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Review article

Role of AMPK and its molecular intermediates in subjugating cancer survival mechanism

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ABSTRACT

The gradual energy dissipation of all organisms allows adapting to energy demands. Pathological situations of uncured diseases such as cancer, diabetes, and other obesity-related diseases are caused by an abrupt energy imbalance. As an energy sensor, AMP-activated kinase (AMPK) can regulate the cellular energy status. In case of increased energy demands or insufficient nutrient supply, cells digest their own interior, which is called autophagy. AMPK-mediated autophagy regulates various metabolic and physiological processes and is dysregulated in different chronic conditions. Because of AMPK's critical role in physiology and pathology, it is an emerging target for both prevention and treatment of these uncured diseases. This review discusses the multifaceted role of AMPK on cancer cell survival and inhibition mechanism. First, we discuss the dual role of AMPK on cancer progression and suppression, and we discuss how different AMPK subunit combinations influence the tumor progression and suppression. Next, we discuss what could be the centering point of AMPK that supports promotion or inhibition of the cancer cell growth. Furthermore, we review the role of connecting mechanism of AMPK-mediated molecular intermediates on cancer cell survival and inhibition pathways. Finally, we discuss how AMPK can affect DNA damage and repairing mechanisms, and immune response of host cell and cancer cells.

1. Introduction

Every cell needs balance or homeostasis for its proper functioning. A number of proteins, enzymes, and other transcription factors and coactivators are involved in the process of taking care of cell's homeostasis. Among them, AMP-activated kinase (AMPK) is an important cellular energy sensorium by which homeostasis can be perpetuated. Since cancer cells require higher energy consumption for their survival, AMPK's role in cancer environment is very important. This review covers how AMPK can help to grow or suppress the cancer cells in different aspects such as AMPK-mediated autophagy effect on cancer cell's survival and inhibition, AMPK's role on influencing inflammatory status, transcription factors, DNA damage/ repairing, and immune response.

2. Dual role of AMPK in cancer

Several molecular intermediates influence the cancer cell survival pathways. Among them, metabolic adaptation and reprogramming are a crucial process by which cancer cells can fulfill their energy demands for survival (Fig. 1). The connection between AMPK and cancer came from the observation that AMPK can mediate the tumor-suppressive signaling of liver kinase B1 (LKB1) for the inhibition of mechanistic target of rapamycin complex 1 (mTORC1), which is activated in most cancer cell types. In contrast, AMPK reprograms the metabolism during metabolic stress that can often occur in the tumor microenvironment, suggesting a pivotal role of AMPK in the tumor survival and growth. For example, the increased expression of LKB1 is associated with different types of cancers including gastric and lung cancers, suggesting a positive role of AMPK in cancer cells survival [1–4]. In addition, the AMPK subunit expression is statistically associated with poor prognosis of many cases including gastric and hepatocellular carcinoma (HCC) [5], and this indicates that AMPK and its further linking pathways are the major survival route for cancer cells. Cancer cells may activate or negate the AMPK in terms of hijacking mechanism for their survival and proliferation. In contrast, AMPK activation can assist in reducing the cancer cells survival [6–13]. For example, metformin, an activator of AMPK, can reduce the tobacco carcinogen-induced lung tumorigenesis in mice model. AMPK and its downstream targets can regulate energy metabolism and mitochondrial biogenesis to suppress the cancer cells survival [14,15]. However, the intermediary of AMPK-mediated cancer cell survival is baffling.

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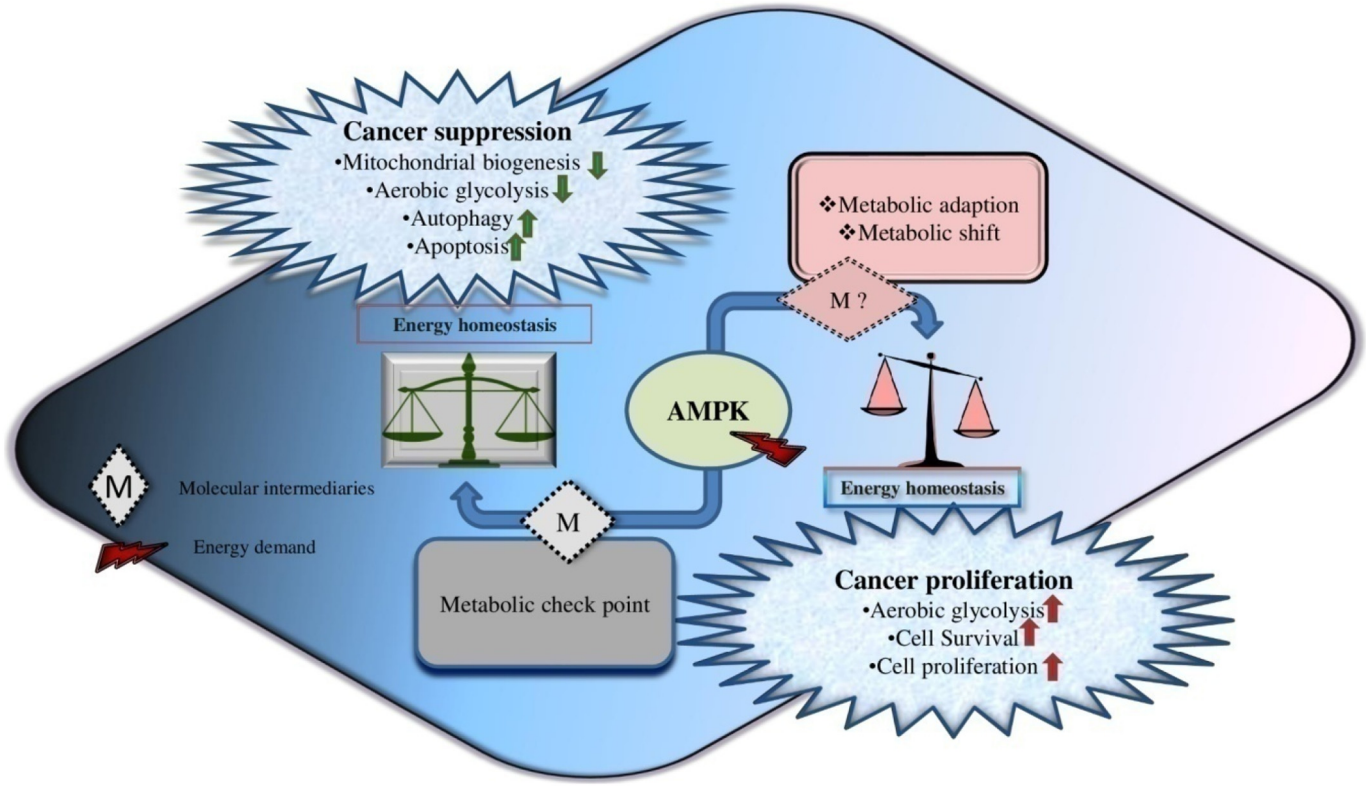

