Regulation of ion channels and transporters by AMP-activated kinase (AMPK)

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Abbreviations: AMPK, AMP activated kinase; B0AT, amino acid transporter; BGT, NaCl coupled betaine, GABA transporter BGT; BKCa, Big Ca2+ activated K⁺ channels; CaMKKβ, Ca2+/calmodulin-dependent kinase kinase-beta; CFTR, cystic fibrosis transmembrane transport regulator; CICκa/barttin, Cl⁻ channels; CIC2, Cl⁻ channels; CreaT, creatine transporter; EAAT, Excitatory amino acid transporter; ENaC, epithelial Na⁺ channel; GAP, GTPase activating protein; GLUT, glucose transporters; GSK, glycogen synthase kinase; hERG, human ether a gogo K⁺ channels; KATP, ATP regulated K⁺ channels; KCa, Ca2+ activated K⁺ channels; KCNQ1, voltage gated K⁺ channels; Kir, inwardly rectifying K⁺ channels; Kv, voltage gated K⁺ channels; LKB1, liver kinase B1; MCT, monocarboxylate transporters; NaPi-IIb, phosphate transporter; Nav, voltage gated Na⁺ channels; Nedd4.2, neuronal precursor cells expressed developmentally downregulated 4-2; NF-κB, Nuclear factor kappa B; OHC, outer hair cells; Orai1, Ca2+ release activated Ca2+ channel; PepT1, peptide transporter; PIKfyve, phosphatidylinositol 3-phosphate 5-kinase; PTEN, Phosphatase and tensin homologue (PTEN) via glycogen synthase; ROMK, renal outer medullary K⁺ channels; SGLT, Na⁺ coupled glucose transporter; SMIT, Na⁺ coupled myo-inositol transporter; SN1, amino acid transporter; STK11, serine/threonine kinase 11; SOCE, store-operated Ca²⁺ entry; TBC1D1, TBC domain Rab GTPase activating protein; TASK, Tandem pore domain K⁺ channels; TREK, Tandem pore domain K⁺ channels

Introduction

The ubiquitously expressed adenosine 5’-monophosphate (AMP) -activated protein kinase (AMPK) is composed of a catalytic α-subunit and regulatory β- and γ-subunits.¹ The α1 isof orm is ubiquitously expressed, whereas the α2 isof orm is mainly expressed in skeletal muscle, heart and liver.² AMPK is activated by increase in the cytosolic AMP/ATP concentration ratio and thus responds to the cellular energy status.³,⁵ AMPK is further activated by increases in the cytosolic Ca²⁺ concentration even in energy-replete cells,⁴,⁶,⁹ an effect involving Ca²⁺/calmodulin-dependent kinase kinase–β (CaMKKβ) dependent phosphorylation of threonine 172 (Thr-172) residue in the AMPK catalytic α subunit.¹⁰,¹¹ Moreover, AMPK is activated by the liver kinase B1 (LKB1) or serine/threonine kinase 11 (STK11),¹¹ the transforming growth factor β-associated kinase 1² and by glucosamine.¹³ AMPK phosphorylates target proteins at serine or threonine within the consensus sequence Φ(XX/XX)XX/XXXΨ (Ψ, hydrophobic; Φ, basic).¹⁴ Phosphorylation modifies the function of target proteins. The cellular functions thus stimulated by AMPK serve in large part to refuel cellular ATP levels.¹⁵ AMPK increases ATP generation by stimulating cellular glucose uptake, glycolysis, fatty acid oxidation and the activity of enzymes required for ATP production.⁵,¹⁶,³⁸ It curtails energy expenditure by decreasing protein synthesis, gluconeogenesis and lipogenesis.⁵,¹⁵,¹⁷,³⁹,⁴¹ AMPK thus protects cells against detrimental effects of energy depletion.¹²,¹³,⁴²,⁴⁴ However, AMPK may trigger

