVE1, revealing the key role played by *ANRIL* in controlling vascular function.[96]

In a recent study, *ANRIL* was found to be a novel AMPK regulator and the specific binding of the AMPK γ subunit and *ANRIL* was determined through an RNA immunoprecipitation assay.[97] This effect is mediated by metformin. Moreover, down-regulation of *ANRIL* reduced metformin-induced AMPK phosphorylation and activation and thereby abrogated in the absence of lncRNA *ANRIL*.[97] Hence, it is speculated that the binding between *ANRIL* and AMPKγ may increase the stability of the AMPKαβγ complex and promotes AICAR sensitivity to AMPK.[97] Based on this, we speculate both AMPK and *ANRIL* may be therapeutic targets for preventing atherosclerosis-related vascular diseases (such as stroke).

In addition, *ANRIL* is involved in the regulation of the AMPK pathway in another way. Specifically, *ANRIL* regulated the key regulator of glucose metabolism, the AML adiponectin receptor 1 (AdipoR1) and its downstream factors AMPK and SIRT1, which are involved in the occurrence and development of AML.[56] AdipoR1 is a key protein closely related to cellular senescence[86,98] and metabolism and is located upstream of the AMPK protein in the AMPK signalling pathway. Knocking out both *ANRIL* and AdipoR1 reduced the phosphorylation levels of AMPK and SIRT1.[56] Thus, the *ANRIL*-AdipoR1-AMPK-SIRT1 signalling pathway in regulating glucose metabolism and the survival of AML cells are relatively new research findings.[56] Based on these recent studies, the specific expression pattern of *ANRIL* is thought to be a promising target for the diagnosis and treatment of AML.

In summary, lncRNAs can directly interact with the α and γ subunits of AMPK to activate the AMPK signalling pathway by promoting AMPK phosphorylation or regulating its expression. The effects of these outcomes influence autophagy, apoptosis, and cellular respiration and ultimately regulate ageing and related diseases.

LncRNAs regulate AMPK gene expression by microRNAs (miRNAs)

LncRNAs can act as competing endogenous RNAs for miRNA targets, thereby increasing the expression of target genes[99] (Fig. 3). The lncRNA sprouty4-intron 1 (*SPRY4-IT1*) is transcribed from the second intron of the *SPRY4* gene in 5q31.3 and is a 687 nt unspliced, polyadenylated transcript originally identified in melanoma.[100] *SPRY4-IT1*'s transcription is up-regulated in various cancers which increased the rates of cancer cell growth, invasion, and apoptosis. Down-regulation of *SPRY4-IT1* can inhibit the development of gastric cancer,[101] breast cancer,[102] and melanoma.[103] *SPRY4-IT1* knockout reduced cell proliferation and migration by sponging *miR101-3p*, inducing significant arrest in the G0/G1 phase, and promoting GC cell apoptosis while simultaneously regulating the expression of the AMPK gene.[104] *MiR-101-3p* targeted both *SPRY4-IT1* and AMPK in a luciferase reporter system, which directly demonstrated that *SPRY4-IT1* acts as a *miR-101-3p* sponge to regulate AMPK expression.[104] Cytological functional experiments showed that *SPRY4-IT1* and *miR101-3p* exerted the opposite effects on cell phenotype acquisition, and a *miR-101-3p* inhibitor restored the biological functions changed by *SPRY4-IT1* silencing.[104] In conclusion, *SPRY4-IT1* inhibits GC progression by negatively regulating *miR-101-3p* mediated by AMPK in GC.[104] Therefore, abnormal up-regulation of *SPRY4IT1* accompanied by down-regulation of *miR-101-3p* can be applied to the early diagnosis and prognosis of GC in patients.