Fig. 1. Dual role of AMPK on cancer cells proliferation and suppression. AMPK acts as a metabolic checkpoint for suppressing cancer progression, whereas cancer cells overcome the metabolic adaptation induced by AMPK and metabolic shift to Warburg effect and selective autophagy to further proliferation.

3. AMPK subunits in cancer survival mechanism

An unknown mechanism decides the AMPK function in cancer progression at various regulatory stages including metabolic reprogramming in favor of cancer cell growth, redox controlling, and supporting cancer cells by biasing the chemopreventive agents. However, AMPK is rarely mutated in order to induce the tumor growth. This may be due to subunit redundancy of AMPK [16]. AMPK subunits consist of different catalytic (α1, α 2), regulatory (β1, β2), and adenine nucleotide binding (γ1, γ2, γ3) types. Understanding of individual subunit expression of AMPK in the cancer development is a major concern in AMPK-mediated cancer progression. Except for α1, other subunits of AMPK like α2, β1, β2, γ1, and γ2 are overexpressed in the ovarian carcinoma [17]. On the contrary, AMPK α1 is amplified in the lung squamous cell, adenocarcinoma, and other cancer types including head, neck, and bladder cancer [18]. The frequency of β1 subunit mutation is less, whereas β2 is amplified in prostate and stomach cancer [6]. Also, the expression of γ2 is consistent with almost all types of cancer cells, suggesting that almost all the subunits of AMPK can participate in the cancer progression [19–21]. Choosing a different pathological mechanism of cancer cells needs a different combination of AMPK subunits. These subunits can shift their combination based on a particular cancer cell's response [6,7]. For example, β2 subunit is required for energy balance during metabolic stress [22], whereas other AMPK subunits' expression induced by metformin is inhibited the lipid biosynthetic pathways in the ovarian cancer cell lines [23]. Also, these subunits decide the stabilization and complete activity of AMPK. However, how shifting of subunits within AMPK can respond to different stimuli is difficult to interpret.

4. LKB1—AMPK in cancer

LKB1 is a serine/threonine kinase and is the first physiological activator of AMPK. LKB dysfunction by AMPK supports the survival of cancer cells. In addition, AMPK switches on or off all its regulatory mediators including LKB1 for cancer cell proliferation [24–35]. However, over activation of LKB1 and AMPK is associated with anti-tumorogenic actions. For example, the higher activation of AMPK suppresses the extracellular signal-regulated kinase (ERK) and cyclooxygenase (COX) signaling pathways for reducing metastasis of melanoma. In addition, these pathways are regulated by LKB1 phosphorylation. A number of kinases can phosphorylate p53 [24–28], and it is a direct tumor suppressor under many metabolic stress conditions. AMPK phosphorylates p53 for its higher transcriptional activity. Studies have found that decreased activity of AMPK results in the reduction of p53 transcription and increased cell growth [36–42]. The AMPK activity may not be governed by LKB1; instead, it is mainly decided by the cancer cells for their survival when encountering stresses. On the other hand, AMPK activity can be directly regulated by AMP/ATP ratio. AMPK is activated under metabolic stress (exercise, glucose deprivation, hypoxia, ischemia, starvation, and stress) that can increase the ATP catabolism or accelerate ATP consumption, resulting in increased cellular ADP/ATP and AMP/ATP ratios. Under energy deprivation, AMPK phosphorylates p53 to restrict cell growth rates for saving energy. LKB1 physically associates with p53 on DNA damage. Also, AMPK with LKB1 acts as a kinase for p53 at the serine 15 phosphorylation site, which indicates that LKB1 phosphorylates p53 with AMPK or it can directly phosphorylate p53. However, the complex interplay between AMPK and LKB1 kinase in triggering or suppressing cancer cells needs more exposition.

5. The connecting mechanism of AMPK, LKB1, and autophagy in cancer

Autophagy is a degradative response to misfolded or improperly aggregated proteins and damaged or superfluous organs of cytoplasm. Autophagy serves to maintain the normal cellular functions by avoiding toxic build-up in the cellular environment, but this mechanism is

utilized by the cancer cells to survive. However, convincing evidence has shown that autophagy mediates cell death [43–47]. Some anticancer drugs induce cell death via autophagy induction [48,49]. This dual function of autophagy in terms of cancer proliferation or suppression has immense interest. Initially, autophagy was thought to involve in the tumor suppression, but certain cell-based assays have shown that autophagy suppression initiates the tumorigenesis [50,51]. Autophagy involves modulation of phenotypic functions of cancer cells, tumor cell motility and invasion, tumor dormancy, immune surveillance, and helps in metastatic success of cancer cells. For example, defects in autophagy promoted the macrophage recruitment of tumors in order to stimulate the pro-invasive signaling in the tumors. However, other direct cancer-causing factors such as oxidative stress, inflammation, and genome instability can be inhibited by autophagy. This multifaceted role of autophagy is a gateway of pro-survival or survival-promoting pathways in normal and cancer-promoting cells.