The energy-sensing AMP-activated kinase AMPK ensures survival of energy-depleted cells by stimulating ATP production and limiting ATP utilization. Both energy production and energy consumption are profoundly influenced by transport processes across the cell membrane including channels, carriers and pumps. Accordingly, AMPK is a powerful regulator of transport across the cell membrane. AMPK regulates diverse K⁺ channels, Na⁺ channels, Ca²⁺ release activated Ca²⁺ channels, Cl⁻ channels, gap junctional channels, glucose carriers, Na⁺/H⁺-exchanger, monocarboxylate-, phosphate-, creatine-, amino acid-, peptide- and osmolyte-transporters, Na⁺/Ca²⁺-exchanger, H⁺-ATPase and Na⁺/K⁺-ATPase. AMPK activates ubiquitin ligase Nedd4-2, which labels several plasma membrane proteins for degradation. AMPK further regulates transport proteins by inhibition of Rab GTPase activating protein (GAP) TBC1D1. It stimulates phosphatidylinositol 3-phosphate 5-kinase PIKfyve and inhibits phosphatase and tensin homolog (PTEN) via glycogen synthase kinase 3β (GSK3β). Moreover, it stabilizes F-actin as well as downregulates transcription factor NF-κB. All those cellular effects serve to regulate transport proteins.

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suicidal death of energy-depleted cells.\textsuperscript{45} It further inhibits cell proliferation,\textsuperscript{46} counteracts hypertrophy,\textsuperscript{47} fosters phagocytosis,\textsuperscript{48} and stimulates autophagy.\textsuperscript{49,50}

The orchestration of cell survival during energy depletion involves regulation of transport across the cell membrane. Avoidance of Ca\textsuperscript{2+} overflow requires regulation of Ca\textsuperscript{2+} transport. The present brief review thus compiles the effects of AMPK on channels, carriers, and pumps. Some examples are provided of how AMPK-sensitive transport could counteract energy depletion and/or Ca\textsuperscript{2+} overflow. The reader is encouraged to consult excellent earlier reviews on similar topics.\textsuperscript{51,52}

**AMPK-Regulated Ion Channels**

AMPK regulates a wide variety of membrane transport proteins.\textsuperscript{51,53-72} K\textsuperscript{+} channels downregulated by AMPK include Ca\textsuperscript{2+}-activated potassium channels such as K\textsubscript{Ca3.1},\textsuperscript{51,73} inwardly rectifying potassium channels such as Kir1.1 (ROMK),\textsuperscript{77} and Kir2.1,\textsuperscript{74} the voltage-gated K\textsuperscript{+} channels Kv1.5,\textsuperscript{78} Kv2.1,\textsuperscript{76} Kv7.1,\textsuperscript{78,79,86} and Kv11.1 (hERG),\textsuperscript{78} as well as 2-P potassium channels such as K\textsubscript{ir}2.1 (TREK-1),\textsuperscript{71} K\textsubscript{ir}3.9 (TASK-3),\textsuperscript{69} and K\textsubscript{ir}10.1 (TREK-2).\textsuperscript{71}

AMPK has been shown to inhibit ATP-sensitive Kir6.x channels,\textsuperscript{78,79} whereas other studies reported a stimulatory effect on cardiac ATP-sensitive Kir6.2,\textsuperscript{72,79} and on Kir6.2 in β-cells.\textsuperscript{70} The large Ca\textsuperscript{2+}-activated K\textsuperscript{+} channel K\textsubscript{Ca}1.1 has similarly been shown to be up-\textsuperscript{41} or downregulated\textsuperscript{82} by AMPK.

