Original Paper

Downregulation of Kv1.5 K⁺ Channels by the AMP-Activated Protein Kinase

Sobuj Mia^a Carlos Munoz^a Tatsiana Pakladok Gulab Siraskar Jakob Voelkl
Ioana Alesutan Florian Lang

Department of Physiology, University of Tübingen, Tübingen, ^acontributed equally and thus share first authorship

Key Words

Kv1.5 • AMPK • Ischemia • Energy depletion

Abstract

Background: The voltage gated K⁺ channel Kv1.5 participates in the repolarization of a wide variety of cell types. Kv1.5 is downregulated during hypoxia, which is known to stimulate the energy-sensing AMP-activated serine/threonine protein kinase (AMPK). AMPK is a powerful regulator of nutrient transport and metabolism. Moreover, AMPK is known to downregulate several ion channels, an effect at least in part due to stimulation of the ubiquitin ligase Nedd4-2. The present study explored whether AMPK regulates Kv1.5. **Methods:** cRNA encoding Kv1.5 was injected into *Xenopus* oocytes with and without additional injection of wild-type AMPK ($\alpha 1 \beta 1 \gamma 1$), of constitutively active γ^{R70Q} AMPK ($\alpha 1 \beta 1 \gamma 1(R70Q)$), of inactive mutant α^{K45R} AMPK ($\alpha 1(K45R)\beta 1 \gamma 1$), or of Nedd4-2. Kv1.5 activity was determined by two-electrode voltage-clamp. Moreover, Kv1.5 protein abundance in the cell membrane was determined by chemiluminescence and immunostaining with subsequent confocal microscopy. **Results:** Coexpression of wild-type AMPK^{WT} and constitutively active AMPK γ^{R70Q} , but not of inactive AMPK α^{K45R} significantly reduced Kv1.5-mediated currents. Coexpression of constitutively active AMPK γ^{R70Q} further reduced Kv1.5 K⁺ channel protein abundance in the cell membrane. Coexpression of Nedd4-2 similarly downregulated Kv1.5-mediated currents. **Conclusion:** AMPK is a potent regulator of Kv1.5. AMPK inhibits Kv1.5 presumably in part by activation of Nedd4-2 with subsequent clearance of channel protein from the cell membrane.

Copyright © 2012 S. Karger AG, Basel

Florian Lang

Department of Physiology, University of Tübingen
Gmelinstr. 5, D-72076 Tübingen (Germany)
Tel. +49-70712972194, Fax +49-7071295618
E-Mail florian.lang@uni-tuebingen.de

Introduction

The voltage-gated K⁺ channel Kv1.5 contributes to the maintenance of the cell membrane potential in a wide variety of tissues, such as pancreatic β -cells [1-3], brain [4], macrophages [5], dendritic cells [6, 7], heart [4, 8-11], skeletal muscle [12], as well as smooth muscles in vessels [13, 14], intestine [15], and airways [16]. In the heart, Kv1.5 generates the ultra-rapid delayed rectifier current (I_{Kur}) [17] and thus contributes to the repolarization of the cardiac action potential [18-20]. Kv1.5 is highly expressed in atrial myocytes [21] and loss-of-function Kv1.5 mutations may cause atrial fibrillation [22]. Kv1.5 is thus an attractive target for the treatment of atrial arrhythmias [13, 23-32]. Kv1.5 is further expressed in several tumor cells and participates in the regulation of adhesion, proliferation and sensitivity to apoptosis [33-39]. Thus, Kv1.5 has been considered a potential target against tumor growth [40].

Kv1.5 activity is downregulated by hypoxia, an effect at least partially explained by 15-HETE formation [41]. Hypoxia is further expected to stimulate the AMP-activated protein kinase (AMPK), a kinase sensitive to cytosolic AMP/ATP concentration ratio and thus the energy status of the cell [42, 43]. AMPK inhibits energy-utilizing mechanisms, including protein synthesis, gluconeogenesis and lipogenesis [43-45] and stimulates energy providing mechanisms, such as cellular glucose uptake, glycolysis, fatty acid oxidation and enzymes required for ATP production [43, 44, 46-66]. Thus, AMPK restores cellular ATP levels [45] and protects against cell death during energy depletion [45, 67, 68].