LncRNAs regulate AMPK through upstream targets

The AMPK signalling pathway is an important energy homeostatic regulation pathway centred on the AMPK protein. A variety of protein targets upstream and downstream of AMPK cooperate in many important regulatory mechanisms (Fig. 3). For example, upstream AMPK targets include TAK1, LKB1, CaMKKβ, AdipoR1, and cystic fibrosis transmembrane conductance regulator. Several lncRNAs have been found to affect AMPK signalling through miRNA/AMPK regulatory networks. These lncRNAs mediate the expression of upstream targets by sponging miRNAs and then regulate the AMPK pathway through the expression of target proteins. The disease is mediated and modulated through changes in protein expression.

LncRNA *DYNLRB2-2*

Intergenic lncRNA dynein light chain roadblock-type 2 (*DYNLRB2*) reduces cholesterol levels by promoting cholesterol efflux and impairing the uptake of oxidized low-density lipoprotein by THP-1 macrophage-derived foam cells.[105] Moreover, *DYNLRB2-2* was found to up-regulate cholesterol efflux by reducing toll-like receptor 2 expression in macrophages.[106] However, other potential mechanisms have not been described.

A recent study found that *DYNLRB2-2* directly targeted *miR-298* to regulate its downstream target, Sirtuin 3 (*SIRT3*).[107] *SIRT3* is a mitochondrial deacetylase that mediates LKB1 deacetylation to facilitate AMPK activation.[108,109] Therefore, *DYNLRB2-2* was proposed to activate the LKB1/AMPK/mTOR signalling pathway through the *miR-298*/*SIRT3* axis. In this pathway, *DYNLRB2-2* activates AMPK by increasing the phosphorylation levels of LKB1 and AMPK in foam cells and inhibits the downstream protein *p*-mTOR to promote autophagy.[107] Autophagy signalling enhances cholesterol efflux, thereby blocking THP-1 macrophage foam cell formation and potentially slowing the

pathological progression of early atherosclerosis.[105] Taken together, these findings indicate that autophagy may be an easily controllable mechanism and that *DYNLRB2-2* may be a promising target for the treatment of atherosclerosis.[107]

LncRNA *MEG3*

Maternally expressed gene 3 (*MEG3*) is an imprinted gene located at 14q32 that encodes a lncRNA and decreased *MEG3* expression plays an important role in multiple cancers.[110] The inhibitory effects of *MEG3* have been demonstrated in various cancers, such as prostate cancer (PCa) and pancreatic cancer.[111,112] Up-regulation of *MEG3* reduced cell viability, inhibited cell proliferation, migration, and invasion, and promoted cell apoptosis.[113] Choriocarcinoma (CC) is a highly malignant tumour that usually arises from gestational trophoblastic dysplasia.[114] A previous study reported that the level of *MEG3* in the human CC cell line JEG-3 was significantly lower than that in normal cells.[115] Therefore, the authors speculated that *MEG3* may be involved in CC progression.

The study found that the expression of *miR-211* positively regulates *MEG3*. *miR-211* overexpression enhances the effect of *MEG3* overexpression, whereas *miR-211* silencing has the opposite effect.[113] Proved by experiment, overexpression of the *MEG3* inhibited PI3K/AKT and AMPK pathway activation by up-regulating the expression of *miR-211*, which *MEG3* was also reported to play a tumour suppressor role in CC by up-regulating *miR-211*.[113] Furthermore, dysregulation of *miR-211* altered the repression of the aforementioned signalling pathways activated by *MEG3* up-regulation.[113] This study laid the foundation for an in-depth study of the function of lncRNA *MEG3* and provided a new perspective for the treatment of CC.

LncRNAs regulate AMPK through downstream targets

LncRNAs present multiple modes of action, providing evidence for their involvement in various physiological processes. For example, lncRNAs regulate various physiological and pathological processes, including various cancers, cardiovascular diseases, and neurological diseases, by sponging miRNAs and preventing their interaction with downstream targets (Fig. 3). Dozens of target proteins downstream of AMPK in the AMPK signalling pathway, including HNF4α, peroxisome proliferator-activated receptor gamma coactivator-1α, SIRT1, mTORC1, and other proteins, which together with AMPK upstream target proteins form a complete AMPK signalling pathway. However, according to the data collected to date, only a few of these downstream target proteins interact with lncRNAs.