K\textsuperscript{+} channels are the most important channels maintaining the cell membrane potential.\textsuperscript{83} Reduced K\textsuperscript{+} fluxes through inhibited K\textsuperscript{+} channels depolarize whereas enhanced K\textsuperscript{+} fluxes through activated K\textsuperscript{+} channels hyperpolarize energy-depleted cells. Depolarization following downregulation of K\textsuperscript{+} channels decreases the electical driving force for electrogenic Na\textsuperscript{+}-coupled transport thus curtailing Na\textsuperscript{+} entry and the subsequent requirement for costly Na\textsuperscript{+} extrusion by Na\textsuperscript{+}/K\textsuperscript{+} ATPase in epithelia such as the proximal renal tubule.\textsuperscript{85}

Depolarization following inhibition of K\textsuperscript{+} channels decreases the electrical driving force for HCO\textsubscript{3}\textsuperscript{-} exit and thus favors alkalinization of cells with HCO\textsubscript{3}\textsuperscript{-} permeable channels or Na\textsuperscript{+}-coupled HCO\textsubscript{3}\textsuperscript{-} cotransport.\textsuperscript{84} Similarly, depolarization alkalinizes the cytosol of cells expressing Cl\textsuperscript{-} channels in parallel to Cl\textsuperscript{-}/HCO\textsubscript{3}\textsuperscript{-} exchange, as it decreases the electrical driving force for Cl\textsuperscript{-} exit thus increasing the cytosolic Cl\textsuperscript{-} concentration and via Cl\textsuperscript{-}/HCO\textsubscript{3}\textsuperscript{-} exchange the cytosolic HCO\textsubscript{3}\textsuperscript{-} concentration. A depolarization by 18 mV doubles the cytosolic equilibrium Cl\textsuperscript{-} concentration, doubles the equilibrium HCO\textsubscript{3}\textsuperscript{-} concentration and thus increases cytosolic pH at equilibrium by 0.3 pH units. The alkalinization fosters glycolytic flux and thus ATP generation from glucose\textsuperscript{85} without the requirement of energy-consuming extrusion of H\textsuperscript{+} by either H\textsuperscript{+}/H\textsuperscript{3}O\textsuperscript{-} or Na\textsuperscript{+}/H\textsuperscript{+} exchanger (see below).

A depolarization further leads to decreased store-operated Ca\textsuperscript{2+} entry (SOCE) through Ca\textsuperscript{2+} release activated Ca\textsuperscript{2+} channels (Fig. 1), which show a prominent inward rectification.\textsuperscript{86} In contrast, depolarization activates voltage-gated Ca\textsuperscript{2+} channels\textsuperscript{87} with subsequent Ca\textsuperscript{2+} entry and energy-consuming excitation in excitable cells. Thus, hyperpolarization rather than depolarization results in a reduction of energy consumption of excitable cells. The impact of K\textsuperscript{+} channel activity on cytosolic Ca\textsuperscript{2+} activity and energy consumption hence depends on the expression and regulation of the Ca\textsuperscript{2+} channel types in the energy-depleted cell.

Cardiac repolarization is expected to be delayed by the AMPK-induced downregulation of the cardiac K\textsuperscript{+} channels Kv11.1\textsuperscript{75} and Kv7.1.\textsuperscript{90} This mechanism may participate in the events causing arrhythmia following cardiac ischemia. Mutations in the AMPK γ2 subunit are associated with potentially fatal cardiac arrhythmias.\textsuperscript{51,73,91} Whether regulation of K\textsuperscript{+} channels contributes to the underlying mechanisms, has, however, remained ill defined.

AMPK activity decreases the frequency of evoked action potentials in cultured hippocampal neurons thus decreasing the energy consumption of those cells.\textsuperscript{76} The increase in K\textsubscript{ATP} current in cardiomyocytes by AMPK activity contributes to hypoxia-induced preconditioning of the heart protecting against myocardial infarction.\textsuperscript{72}
AMPK-dependent stimulation of K\textsubscript{ATP} channel activity inhibits and AMPK-dependent inhibition of K\textsubscript{ATP} channel activity stimulates insulin release.\textsuperscript{78-80,88-90} The decrease of K\textsubscript{Ca,1.1},\textsuperscript{70,91} K\textsubscript{Ca,2.1},\textsuperscript{69,91} K\textsubscript{Ca,2.1}\textsuperscript{17} and/or K\textsubscript{Ca,10.1}\textsuperscript{171} activity by AMPK presumably contributes to oxygen sensing within type I cells of the carotid body.\textsuperscript{51} Hypoxia leads to K\textsuperscript{+} channel inhibition with subsequent cell membrane depolarization, Ca\textsuperscript{2+} entry and degranulation in those cells.\textsuperscript{82,92}