Effects of AMPK include downregulation of ion channels, such as the epithelial Na⁺ channel ENaC [69-72], the inwardly rectifying K⁺ channel Kir2.1 [73] and the outwardly rectifying K⁺ channel KCNQ1/KCNE1 [74]. AMPK is at least partially effective by stimulation of the ubiquitin ligase Nedd4-2 [70]. The ubiquitin ligase labels channel and carrier proteins for subsequent proteasomal degradation [75]. Channel proteins targeted by Nedd4-2 include the Na⁺ channels ENaC [75, 76] and Nav1.6 [77], the Ca²⁺ channels Orai [78] and TRPV6 [79], as well as the K⁺ channels KCNE1/KCNQ1 [74, 80, 81], KCNQ2/3 and KCNQ3/5 [82], HERG [83] Kir2.1 [73], Kv4.3 [84], Kv7.1 [85] and Kv1.5 [86]. Carriers targeted by Nedd4-2 include the Na⁺/Cl⁻ Cotransporter NCC [87], the phosphate transporter NaPiIb [88], the glutamate transporter EAAT2 [89], the glucose transporter SGLT1 [90], and the myo-inositol transporter SMIT1 [91].

The present study explored whether Kv1.5 K⁺ channels are regulated by AMPK. To this end, voltage-gated current was determined in *Xenopus* oocytes expressing Kv1.5 with or without additional coexpression of wild-type, of constitutively active or of inactive mutant AMPK. Additional experiments were performed to elucidate whether AMPK influences Kv1.5 K⁺ channel protein abundance in the cell membrane and whether Kv1.5-mediated currents are modified by the ubiquitin ligase Nedd4-2.

Materials and Methods

Constructs

For generation of cRNA, constructs were used encoding wild-type human Kv1.5 [92], Kv1.5-HA containing an extracellular hemagglutinin epitope [93], wild-type human AMPK α 1-HA, AMPK β 1-Flag, AMPK γ 1-HA [94], constitutively active AMPK γ 1^{R70Q}-HA [95], kinase dead mutant AMPK α 1^{K45R}-HA [72], and wild-type human Nedd4-2 [86]. The constructs were used for the generation of cRNA as described previously [96].

Voltage clamp in *Xenopus* oocytes

Xenopus oocytes were prepared as previously described [97-99]. cRNA encoding Kv1.5 (2.5 ng) was injected with or without 4.6 ng of cRNA encoding either AMPK α 1-HA + AMPK β 1-Flag + AMPK γ 1-HA (AMPK^{WT}), or AMPK α 1-HA + AMPK β 1-Flag + AMPK γ 1^{R70Q}-HA (AMPK ^{γ R70Q}) or AMPK α 1^{K45R}-HA + AMPK β 1-Flag + AMPK γ 1-HA (AMPK ^{α K45R}) with or without 10 ng cRNA encoding Nedd4-2 on the day of preparation of the *Xenopus* oocytes. All experiments were performed at room temperature 3 days after injection. In two-

electrode voltage-clamp experiments Kv1.5 channel currents were elicited every 20 s with 2 s pulses from -80 mV to +50 mV applied from a holding potential of -100 mV. Pulses were applied in 10 mV increments. The data were filtered at 1 kHz and recorded with a Digidata 1322A A/D-D/A converter and Chart V4.2 software for data acquisition and analysis (Axon Instruments) [100]. The analysis of the data was performed with Clampfit 9.01 (Axon Instruments) software.

Detection of Kv1.5 cell surface expression by chemiluminescence

Oocytes expressing HA-tagged Kv1.5 were incubated with 1 µg/ml primary rat monoclonal anti-HA antibody (clone 3 F10; Boehringer, Biberach, Germany) and 2 µg/ml secondary, peroxidase-conjugated goat anti-rat antibody (Cell Signaling, Danvers, MA, USA). Individual oocytes were placed in 96-well plates with 20 µl of SuperSignal ELISA Femto Maximum Sensitivity Substrate (Pierce, Rockford, IL). The chemiluminescence of single oocytes was quantified in a luminometer (WalterWallac2 plate reader; Perkin Elmer, Jügesheim, Germany) by integrating the signal over a period of 1 s. Results display normalized arbitrary light units, which are proportional to the detector voltage.