LncRNA *LINP1*

LncRNA in nonhomologous end joining pathway 1 (*LINP1*) is overexpressed in human triple-negative breast cancer and plays an oncogenic role.[116] Blockade of *LINP1* signalling increased the sensitivity of breast and cervical cancer cells to radiotherapy.[116,117] In addition, *LINP1* was found to be abnormally overexpressed in AML patients and to promote AML progression by mediating the glucose metabolism pathway.[118] When *LINP1* was overexpressed in AML cells, the expression levels of *p*-AMPK, WNT family member 5 A (WNT5A), glucose transporter 1, and lactate dehydrogenase A were increased.[118] Mechanistically, *LINP1* inhibited glucose metabolism by inhibiting the expression of HNF4α. Down-regulation of both *LINP1* and HNF4α decreased AMPK phosphorylation and WNT5A expression levels, suggesting, for the first time, that *LINP1* is involved in cellular glucose metabolism regulation and AML cell survival by enhancing the HNF4α-AMPK/WNT5A signalling pathway.[118] The authors also suggested that *LINP1* and its downstream genes may be promising diagnostic and therapeutic targets for AML.[118]

LncRNA *LOC100996425*

LncRNAs are efficient emerging biomarkers for the diagnosis and prognosis of PCa. As a transcription factor, HNF4α belongs to the nuclear hormone receptor superfamily and is mainly expressed in the liver, kidney, and pancreatic islets.[119] HNF4α is a downstream signalling molecule of AMPK and has been reported to regulate cell proliferation in various cancers, such as pancreatic, gastric, and hepatocellular carcinoma.[120–123] Research performed to date suggests that HNF4α may be a direct regulator of gene expression by interacting with gene transcriptional regulatory elements.[124] In addition, clinical observation shows that HNF4α can be used as the gold standard marker to distinguish primary gastric cancer from breast metastasis, which has a potential clinical application value.[125] A study found that *LOC100996425* targeted HNF4α through the AMPK/mTOR pathway to regulate cell proliferation, migration, apoptosis, and autophagy in human PCa cells.[126] The survival curve showed that the overall survival rate of patients with low *LOC100996425* was significantly higher than that of patients with high *LOC100996425*.[126] Moreover, knocking out *LOC100996425* promoted HNF4α expression and inhibited human PCa cell proliferation, migration, and apoptosis, thereby helping prevent the attenuation of PCa; the mechanism was related to the AMPK/mTOR pathway.[126] In this study, evidence is provided showing the therapeutic potential of lncRNAs and their ability to be promising prognostic markers.

LncRNA *SNHG12*

The lncRNA small nucleolar RNA host gene 12 (*SNHG12*) was first found to be elevated in several cancer cells and to play a key role in cancer cell proliferation and migration.[127] LncRNA *SNHG12* regulates gene expression and influences a variety of cellular processes in health and disease, including cell proliferation, differentiation, and apoptosis.[128–130] Furthermore, *SNHG12* has been reported to be among the most up-regulated lncRNAs after 16-h oxygen-glucose deprivation.[131] *SNHG12* expression was also up-regulated in mouse brain microvascular endothelial cells after cerebral ischemia.[127]

SNHG12 has been found to be an endogenous sponge of *miR-199a/b-5p*, promoting the occurrence and metastasis of hepatoma and suggesting that SNHG12 may regulate cerebral I/R injury by targeting *miR-199a*.[128] *SNHG12* has been reported to directly interact with *miR-199a* and SIRT1, as a direct target of *miR-199a* identified in other diseases.[127] Then, *SNHG12* interacted with *miR-199a* to reduce its expression through a specific mechanism, though *miR-199a* could target SIRT1 and inhibit the expression level of