AMPK-sensitive stimulation of K\textsubscript{Ca,1.1} channel activity contributes to the protection of outer hair cells (OHC) of the inner ear against acoustic trauma.\textsuperscript{81} Accordingly, recovery from hearing loss following acoustic overexposure is significantly delayed in AMPK\textsubscript{α1}-deficient mice.\textsuperscript{81}

AMPK participates in the regulation of Cl secretion. It reduces the activity of some Cl channel proteins implicated in epithelial transport and cell volume regulation.\textsuperscript{51,93-96} In particular, AMPK inhibits the Cl channel CFTR (cystic transmembrane transport regulator), which is expressed in the apical cell membrane of Cl-secreting epithelial cells.\textsuperscript{51,93-96}

AMPK activity slows the inactivation of the voltage-gated cardiac Na\textsuperscript{+} channel Nav1.5 and shifts the voltage activation curve toward hyperpolarized values, an effect which could prolong the action potential.\textsuperscript{97} Activation of AMPK and subsequent AMPK-sensitive regulation of this channel may contribute to the arrhythmia following cardiac ischemia.

AMPK reduces the activity of the epithelial Na\textsuperscript{+} channel ENaC\textsuperscript{97,98,99} and may therefore decrease Na\textsuperscript{+} transport in a variety of epithelia\textsuperscript{100} and nonepithelial tissues including endothelia.\textsuperscript{101} Decrease of Na\textsuperscript{+} entry lowers the work load of the respective epithelial cell and thus protects against energy depletion. As enhanced expression of endothelial ENaC is followed by endothelial stiffening with decreased endothelial NO release,\textsuperscript{101,102} reduction of ENaC activity by AMPK may at least in theory contribute to the stimulation of AMPK-sensitive endothelial NO release following ischemia.\textsuperscript{103}

AMPK contributes to the regulation of the pore-forming subunits of Ca\textsuperscript{2+} release activated Ca\textsuperscript{2+} channels Orai1, Orai2, and Orai3 (Fig. 1), which are activated by the Ca\textsuperscript{2+}-sensing subunits STIM1 and STIM2.\textsuperscript{104-106} Along those lines, the increase in the intracellular Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]) following stimulation of the chemokine receptor CXCR4 with its ligand CXCL12 was more pronounced in dendritic cells (DCs) isolated from gene-targeted mice lacking functional AMPK\textsubscript{α1} (ampk\textsuperscript{−/−}) than in DCs isolated from wild type mice (ampk\textsuperscript{+/+}).\textsuperscript{105} Inhibition of endosomal Ca\textsuperscript{2+} ATPase with thapsigargin in the absence of extracellular Ca\textsuperscript{2+} leads to a similar release of Ca\textsuperscript{2+} from the cytoplasmic stores, indicating that AMPK does not significantly modify Ca\textsuperscript{2+} stores.\textsuperscript{105} The increase in cytosolic Ca\textsuperscript{2+} activity following readduction of extracellular Ca\textsuperscript{2+} is, however, more pronounced in ampk\textsubscript{−/−} DCs than in ampk\textsubscript{+/+} DCs.\textsuperscript{105} AMPK further plays a role in the regulation of Orai1 in lymphocytes.\textsuperscript{107} The inhibition of Ca\textsuperscript{2+} channels by AMPK is part of a negative feedback,\textsuperscript{106} as an increase in [Ca\textsuperscript{2+}i] is followed by activation of Ca\textsuperscript{2+}/calmodulin-dependent kinase kinase-B (CaMKKB) and CaMKKB-dependent phosphorylation and thus activation of AMPK.\textsuperscript{7} Along those lines, AMPK phosphorylation following hypoxia is blunted by silencing of STIM1.\textsuperscript{7} Without this negative feedback, energy depletion would be expected to activate Orai1 due to impaired function of the endoplasmatic reticulum Ca\textsuperscript{2+} ATPase SERCA with subsequent depletion of intracellular Ca\textsuperscript{2+} stores and activation of Orai by STIM. AMPK-mediated inhibition of Ca\textsuperscript{2+} entry presumably contributes to the regulation of a wide variety of functions even without energy depletion, such as inhibition of cell proliferation,\textsuperscript{46,107} and of cell migration\textsuperscript{105} by AMPK. For instance, the chemokine CXCL12 enhances migration of immature ampk\textsuperscript{−/−} DCs more potently than migration of immature ampk\textsuperscript{+/+} DCs.\textsuperscript{105} Notably, activation with bacterial lipopolysaccharides downregulates AMPK phosphorylation in DCs and thus stimulates migration to a similar extent in ampk\textsuperscript{−/−} DCs and ampk\textsuperscript{+/+} DCs.\textsuperscript{105} AMPK further blunts DC activation,\textsuperscript{108} AMPK counteracts metabolic transition to aerobic glycolysis and cytokine release following triggering of Toll-like receptors.\textsuperscript{108,109}