Immunocytochemistry and confocal microscopy

After 4% paraformaldehyde fixation for at least 12 hours, oocytes were cryoprotected in 30% sucrose, frozen in mounting medium and placed on a cryostat. Sections were collected at a thickness of 8 µm on coated slides and stored at -20°C. For immunostaining, sections were dehydrated at room temperature, fixed in acetone/methanol (1:1) for 15 min at room temperature, washed in PBS and blocked for 1 hour in 1% bovine serum albumin in PBS. The primary antibody used was rat monoclonal anti-HA antibody (diluted 1:100; clone 3 F10; Boehringer, Biberach, Germany). Incubation was performed in a moist chamber overnight at 4°C. The binding of primary antibody was visualized with an anti-rat Alexa488-conjugated antibody (diluted 1:200; Invitrogen, Carlsbad, CA). Next, oocytes were analyzed by a fluorescence laser scanning microscope (LSM 510; CarlZeiss MicroImaging, Göttingen, Germany) with A-Plan 40x/1.2W DICIII. Brightness and contrast settings were kept constant during imaging of all oocytes in each injection series.

Statistical analysis

Data are provided as means ± SEM, n represents the number of experiments. All experiments were repeated with at least three batches of oocytes; in all repetitions qualitatively similar data were obtained. Data were tested for significance using ANOVA and results with $p < 0.05$ were considered statistically significant.

Results

In *Xenopus* oocytes expressing Kv1.5, but not in water-injected *Xenopus* oocytes, depolarization triggered an outwardly directed current (I_{Kv}), which was significantly decreased by coexpression of wild-type AMPK^{WT} (AMPK α 1 + AMPK β 1 + AMPK γ 1). At +50 mV, I_{Kv} was in average $28.5 \pm 4.8\%$ ($n = 12-15$) lower in *Xenopus* oocytes expressing Kv1.5 together with wild-type AMPK than in *Xenopus* oocytes expressing Kv1.5 alone (Fig. 1B). Fig. 1C illustrates the IV curve in *Xenopus* oocytes expressing Kv1.5 alone and in *Xenopus* oocytes expressing Kv1.5 together with wild-type AMPK. At each holding voltage, the current was lower in *Xenopus* oocytes expressing Kv1.5 together with wild-type AMPK than in *Xenopus* oocytes expressing Kv1.5 alone.

As illustrated in Fig. 2, coexpression of the constitutively active AMPK ^{γ R70Q} (AMPK α 1 + AMPK β 1 + AMPK γ 1^{R70Q}) similarly decreased the outward current in Kv1.5-expressing *Xenopus* oocytes. In contrast, the inactive mutant AMPK ^{α K45R} (AMPK α 1^{K45R} + AMPK β 1 + AMPK γ 1) did not significantly modify I_{Kv} . Accordingly, AMPK kinase activity was required for the inhibitory effect on Kv1.5 currents (Fig. 2).

Additional experiments were performed to test whether Kv1.5 is regulated by the AMPK-sensitive ubiquitin ligase Nedd4-2. To this end, Kv1.5 was expressed with or without wild-type Nedd4-2. As shown in Fig. 3, Nedd4-2 indeed decreased Kv1.5-dependent currents (Fig. 3).