SIRT1.[127] Therefore, the authors concluded that *SNHG12* targeted *miR-199a* and then activated the expression of SIRT1, which ultimately led to the activation of the AMPK signalling pathway, reducing cerebral I/R injury.[127] In conclusion, the *SNHG12*/miR-*199a*/SIRT1/AMPK axis is important in cerebral I/R injury involving neuronal cells, specifically indicating the protective effect of *SNHG12* on cerebral I/R injury, which is helpful for the development of more effective drugs for cerebral I/R injury and ischaemic stroke.[127,128] However, these studies were performed only at the cellular level. Thus, further investigation of the role played by *SNHG12* in I/R injury *in vivo* is needed.

LncRNA *TUG1*

The lncRNA taurine up-regulated gene 1 (*TUG1*) is located on chromosome 22q12 and has a sequence length of 7.1 kb[132]. In recent years, an increasing number of studies have highlighted the protective role played by *TUG1* in various abnormal physiological processes induced by sepsis; for example, overexpression of *TUG1* in the ALI mice can improve lung damage caused by sepsis by inhibiting apoptosis and inflammation.[133] The *TUG1* gene was found to be a target of miR-200a-3p, and the expression level of m*iR-200a-3p* was negatively regulated by *TUG1*.[132] *MiR-200a-3p* has been shown to exhibit extensive functions in human malignancies and has been found to aggravate oxidative stress-stimulated liver cell death.[134,135] In addition, *miR-200a-3p* was up-regulated in sepsis models, and overexpression of *miR-200a-3p* promoted inflammatory responses in sepsis-induced brain injury.[136] The study found that the overexpression of *miR-200a-3p* impaired mitochondrial function and autophagy, which reversed the protective effect of *TUG1* overexpression and ginsenoside R3 (Rg3) in lipopolysaccharide-treated hepatocytes to some extent. These data suggest that *miR-200a-3p* is involved in the Rg3-mediated sepsis regulatory network as a target of *TUG1*.[132]

The expression of another gene, SIRT1, a target of *miR-200a-3p*, was also positively regulated by *TUG1*.[132] SIRT1, a member of the sirtuin family, is a cellular regulatory enzyme critical for protein deacetylation and broadly involved in metabolic control and mitochondrial biogenesis.[137] SIRT has been shown to accelerate AMPK-activated autophagy.[138] Furthermore, an analysis of an online database (StarBase) indicates that both *TUG1* and SIRT1 had complementary binding regions for *miR-200a-3p*, implying an association between *miR-200a-3p* and *TUG1* or SIRT1 in sepsis-induced liver injury.[132] Studies have found that Rg3 enhances autophagy and attenuates sepsis-induced liver damage and mitochondrial dysfunction by up-regulating *TUG1*, reducing *miR-200a-3p*, and stimulating the SIRT1/AMPK pathway.[132]

LncRNA *HCP5*

LncRNAs exert significant effects on multiple cancer-related metabolism pathways, such as lipid metabolic and glycolytic pathways.[139,140] An increasing number of studies have shown that chemoresistance is attributable to certain lncRNAs.[141,142] LncRNA human histocompatibility leukocyte antigen complex P5 (*HCP5*) has been defined as a new genetic locus in clinical thyroid disease.[143] However, *HCP5* has not been reported to be a regulatory gene associated with follicular thyroid carcinoma progression.[144]