Augmentation of AMPK response can induce autophagy [52–54]. In cancer cells, autophagy defect initiates the tumor growth. For example, p53 can inhibit the autophagy response, and it is a direct tumor suppressor on many cancer types. In this case, AMPK is a direct mediator of p53 by either LKB1 or AMPK alone. Autophagy defect may lead the tumor initiation to reactive oxygen species (ROS) and impaired mitochondria. AMPK is important to generate the ROS and mitochondrial quality. Autophagy activation suppresses the tumor growth. For example, AMPK inhibited the U937 cells through autophagy activation [55]. LKB1-mediated autophagy and AMPK-mediated autophagy are inhibited cancer cell proliferation [29–34,56–58]. In addition, AMPK failed its activity in the absence or inhibition of LKB1, suggesting the coordinated role of AMPK, LKB1, and autophagy in the inhibition or controlling cancer development. Another study showed that AMPK-mediated autophagy controlled the breast cancer cell proliferation through glycogen synthase kinase K-3beta (GSK-3 beta) suppression [57,59]. In contrast, glucose starvation induces the LKB1–AMPK-mediated matrix metallopeptidase 9 (MMP-9) expressions for cancer invasiveness and migration through selective autophagy. LKB1 and AMPK facilitate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) accumulation for supporting the survival mechanism of cancer cells through autophagy [60,61]. On the one hand, AMPK promotes the TSC/1and TSC/2 in order to inhibit the autophagy (Fig. 2). On the other hand, AMPK can directly phosphorylate the mechanistic target of rapamycin (mTOR) to inhibit the autophagy. In cancer cells, autophagy defects are a common phenomenon due to the mutation of autophagy regulatory molecules such as AMPK and mTOR, but it happens in the specific conditions, for example, some cancer cells increase their proliferation in the autophagy defect, while other cancer cells increase the proliferation even in normal condition, which indicates that every cancer cell has its own priority in selecting a particular signaling in order to increase its surveillance [62–69]. As discussed above, autophagy simply supports the metabolic needs of cancer cells for preventing energetic catastrophe. Alternatively, autophagy activation promotes the quiescence in the cancer cells through LKB1 and AMPK activation.

6. The AMPK signaling pathway influences the energy source of cancer cells

Lipogenesis is a crucial subsidy in which cancer cells can compensate for their energy demands. Acetyl CoA carboxylase (ACC) is an important enzyme in the regulation of lipogenesis. AMPK phosphorylates ACC to inhibit its activity [70]. Indeed, different subunits of ACC have been overlooked for the role in the cancer development. For example, AMPK inhibits ACCα (ACCA) for blocking the de novo synthesis of fatty acid to reduce the cancer cell proliferation, whereas ACCβ (ACCB) inhibition by AMPK increases the fatty acid synthesis required for energy storage, membrane proliferation, and the generation of signaling molecule in favor of cancer cell survival mechanism [71]. In fact, to date, many arguments regarding this concept still exist. However, endogenous lipids alone do not participate in the cancer cells proliferation. Reducing exogenous lipids can significantly influence the inhibition cancer cells proliferation. Targeting AMPK-phosphorylating ACCA for inhibition of cancer cells proliferation is possibly mediated by autophagy-induced cell survival in the cancer microenvironment. For example, increased ACC inhibits the maladaptive autophagy and reduced ACC depletes the acetyltransferase EP300, a suppressor of autophagy, which indicates that increase in the ACC can facilitate the autophagy induction in the tumor survival process. Also, TCA intermediates such as citrate, a precursor of fatty acid synthesis, can facilitate the tumor growth. Changes in the citrate levels increased the chances of prostate cancer cells [72]. ATP citrate lyase (ACLY) is a citrate cleavage enzyme converting citrate into acetyl CoA which can act as a regulator of lipogenesis. In this context, ACLY physically interacted with catalytic subunit of AMPK for its inhibition, resulting in apoptosis. For example, ACLY-silencing-induced p53activation facilitated DNA damage-induced cell death [73], indicating that ACLY silencing may fail in the conversion of citrate into acetyl CoA and stops the lipogenesis to reduce the tumor growth, but all these scenarios can be mediated by the AMPK. However, these speculations can be investigated further.

7. Role of AMPK in modulating inflammatory process of cancer cells

The link between inflammation and cancer development is apparent. However, AMPK-mediated inflammation in cancer is undefined. Metabolic changes take part in inflammation cascades including neutrophils, macrophages, and T-helper cells, resulting in the increased glucose uptake and aerobic glycolysis. Since AMPK is involved in regulating metabolic process, it can regulate or modulate the inflammatory process. A study found that AMPK deficiency exhibited a high inflammatory response which promotes the T-helper cells such as Th1 and Th17 play a crucial role in increasing or suppressing the tumor growth [74]. Furthermore, AMPK-activating drugs such as metformin and berberine have been shown to reduce the inflammatory responses in various models, suggesting a role of AMPK in regulating inflammation [75–77]. AMPK phosphorylated by IKK reduces the inflammatory cytokines IL-1 β or TNF-α in cancer. Transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) regulates the cell death and survival. Notably, TNF-related apoptosis-inducing ligand (TRAIL)-induced TAK1–AMPK signaling induces the autophagy in untransformed cells [78,79]. Since TRAIL is involved in inducing apoptosis in a number of cancer types, this TRAIL-induced TAK1–AMPK pathway may be a target of suppressing cancer.