Fig. 1. Coexpression of AMPK decreased K⁺ current in Kv1.5-expressing *Xenopus* oocytes. A. Original tracings of the current following depolarization from -80 to +50 mV in *Xenopus* oocytes injected with water (a), expressing Kv1.5 without (b) or with additional coexpression of wild-type AMPK (c). B. Arithmetic means $\pm$ SEM (n = 12-15) of K⁺ current at +50 mV in *Xenopus* oocytes injected with water (H₂O, dotted bar), or expressing Kv1.5 without (white bar) or with additional coexpression of wild-type AMPK (AMPK^{WT}, dark grey bar). *** (p<0.001)

indicates statistically significant difference from the value obtained in *Xenopus* oocytes expressing Kv1.5 alone. C. Current as a function of voltage in *Xenopus* oocytes injected with water (H₂O, closed squares), or expressing Kv1.5 without (Kv1.5, open circles) or with additional coexpression of wild-type AMPK (Kv1.5 + AMPK, closed circles).

Fig. 2. Constitutively active AMPK^{R70Q} but not inactive mutant AMPK ^{α K45R} decreased K⁺ current in Kv1.5-expressing *Xenopus* oocytes. A. Original tracings of the current following depolarization from -80 to +50 mV in *Xenopus* oocytes injected with water (a) or expressing Kv1.5 without (b) or with additional coexpression of inactive mutant AMPK ^{α K45R} (c) or of constitutively active AMPK^{R70Q} (d). B. Arithmetic means $\pm$ SEM (n = 12-19) of the normalized outwardly rectifying K⁺ current at +50 mV in *Xenopus* oocytes injected with water (dotted

bar), expressing Kv1.5 without (white bar) or with additional coexpression of inactive mutant AMPK ^{α K45R} (AMPK ^{α K45R} light grey bar) or of constitutively active AMPK^{R70Q} (AMPK^{R70Q}, black bar). *, *** (p<0.05, p<0.001) indicate statistically significant difference from the value obtained in *Xenopus* oocytes expressing Kv1.5 alone. C. Current as a function of voltage in *Xenopus* oocytes expressing Kv1.5 without (Kv1.5, open circles) or with additional coexpression of inactive mutant AMPK ^{α K45R} (Kv1.5 + AMPK ^{α K45R}, closed triangles) or of constitutively active AMPK^{R70Q} (Kv1.5 + AMPK^{R70Q}, closed rombi). For comparison, water injected oocytes (H₂O, closed squares) are shown.

Fig. 4. Coexpression of AMPK decreased the Kv1.5-HA protein abundance within the plasma membrane of *Xenopus* oocytes. A. Confocal images reflecting Kv1.5-HA membrane protein abundance in *Xenopus* oocytes injected with water (H₂O), expressing Kv1.5-HA without (Kv1.5-HA) or with additional coexpression of wild-type AMPK (Kv1.5-HA + AMPK^{WT}), of inactive mutant AMPK ^{α K45R} (Kv1.5-HA + AMPK ^{α K45R}) or of constitutively active AMPK ^{γ R70Q} (Kv1.5-HA + AMPK ^{γ R70Q}). B. Arithmetic means $\pm$ SEM (n = 48-60) of Kv1.5-HA protein abundance in the plasma membrane of *Xenopus* oocytes injected with water (H₂O, dotted bar), expressing Kv1.5-HA without (white bar) or with additional coexpression of wild-type AMPK^{WT} (AMPK^{WT}, dark grey bar), of inactive mutant AMPK ^{α K45R} (AMPK ^{α K45R}, light grey bar) or of constitutively active AMPK ^{γ R70Q} (AMPK ^{γ R70Q}, black bar). *** (p<0.001) indicates statistically significant difference from respective value obtained in oocytes expressing Kv1.5-HA alone.

The observed decrease of Kv1.5 currents could reflect reduced channel activity or a decline of channel protein abundance in the cell membrane. In order to estimate protein abundance of Kv1.5 channels, chemiluminescence was employed using an HA-tagged Kv1.5 construct. Fig. 4B illustrates the chemiluminescence of *Xenopus* oocytes injected with water and in oocytes expressing Kv1.5-HA alone or together with wild-type AMPK^{WT}, with inactive