AMPK downregulates the gap junctional protein connexin 26 (CX26) and may thus disrupt the connection between neighboring cells.\textsuperscript{55} Open gap junctions to intact neighboring cells support the survival of energy-depleted cells, as Na\textsuperscript{+} and K\textsuperscript{+} fluxes through gap junctions maintain ion gradients and the cell membrane potential difference across the cell membrane of the energy-depleted cells despite impaired Na\textsuperscript{+} extrusion and K\textsuperscript{+} uptake. The gap junctional fluxes impose, however, an additional burden to the Na\textsuperscript{+}/K\textsuperscript{+} ATPase of the adjacent cell. Closure of the gap junctions thus jeopardizes the survival of the energy-depleted cell but by the same token protects the adjacent intact cells, which could otherwise be ripped to death by the energy-depleted neighboring cell.
AMPK Regulates Carriers

AMPK regulates a wide variety of carriers. Most importantly, AMPK upregulates both Na⁺-independent (GLUT₅)³³,³⁴,¹⁰,¹³ and Na⁺-coupled (SGLT1)¹⁰,¹⁵ glucose carriers (Fig. 1). The carriers supply energy-depleted cells with glucose, which could be utilized for ATP generation by anaerobic glycolysis, i.e., without consumption of oxygen.¹⁶ Besides cells exposed to hypoxia, glycolysis is the preferential source of ATP in inflammatory immune cells and tumor cells.¹¹⁶ At first glance, it appears counterintuitive to employ secondary active Na⁺-coupled transport (SGLT1) for cellular glucose uptake into energy-depleted cells, as Na⁺ entering in parallel to glucose needs to be extruded by energy-consuming Na⁺/K⁺ ATPase. However, the amount of ATP generated from glycolytic degradation of glucose by far exceeds the amount of ATP required for extrusion of the cotransported Na⁺. In contrast to GLUT transporters, SGLT1 accomplishes cellular glucose uptake even at extracellular glucose concentrations lower than those prevailing in the cell. Thus, AMPK-stimulated SGLT1 activity could indeed contribute to energy repletion.

The utilization of glucose for glycolytic energy production requires an alkaline cytosolic pH, as the glycolytic enzymes are highly sensitive to cytosolic pH and are inhibited by cytosolic acidification.⁸⁵ Cytosolic alkalization may be caused by inhibition of K⁺ channels with subsequent depolarization of the cell membrane (Fig. 2). Beyond that AMPK stimulates H⁺ extrusion by the Na⁺/H⁺ exchanger¹¹⁷ and thus sets the stage for glucose utilization (Fig. 2). The lactate produced by anaerobic glycolysis could exit via the monocarboxylate transporters MCT1 and MCT4, which are both upregulated by AMPK.¹¹⁸ As lactate exit through MCT1 and MCT4 is paralleled by exit of H⁺,¹⁹ the carriers counteract cytosolic acidification.