8. AMPK on transcription factors and coactivators in cancer

A number of kinases including AMPK mediate the regulatory function of transcription factors (TFs). TFs and coactivators are commonly deregulated in the pathogenesis. As a consequence, TF-regulated or deregulated genes are involved in cancer progression. AMPK regulates the gene expressions by phosphorylating transcription factors, which facilitate the cancer growth like adjusting the metabolic adaptation during metabolic stress. Forkhead box O3a (FOXO3a) is a member of the FOXO subfamily of forkhead transcription factors that mediate various cellular processes such as apoptosis, proliferation, DNA damage, and tumorigenesis. Studies have observed that FOXO3a suppresses the cancer cells, and its reduced activity is associated with the initiation and progression of cancer [80–82]. The transcriptional activity of FOXO3a is influenced by AMPK. A recent study has shown that AMPK regulated the FOXO3 in hypoxia-induced autophagy [83]. Since cancer cells depend on acute and chronic hypoxia for their metabolic adaptation and metastasis, AMPK-mediated autophagy can facilitate the cancer cells to survive in the microenvironmental stress. As we mentioned earlier, AMPK may act as a metabolic checkpoint to suppress the cancer progression. However, this dual role of AMPK in relation to

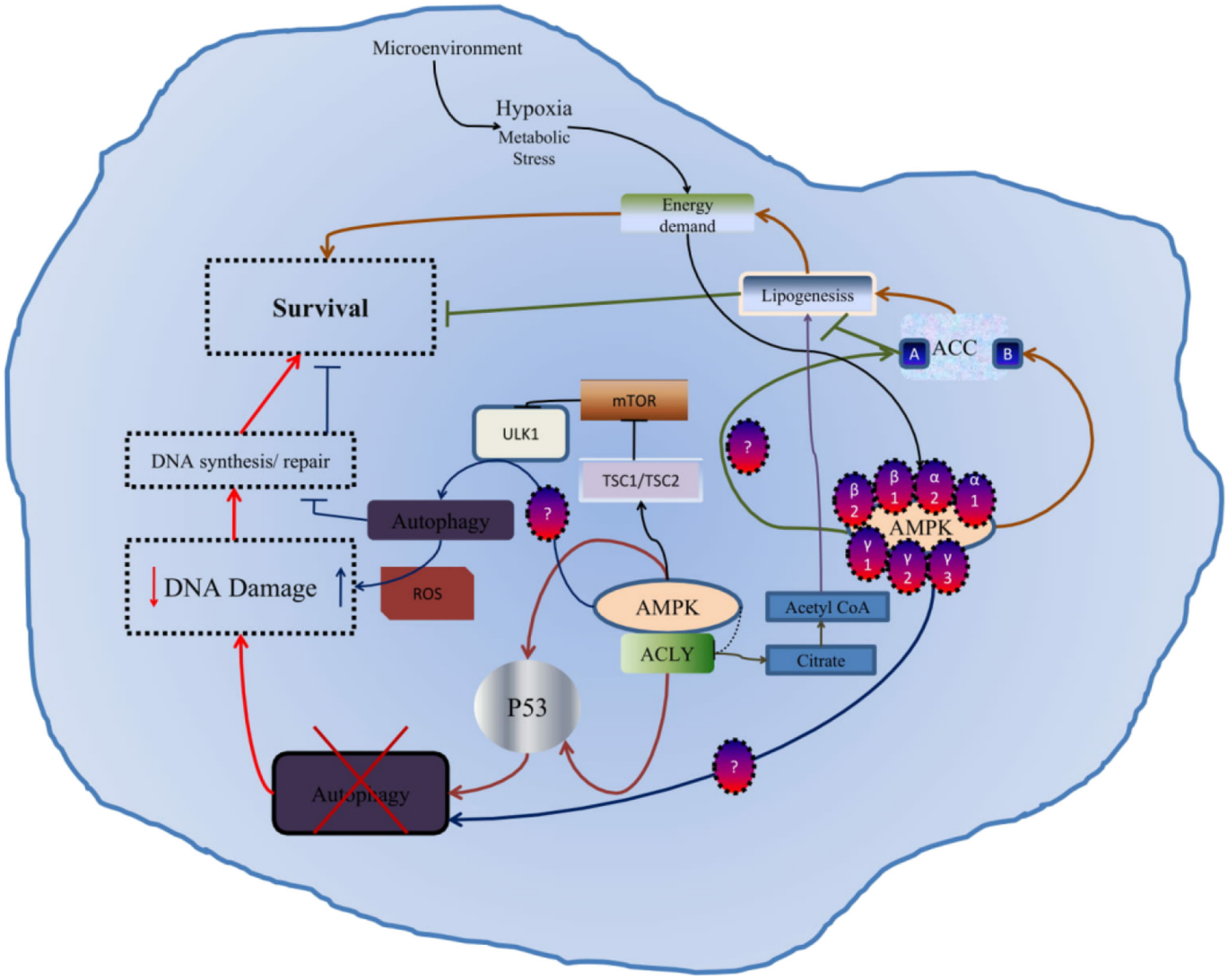

Fig. 2. Autophagy-dependent and autophagy-independent AMPK role on cancer survival mechanism and AMPK activation on acetyl carboxylase (ACC) for cancer survival. AMPK can inhibit the tumor growth through p53 phosphorylation by blocking autophagy. AMPK inhibits the mTOR for tumor survival and suppression in an autophagy-dependent manner. AMPK phosphorylates ULK1 directly to induce the autophagy-dependent tumor survival and inhibition. Microenvironmental stress results in fluctuation in the energy demand and consequent activation of AMPK. AMPK activates the ACC to lipogenesis to overcome the energy demand, but its subunits' role is undefined.