mutant AMPK α K45R or with constitutively active AMPK γ R70Q. As a result, the cell surface expression of the Kv1.5-HA channel protein in Kv1.5-HA expressing *Xenopus* oocytes was significantly decreased following coexpression of constitutively active AMPK γ R70Q, but not following coexpression of inactive mutant AMPK α K45R. Coexpression of wild-type AMPK tended to decrease Kv1.5-HA protein abundance in the cell membrane, an effect, however, not reaching statistical significance. The effect of AMPK α R70Q on chemiluminescence was seemingly larger than the effect of AMPK γ R70Q on the current. However, the experiments have been done in different batches of oocytes precluding safe conclusions from comparisons of current and chemiluminescence. In any case, AMPK downregulated both, current and channel protein in the cell membrane. Confocal microscopy of Kv1.5 expressing oocytes again revealed decreased channel protein abundance following coexpression of AMPK thus confirming the results obtained with chemiluminescence (Fig. 4A).

Discussion

The present study reveals a novel function of AMP-activated protein kinase, i.e. the regulation of the voltage-gated K⁺ channel Kv1.5. The AMP-activated protein kinase decreases the channel protein abundance in the cell membrane. AMPK may thus decrease K⁺ conductance and repolarization.

The effect of AMPK is mimicked by coexpression of the ubiquitin ligase Nedd4-2. According to previous observations [70], AMPK phosphorylates Nedd4-2 thus fostering the interaction of the ubiquitin ligase with the epithelial Na⁺ channel ENaC [69-71]. As AMPK, Nedd4-2 and Kv1.5 are widely expressed, the AMPK and Nedd4-2 sensitivity of endogenous Kv1.5 may play a role in the regulation of a variety of cells. Moreover, Nedd4-2 may similarly contribute to the AMPK induced down-regulation of the inwardly rectifying K⁺ channel Kir2.1 [73] and the outwardly rectifying K⁺ channel KCNQ1/KCNE1 [74].

In contrast to its effect on ENaC, Kir2.1, KCNQ1/KCNE1 and Kv1.5, AMPK stimulates the activity of the facilitative glucose carriers GLUT1, GLUT2, GLUT3 and GLUT4 and thus increases the cellular uptake of glucose [47, 50, 53-58, 60, 63-65]. Stimulation of cellular glucose uptake provides substrate, which is subsequently utilized by AMPK stimulated glycolysis [43, 44]. AMPK further enhances ATP generation by stimulation of fatty acid oxidation and expression of enzymes required for ATP production [43, 44].

The inhibitory effect of AMPK on K⁺ channels is expected to depolarize the cell membrane with decrease of the driving force for electrogenic HCO₃⁻ exit leading to cytosolic alkalinization, which enhances the flux through glycolysis [101]. The alkalinization inhibits Na⁺/H⁺ exchangers [102], which curtails Na⁺ entry and thus decreases the requirement for energy-consuming Na⁺ extrusion by the Na⁺/K⁺ ATPase [102]. On the other hand, AMPK stimulates the Na⁺/H⁺ exchanger [103], which contributes to cytosolic alkalinization. Inhibition of K⁺ channels is further expected to limit cellular K⁺ loss during impaired function of Na⁺/K⁺ ATPase in energy-depleted cells. Cellular K⁺ loss is well known to stimulate suicidal cell death or apoptosis [104-108]. Apoptosis is further sensitive to cytosolic pH and fostered by cytosolic acidification [109].

The depolarization is, however, expected to foster Cl⁻ entry, which may eventually lead to deleterious cell swelling [110, 111]. In the heart, inhibition of K⁺ channels compromises maintenance of the cell membrane potential and repolarization thus jeopardizing cardiac function. Thus, inhibition of K⁺ channels in energy depletion may be considered a double edged sword.

AMPK is not only activated by energy depletion, but in addition by an increase in cytosolic Ca²⁺ activity [42], by a decrease of O₂ levels [112] and by exposure to nitric oxide [113]. Thus, AMPK may mediate effects of Ca²⁺ activity, hypoxia and nitric oxide on Kv1.5 activity.

In conclusion, the present observations disclose an inhibitory effect of the AMP-activated kinase on voltage gated K⁺ channels Kv1.5. The effect presumably participates in

the regulation of Kv1.5 channel activity during energy depletion, hypoxia, excessive cytosolic Ca^{2+} activity, and exposure to nitric oxide.