In contrast to its effect on SGLT1, AMPK downregulates a variety of Na⁺ coupled transporters, such as the Na⁺ coupled phosphate transporter NaPi-IIa,¹¹⁹ the Na⁺ coupled creatine transporter CreaT,¹₂¹ the Na⁺ coupled myoinositol transporter SMIT, the NaCl coupled betaine,GABA transporter BGT¹²² as well as the Na⁺ coupled amino acid transporters EAAT3 and EAAT4.¹²³ Inhibition of those transporters decreases the Na⁺ burden for the Na⁺/K⁺ ATPase and thus energy consumption. AMPK further downregulates the H⁺ driven peptide transporter PepT.¹²⁴ Decreased activity of this carrier lowers the acid load of the cell.

AMPK inhibits Na⁺/Ca²⁺ exchangers¹⁰⁵ (Fig. 2), which may limit Na⁺ entry but by the same token disrupts Ca²⁺ extrusion by this carrier.¹⁰⁶ The purpose of this inhibition is presumably the avoidance of Ca²⁺ uptake into energy-depleted cells. Energy deprivation compromises Na⁺/K⁺ ATPase function due to lack of ATP and due to inhibition by AMPK. A decrease of Na⁺/K⁺ ATPase activity increases cytosolic Na⁺ activity and depolarizes the cell membrane which eventually leads to the reversal of the electrochemical gradients for the carrier. Without inhibition by AMPK the carrier would presumably contribute to cellular Ca²⁺ accumulation during energy depletion.

AMPK Regulated Pumps

AMPK downregulates the vacuolar H⁺ ATPase¹²⁵⁻¹²⁷ and thus directly energy-consuming proton extrusion. Inhibition of the H⁺ ATPase in intercalated cells of the distal nephron impairs urinary acidification.

AMPK has been reported to inhibit the Na⁺/K⁺ ATPase and to contribute to its downregulation during hypoxia.¹²⁸ AMPK-sensitive inhibition of Na⁺/K⁺ ATPase hence leads to downregulation of pulmonary transepithelial Na⁺ transport in hypoxia.¹²⁹ As Na⁺/K⁺ ATPase is the most important ATP-consuming transport protein in the cell membrane, its downregulation has a profound effect on the energy balance of the cell. Inhibition of Na⁺/K⁺ ATPase is at least in some cells followed by inhibition of K⁺ channels with subsequent depolarization.⁸³ As outlined above, the depolarization decreases the driving force for Na⁺ coupled transport and results in cytosolic alkalization, which in turn favors glycolysis and lowers the requirement of primary or secondary active extrusion of H⁺.

In active skeletal muscle, however, AMPK is activated in parallel to Na⁺/K⁺ ATPase and contributes to the upregulation of the pump under this condition.¹³⁰ It should be kept in mind that excitable cells would presumably not decrease energy consumption following depolarization (see above). Moreover, inhibition of Na⁺/K⁺ ATPase would be expected to increase the cytosolic Na⁺ concentration, which could, at least in theory, reverse the Na⁺/Ca²⁺ exchanger action thus resulting in Ca²⁺ uptake with subsequent energy-consuming muscle contraction. Clearly, inhibition of Na⁺/K⁺ ATPase serves to reduce energy expenditure but by the same token jeopardizes the second function of AMPK; i.e., the maintenance of low cytosolic Ca²⁺ activity.