metabolic adaptation is equivocal. Furthermore, AMPK regulates the mesenchymal phenotype of cancer cells by targeting FOXO3a signaling through an AKT-dependent mechanism [84]. PGC1 alpha is a transcriptional coactivator that can play an important role in cancer. Studies have shown that PGC 1 alpha expression is associated with poor prognosis [85,86]. In addition, it is correlated with the invasivity and metastasis. Activation of AMPK by its upstream kinase LKB1 or SIRT1 can target the PGC1 alpha. In prostate cancer, AMPK activation leads to increased PGC1 alpha mitobiogenesis and oxidative phosphorylation, but also glycolysis that supports tumor growth [87]. The cyclic AMP response element-binding protein (CREB) integrates the signals from various cellular pathways to regulate the gene transcription. Deregulated CREB activity can contribute to pathogenesis of variety of cancers. Increased expression and phosphorylation of CREB have been associated with non-small cell lung cancer [88,89]. In addition, it plays a key role in mediating malignant behavior of tumor cells. AMPK activates the CREB through phosphorylation (Fig. 3). A study found that AMPK plays a dual role in the regulation of CREB like positive regulation via phosphorylation and negative effect on the CREB expression by up-regulating SIRT1 [90]. Hypoxia-inducible factors (HIFs) are transcription factors that respond to low available oxygen in the cellular environment, or hypoxia. Many recent studies have found that there is a strong correlation between elevated HIF-1 and tumor metastasis, angiogenesis, and poor patient prognosis [91–93]. Cancer cells activate a number of survival cascades for their adaptation mechanisms to hypoxic stress. HIF-1α and AMPK appear to be overlapped at a molecular level and may act as components to mount the cellular response onto hypoxic stress in cancer (Fig. 3). AMPK activity is important for HIF-1α transcriptional activity in hypoxia conditions. In addition, AMPK activity induced by hypoxia conditions may trigger the autophagy-dependent cancer survival and enhanced cellular adaptation. However, additional investigation is to be needed to understand the HIF-1α and AMPK overlapping mechanism in cancer. Notch1 is a transmembrane protein that can act as a cofactor for the TF CSL (CBF1, Suppressor of Hairless, Lag-1). Aberrant expression of notch has been linked with various cancers including cervical and breast cancers. Notch also acts as tumor suppressor. Its activation with ligand translocates the intracellular domain (ICN) of notch to nucleus, where it acts as a cofactor for the TF CSL [94]. The Notch1 signaling and its cofactor CSL can keep the cells into undifferentiated form, and therefore, this is

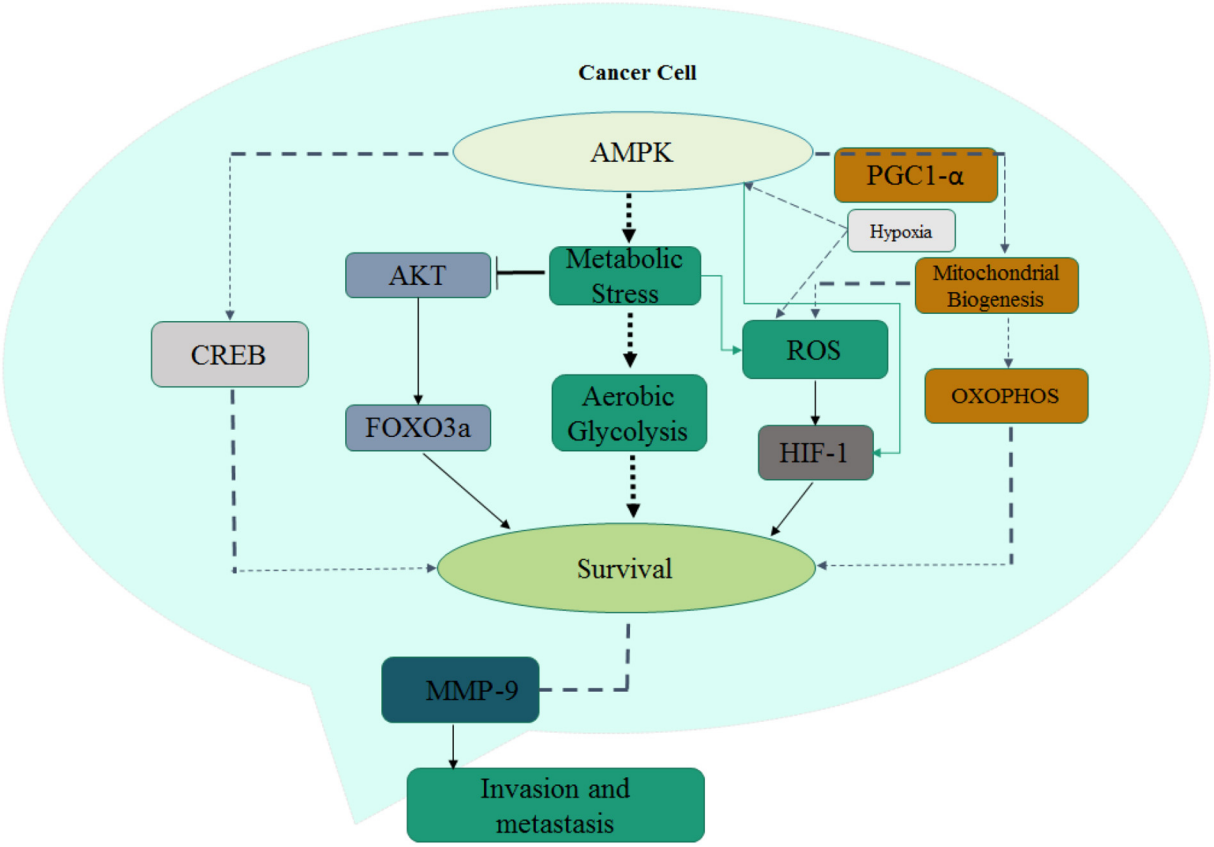

Fig. 3. Role of AMPK and transcription factors (Tfs) and coactivators on cancer. Hypoxia condition activates the AMPK and HIF-1α. AMPK activates the PGC1-α which supports the cancer cells survival via ROS production and further HIF-1α activation. AMPK activates the aerobic glycolysis for cancer survival. AMPK activates the CREB to cancer survival. AMPK inhibits the AKT through phosphorylation resulting in inhibition of the FOXO3 for cancer survival. AMPK activates MMP-9 for further invasion and metastasis.