HCP5 has been reported to promote cell proliferation and metastasis in various cancers, such as thyroid cancer,[144] lung cancer,[145] and colorectal cancer.[146] Specifically, overexpression of *HCP5* conferred chemo-resistance and improved stemness of GC cells.[147] Combined with the Gene Expression Omnibus database and experimental analysis, only *HCP5* was induced by mesenchymal stem cell co-culture in GC cells, indicating that MSC might affect GC cells by regulating *HCP5*.[147] The AMPK pathway plays a regulatory role in fatty acid oxidation (FAO) metabolism.[148,149] *MiR-3619-5p* targets PPARG coactivator 1 alpha, an important factor in the AMPK pathway.[147] *PPARGC1A* encodes the protein PGC1α, a transcriptional coactivator in FAO.[150] In addition, carnitine palmitoyl transferase 1 (CPT1) has been shown to be a major regulator of FAO, and the PGC1α/CEBPB complex transcriptionally activates CPT1 to promote FAO effects on cancer cells.[151] *HCP5* increased *PPARGC1*α expression and promoted PGC1α production and PGC1α/CEBPB complex formation. Thus, *HCP5* led to the transactivation of CPT1 in GC cells to promote FAO.[147] In conclusion, MSC-induced *HCP5* activation drove FAO to promote GC stemness and chemoresistance through the *miR-3619-5p*/AMPK/PGC1α/CEBPB axis.[147] These findings suggest that *HCP5* may be a promising target for improving the efficacy of chemotherapy in GC.

AMPK induces lncRNA expression

The lncRNA metabolism-induced tumour activator 1 (*MITA1*) is a chromatin-enriching lncRNA discovered by nuclear RNA sequencing.[152] *MITA1* is a powerful driver of hepatocellular carcinoma metastasis by enhancing epithelial—mesenchymal transition (EMT), an early and critical step in cancer metastasis. *MITA1* was epigenetically induced by the LKB1-AMPK signalling pathway under nutrient deprivation conditions.[152] Moreover, *MITA1* expression was up-regulated in HCC tumours, and its deletion inhibited the metastasis of HCC cells *in vitro* and *in vivo*.[152] These results not only revealed the regulatory mechanism of lncRNA-mediated AMPK pre-tumorigenic function, linking energy stress with cancer metastasis but also provided a promising target for the treatment of HCC.[152] Mechanistically, *MITA1* promoted EMT, possibly, in part, because of increased transcription of snail family zinc finger 2 (Slug). Loss of *MITA1* reduced Slug expression, while Slug overexpression greatly attenuated the effect of *MITA1* deletion on HCC cell migration and invasion. However, *MITA1* was positively correlated with the level of the Slug precursor in HCC tissues.[152] Therefore, *MITA1* may enhance EMT in part by increasing Slug transcription, and the AMPK-*MITA1*-EMT axis may be a potential therapeutic target for HCC.

Conclusion

AMPK, a central regulator of energy homeostasis, balances nutrient supply and energy demand by coordinating energy metabolism pathways. Due to the favourable physiological consequences of AMPK activation on metabolism, AMPK is considered an important therapeutic target for the control

of human diseases, including metabolic syndrome and cancer. Since the veil of "transcription noise" has been lifted, lncRNAs have constituted a new research hotspot. Recently, lncRNAs have been widely found to be involved in various ageing processes. Ageing involves degenerative changes in the structure and function of an organism and is an irreversible process. It is the cause of neurological and cardiovascular diseases, cancer, and other diseases that seriously threaten human health. Therefore, characterizing the relationship between AMPK, lncRNAs, and ageing is a very important aspect of anti-ageing research. We think follow-up research on the relationship between lncRNAs and AMPK can be effectively focused on energy metabolism and ageing, and a more thorough study of the role played by lncRNAs may lead to further prevention and treatment of ageing and age-related diseases.

Author contributions

Jiamei Li: concept and design, literature search, manuscript preparation, and manuscript editing. Xiao Feng and Siqi Wang: literature search, manuscript editing, and manuscript review. Deying Yang and Zhi He: conceptual design, writing guidance, and manuscript review. Mingyao Yang and Xiaolan Fan: conceptual design anddirected review. Taiming Yan and Zhang Jia: manuscript review. Jiamei Li, Feng Xiao, and Siqi Wang: manuscript editing. All authors approved the final version of the review.

Conflict of interests

The authors declare no conflict of interests.

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