Mechanisms Employed in AMPK-Sensitive Transport Regulation

AMPK may regulate transport proteins by direct phosphorylation,⁵¹ as shown for Kv₁.₁,₁², Kv₂.₁,¹⁷, Kir6.2,⁷⁹, Kᵥ₂.₁,⁷¹ and Kᵥ₁₀.₁,⁷¹ CFTR,⁸³-⁹⁵ as well as for H⁺ ATPase.¹²⁵ AMPK stimulates Nedd4–2 (neuronal precursor cells expressed developmentally downregulated), an ubiquitin ligase labeling transport proteins for clearance from the cell membrane and subsequent degradation.⁵⁷,⁵⁸,⁹⁸,⁹⁹ For instance, Nedd4–2 mediates the downregulation of the epithelial Na⁺ channel ENaC,⁷⁹,⁹⁸,⁹⁹ the inwardly rectifying K⁺ channel Kir2.1,¹⁴ and the voltage gated K⁺ channels Kv7.1.⁵¹,⁵⁶,⁵⁸ In theory, AMPK could similarly downregulate other Nedd4–2 sensitive transport proteins including the ion channels Nav1.5, Kv1.3, Kv1.5, Kv4.3, Kv7.2/3, CLCKa/barttin, Orai1, and CIC2,¹³¹-¹³⁴ the carriers SGLT1, NaPi-IIb, SN1, EAAT1, EAAT2, EAAT4,¹³⁵,¹³⁷ AMPK may enhance GLUT4 insertion into the cell membrane by phosphorylation and thus inhibition of TBC1D1, the Rab GTase activating protein (GAP), which otherwise counteracts GLUT4 translocation into the plasma membrane.¹³⁸ AMPK may upregulate carriers such as GLUT4 further by stimulating the
phosphatidylinositol 3-phosphate 5-kinase PIKfyve, a kinase generating PtdIns(3,5)P2, which in turn mediates the trafficking of carrier-containing vesicles to the cell membrane. It is noteworthy that several further transport proteins are regulated by PIKfyve, such as the AMPA-type glutamate receptor GluA1, the K+ channels Kv11.1, Kir2.1, and Kir2.2, the Ca2+-channel TRPV6, the Cl- channel CIC2, the Na+, glucose cotransporter SGLT1, the creatine transporter CreaT166 as well as the amino acid transporters B0AT1, EAAT2, EAAT3, and EAAT4. Whether or not AMPK-sensitivity of PIKfyve contributes to the regulation of those channels and carriers, remains, however, to be shown.

AMPK has been shown to modify KATP channel trafficking by inhibition of phosphatase and tensin homolog (PTEN) via glycogen synthase kinase 3B (GSK3B). Moreover, AMPK-sensitive KATP channel trafficking is impaired by stabilization of F-actin and stimulated by destabilization of F-actin. Whether those signaling mechanisms play a role in the regulation of other channels or carriers, is not known.

AMPK is further effective through downregulation of NF-κB (nuclear factor kappa B). As NF-κB stimulates the expression of Orai1, the inhibitory effect of AMPK on Orai1 may be partially due to downregulation of NF-κB. Channels upregulated by NF-κB further include the voltage-gated K+ channel Kv1.3 and the epithelial Cl- channel CFTR. CFTR in turn downregulates the expression of the transcription factor. Channels downregulated by NF-κB include the epithelial Na+ channel ENaC. Among the carriers upregulated by NF-κB is the Na+/H+ exchanger NHE3. carriers downregulated by NF-κB include SGLT1. NF-κB presumably regulates the expression of multiple further transport proteins and/or several signaling cascades involved in transport regulation. For instance, NF-κB downregulates the expression of the serum and glucocorticoid inducible kinase SGK1, a powerful regulator of a wide variety of channels, carriers and Na+/K+ ATPase. Along those lines, NF-κB inhibits ENaC in the renal collecting duct by downregulating SGK1. However, the contribution of NF-κB or other transcription factors to AMPK-sensitive transport regulation has hitherto remained ill defined.

**Conclusions**

In conclusion, AMPK is a powerful regulator of a wide variety of channels, carriers and pumps. The kinase is at least partially effective by directly phosphorylating transport proteins, by stimulating Nedd4-2-sensitive transport protein degradation and by interference with NF-κB-sensitive transcription. AMPK-dependent regulation of transport proteins is an integral part of the cell survival strategy during energy depletion, Ca2+ overload and further threats of cell survival. Clearly, additional experimental effort is needed to fully understand the AMPK-dependent orchestration of transport under physiological and pathophysiological conditions.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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