associated with a number of cancers. Several kinases including AMPK can activate notch to other signaling. AMPK regulates the notch signaling through mTORC1 under the influence of nutrient status [95]. Oncogenic notch induced the aerobic glycolysis and metabolic stress resulting in the activation of AMPK. ICN of notch can also allow the coactivation of histone acetyltransferases such as p300 to create a short-lived transcriptional activation complex [96]. Histone acetyltransferases (HATs) are involved in the gene transcription. HATs have been shown to suppress and induce the cancer growth. AMPK/SNF signaling activates the histone acetyltransferases and, consequently, enhances the histone acetylation [97].

9. Regulation of glycolysis by AMPK in cancer

Cancer cells' rapid proliferation has significant bioenergetics challenges such as producing enough energy and synthesizing biomolecules at a sufficient rate. Many cancer cells adapt to metabolic transformation that supports high glucose uptake and lactate production (Warburg effect). The metabolic shift to Warburg effect is a crucial phenomenon in which most of the energetic and biosynthetic advantages are acquired by cancer cells proliferation and growth. Several cancer cells have defect in mitochondrial function, and they rely on glycolysis rather than oxidative phosphorylation. For example, activated H-Ras decreases mitochondrial complex activity, and increases glycolysis. However, the signal transduction pathways that regulate aerobic glycolysis are poorly understood. In case of AMPK, loss or dysfunction may favor the aerobic glycolysis in cancer cells; it may also overcome the metabolic checkpoints essential for cellular adaptation to stress. For example, silencing AMPK alpha increases the Warburg effect with lactate production from glucose and cellular biosynthesis in cancer cells [98]. HIF-1 alpha is a major player to induce the AMPK-dependent Warburg effect, and AMPK is a negative regulator of Warburg effect and suppresses the cancer cells growth [98]. However, recent studies suggest that AMPK is involved in the stress resistance and tumor survival. AMPK-phosphorylated PDH induces the Warburg effect under low-nutrient conditions in ROS-dependent manner [99]. AMPK regulates the Warburg effect by phosphorylating number of rate-limiting enzymes. For example, AMPK phosphorylates the PFKFB3, one of the 6-phosphofructo-2-kinase/fructose-2,6-bisphophatase. This increases the fructose-2,6-bisphosphate, a potent allosteric regulator of glycolysis enzyme PFK1 [100–102]. However, AMPK-regulating metabolic enzymes that are closely connected with the oncogenic signaling and cell transformation are yet to be established well.

10. AMPK-mediated immune response to neoantigen

The antigen-specific immune response is undeniable. However, immune system recognition for different antigens is obscure. Recent research has revealed that tumor cells have different mutated peptides called neoantigens, and identification of tumor-specific mutations can be the crucial target for cancer immunotherapies. Several factors are connected with specific immune response that recognizes mutated antigens such as rate of DNA damage, and consequent structural variants including nucleotide variants, insertion or deletion, and RNA splicing. As an energy sensor, AMPK can influence in modifying the DNA damage rate and its consequent structural variants in the tumor cells for evasion. In contrast, AMPK can modify the immune response of host to those structural variants. However, whether AMPK-mediated immune response can evade the tumor cells is questionable. AMPK can involve in modifying the immunoregulatory proteins when there is high tumor

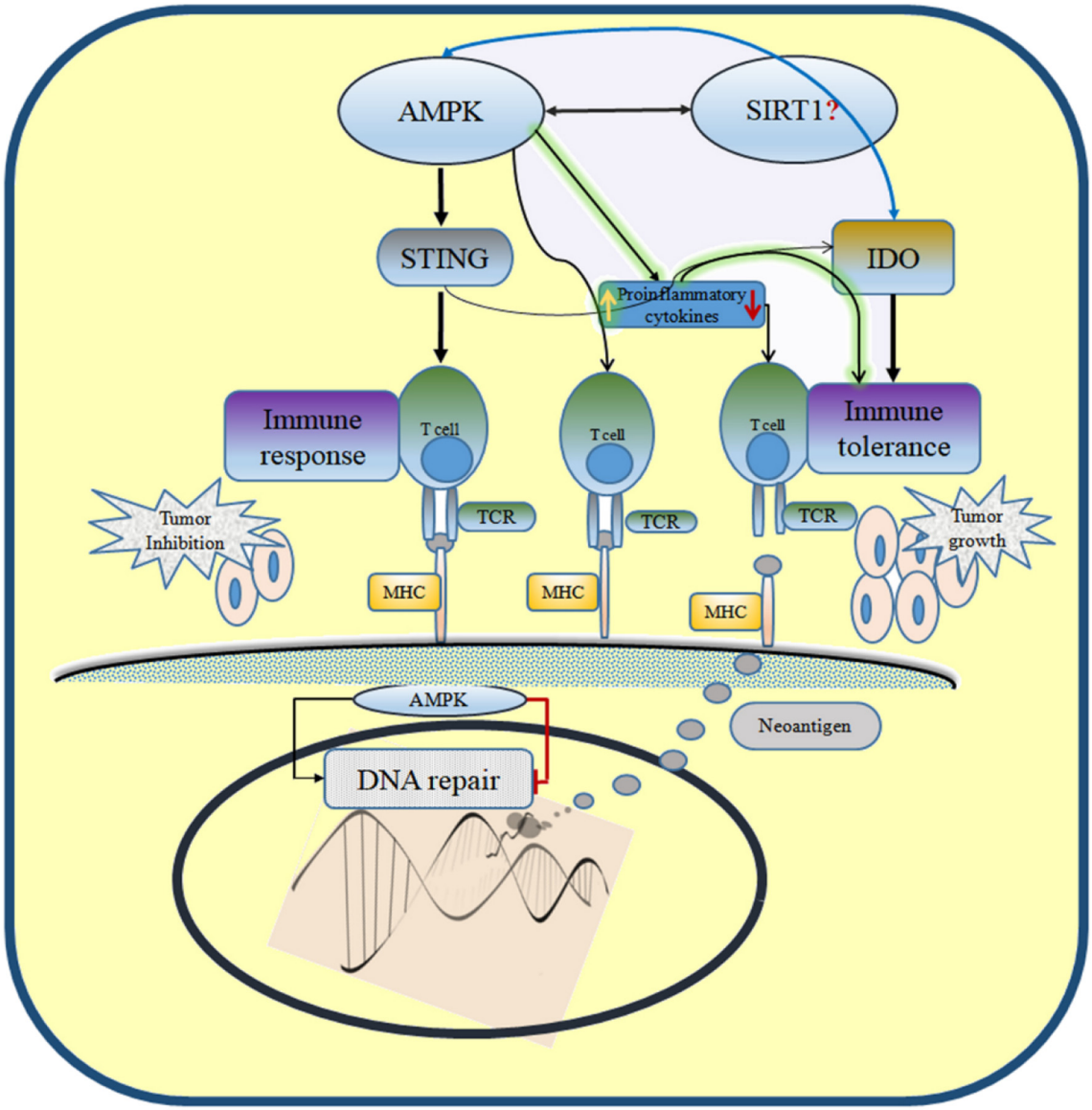

Fig. 4. AMPK-mediated immune response of host and cancer cells. Yellow color indicates that AMPK regulated proinflammatory cytokines effectively induce the immune response to neoantigen. Red color indicates that AMPK suppresses the activity of proinflammatory cytokines in resulting to compromise the recognition of neoantigens by T cell population. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

antigenicity. For example, AMPK modulates the stimulator of interferon genes (STING) for negating immune response through suppressing indoleamine-pyrrole 2,3-dioxygenase (IDO) which is an enzyme that can modulate the T cell function and engage in immune tolerance [103,104]. However, neoantigen does not require STING activation for tumor antigenicity, suggesting that AMPK may involve in the activation of STING to increase the immune response when tumor antigenicity is high. In addition, AMPK possibly involves in the regulation of the IDO via SIRT1 activation because IDO biological effect depends on the conversion of tryptophan into kynurenine. In another way, AMPK-induced proinflammatory cytokines can negate the immune response via IDO activation. AMPK can activate the proinflammatory signals of host according to the need of immune response for evading tumor cells. [105]. In contrast, AMPK-suppressed proinflammatory signals of host, and reduce the activity of different subtypes of T cells. Therefore, the recognition characteristic of T cells to neoantigens can be compromised (Fig. 4). In addition, AMPK-mediated proinflammatory signals affect the immune surveillance phases of the normal cells, which leads the cancer variants to get resistance over normal cells. However, how long AMPK-mediated proinflammatory signals can affect the immune surveillance is enigmatic since the immunoediting process involves shaping the tumor antigenicity/immunogenicity through Darwinian selection process. Also, whether mutated antigens can improve the MHC binding to T cell by AMPK is unknown. A number of factors are associated with AMPK involved in immune response recognition to neoantigen such as affecting T cell population in terms of supporting metabolic needs because higher T cell population can effectively recognize specific neoantigen, and affecting neoantigen repertoire by chromatin remodeling. T cell subsets have different cytokine profiles. Thus, T cell subsets elicit different immune response to various neoantigens. For example, Th1cells produce interferon (IFN-γ)-γ, whereas Th2 cells produce IL-4 and other cytokines, and the balance between the Th1 and Th2 can influence immune response to recognize neoantigens. IFN -γ can efficiently present antigens to Th1 response than Th2 producing IL-4 and other cytokines. AMPK impedes the Th1 producing IFN-γ signaling [106], suggesting AMPKs' positive role on tumor progression. In contrast, AMPK-regulated T cell populations can have a positive effect on tumor regression. For example, depletion in

the CD4+ population can increase the immunity against tumor through CD4+ CD25+ T cell population suppression. A study by Blagih et al. 2015 [107] has shown that AMPK regulates the T cell metabolic adaptation and effector responses. Altogether, AMPK has its role on supporting metabolic needs of T cell activation and proliferation, regulating proinflammatory signaling for balancing different T cell subsets that support selective T cell function to neoantigens, and regulating immunomodulatory proteins to immune tolerance response to neoantigens. In contrast, AMPK may involve in influencing the neoantigen repertoire by chromatin remodeling.

11. Role of AMPK in DNA damage and repairing

DNA damage and subsequent DNA repairing are crucial for tumor progression and regression. Several proteins and metabolic intermediaries are involved in such process, and proper chromatin packaging can decide the cell fate, and cancer cells often possess deregulated chromatic structure with altered level of chromatin machinery complexes. Metabolic stress and subsequent activation of AMPK impact chromatin structure. Chromatin structure is composed of an octamer of core histones that tightly binds and wraps DNA. AMPK affects the charge density interaction between histone and DNA in terms of providing or restricting substrates and cofactors that are necessary for maintaining the chromatin structure. Modification of chromatin machinery proteins such as histones (methylation and acetylation) can impact the chromatin organization. Methylation to lysine residue of histones can determine the repair pathway upon double-strand breaks (DSBs), and failing or not having well-repaired DSBs can lead to tumor progression [108]. For example, histone methylation can remodel the chromatin structure transcriptional repression complex to affect the expression of repair proteins and their loading onto DSBs. Usually, histone methylation occurs on lysine or arginine. Methylation of lysine on histone H3 (H3K4me3) is used by newly created DSBs, and AMPK may help to provide the methyl donor to this process. However, failing in this modification can significantly decrease the DNA repair breaks by the non-homologous end-joining (NHEJ) pathway, and inappropriate NHEJ can lead to chromosome translocation and abnormal telomere fusion, hallmark of cancer progression. Lysine- and arginine-specific histone methyl transferases use S-adenosyl methionine (SAMe) as cofactors to transfer methyl groups. Under metabolic stress or higher energy demands in the tumor microenvironment use higher ATP and methionine by SAM to methylate histones, and this process activates the AMPK for higher gene expression. Recent observation found that stimulating SAMe increases the cell longevity through the activation of AMPK [109]. In addition, AMPK may involve in demethylation of histones. For example, under metabolic stress or greater energy demand, the TCA intermediates are reduced, and thus AMPK is stimulated. TCA intermediaries are necessary for demethylase activity of histones. AMPK can increase the availability of α-ketoglutarate level by phosphorylating fumerase for demethylating histones [110]. For example, increased level of fumarate can inhibit the lysine-specific demethylase 2A (KDM2A), restoring H3K36 dimethylation (H3K36me2) [111]. Overexpression of KDM2A is associated with increased proliferation and invasion. In contrast, AMPK is involved in methylate Polycomb group (PcG) proteins and plays a key role in establishing and maintaining proper gene expression. For example, AMPK affects the methyltransferase polycomb repressive complex 2 (PRC2) activity toward lysine 27 on histone H3 (H3K27) and histone methyltransferase-containing COMPASS complex (complex proteins associated with set1). PRC2 is required for cancer cell proliferation, and overexpression of PRC2 is often linked with poor prognosis [112]. However, a number of methyl group transfer and cosubstrate level may be associated with AMPK activity. AMPK may also involve deacetylatingthe histone for obtaining euchromatin state. Acetyl CoA plays an important role for transferring an acetyl group to the NH_3^+ of lysine residue of histone acetyltransferases (HATs). Acetate from acetyl coA can acetylate histone, and imbalance of this process could influence the tumor suppressors and protooncogenes. Aberrant acetylation of histones can hyperactivate the oncofusion proteins or viral oncoproteins to boost carcinogenesis. AMPK may involve in reduction of aberrant acetylation of histones. In addition, tumor suppressors can be silenced by hypoacetylation [113]. AMPK is the main player of balancing HAT and HDAC in terms of serving or balancing acetate group to HAT. For example, AMPK phosphorylates the ACC to prevent the conversion of acetyl CoA to malonyl CoA for increasing the availability of acetyl groups to HAT. This results in increasing the HAT acetylation of H3 at the transcription factor EB (TFEB)-responsive promoters to increase the gene expression. Loss of acetylated Lys16 (K16-H4) of histone H4 is a common event in human cancer [114]. Also, decrease in the histone acetylation involves tumor invasion and metastasis [115]. In response to DNA damage, histones are phosphorylated by its kinases using ATP, and this process changes the ATP/ADP ratio, resulting in activation of the AMPK. For example, H2AX is a variant of histone that can be phosphorylated to DNA damage at higher percentage [116], and this reaction needs a large number of ATPs which could induce the activation of AMPK. In addition, AMPK affects the conversion metabolic intermediaries G-6-P by inhibiting G6DH [117] and is an important substrate for balancing the nucleotides, which is necessary for DNA replication and repairing including nucleotide and base excision repair. For example, PPP is the ribose backbone for purines and pyrimidines, and G-6-P from glycolysis is the rate-limiting step in the PPP. AMPKα1 ablation reduced isocitrate dehydrogenase 2 activity and cellular α-KG levels [118], and α-KG synthesis the glutamine, which is the intermediate to de nova synthesis of purines through IMP. On the whole, many factors influence AMPK-associated chromatin remodeling in tumor progression or regression such as affecting repair proteins expression and their loading onto DSBs, restricting provision of substrate to histone modification and influencing metabolic intermediaries level for nucleotide synthesis.

12. Conclusion and perspectives

Since most of the current mechanisms regarding caner target are equivocal, a number of challenges are awaiting to be solved. Several intermediary molecules are activated or meditated by AMPK in order to support or suppress the cancer cells growth. However, how AMPK is activated or inhibited while a cell becoming cancerous is debatable. Numerous reports support that AMPK is an important target in controlling cancer cells proliferation, but its multi-targeting mechanisms allow to indecision the conclusion on cancer cells inhibition. Cells with proliferative advantage have higher percentage of mutation rate, increase in tumor volume, and fluctuation in the oxygen availability and nutrient. This scenario makes a cancer cell to depend or activate the AMPK for all possible ways. Therefore, AMPK becomes a crucial player in tumor environment. In addition, cancer cells can coin the subunits of AMPK according to their need of survival in microenvironment. As a result, AMPK can mediate all the regulatory pathways including autophagy to support the cancer survival. On the other hand, autophagy induction is a way of autophagy mediating cell death in cancer cells. Some cancer cells are adapting to escape or inhibit the apoptosis. In this scenario, autophagy-induced cell death is an important target, and various studies have reported that AMPK-mediated autophagy induction increased the cell death of cancer. However, what condition in the tumor environment allows this AMPK-mediated autophagy-induced cell death is questionable, and it can be the futuristic research of cancer prevention. Altogether, AMPK is a central player of either tumor survival or regression, and needing a profound understand of AMPK-mediated pathways.

Conflicts of interest

The authors declare that there is no conflict of interest.

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