Acknowledgements

This study was supported by the Deutsche Forschungsgemeinschaft (GK 1302). The authors acknowledge the technical assistance of E. Faber. The manuscript was meticulously prepared by L. Subasic and S. Rube. The authors are indebted to Scott Fraser and Bruce E. Kemp for providing the AMPK constructs.

Declaration of Interests

The authors of this manuscript declare that they have neither financial nor any other conflicts of interests.

Reference

- MacDonald PE, Wheeler MB: Voltage-dependent K^+ channels in pancreatic beta cells: role, regulation and potential as therapeutic targets. *Diabetologia* 2003;46:1046-1062.
- Roe MW, Worley JF, III, Mittal AA, Kuznetsov A, DasGupta S, Mertz RJ, Witherspoon SM, III, Blair N, Lancaster ME, McIntyre MS, Shehee WR, Dukes ID, Philipson LH: Expression and function of pancreatic beta-cell delayed rectifier K^+ channels. Role in stimulus-secretion coupling. *J Biol Chem* 1996;271:32241-32246.
- Su J, Yu H, Lenka N, Hescheler J, Ullrich S: The expression and regulation of depolarization-activated K^+ channels in the insulin-secreting cell line INS-1. *Pflugers Arch* 2001;442:49-56.
- Fedida D, Eldstrom J, Hesketh JC, Lamorgese M, Castel L, Steele DF, Van Wagoner DR: Kv1.5 is an important component of repolarizing K^+ current in canine atrial myocytes. *Circ Res* 2003;93:744-751.
- Vicente R, Escalada A, Villalonga N, Texido L, Roura-Ferrer M, Martin-Satue M, Lopez-Iglesias C, Soler C, Solsona C, Tamkun MM, Felipe A: Association of Kv1.5 and Kv1.3 contributes to the major voltage-dependent K^+ channel in macrophages. *J Biol Chem* 2006;281:37675-37685.
- Matzner N, Zemtsova IM, Nguyen TX, Duzsenko M, Shumilina E, Lang F: Ion channels modulating mouse dendritic cell functions. *J Immunol* 2008;181:6803-6809.
- Tyan L, Sopjani M, Dermaku-Sopjani M, Schmid E, Yang W, Xuan NT, Shumilina E, Lang F: Inhibition of voltage-gated K^+ channels in dendritic cells by rapamycin. *Am J Physiol Cell Physiol* 2010;299:C1379-C1385.
- Almquist J, Wallman M, Jacobson I, Jirstrand M: Modeling the effect of Kv1.5 block on the canine action potential. *Biophys J* 2010;99:2726-2736.
- Bielanska J, Hernandez-Losa J, Moline T, Somoza R, Ramon YC, Condom E, Ferreres JC, Felipe A: Voltage-dependent potassium channels Kv1.3 and Kv1.5 in human fetus. *Cell Physiol Biochem* 2010;26:219-226.
- Gaborit N, Le Bouter S, Szuts V, Varro A, Escande D, Nattel S, Demolombe S: Regional and tissue specific transcript signatures of ion channel genes in the non-diseased human heart. *J Physiol* 2007;582:675-693.
- Grandi E, Pandit SV, Voigt N, Workman AJ, Dobrev D, Jalife J, Bers DM: Human atrial action potential and Ca^{2+} model: sinus rhythm and chronic atrial fibrillation. *Circ Res* 2011;109:1055-1066.
- Kang LS, Kim S, Dominguez JM, Sindler AL, Dick GM, Muller-Delp JM: Aging and muscle fiber type alter K^+ channel contributions to the myogenic response in skeletal muscle arterioles. *J Appl Physiol* 2009;107:389-398.

- 13 Hald BO, Jacobsen JC, Braunstein TH, Inoue R, Ito Y, Sorensen PG, Holstein-Rathlou NH, Jensen LJ: BK(Ca) and K(V) channels limit conducted vasomotor responses in rat mesenteric terminal arterioles. *Pflügers Arch* 2012;463:279-295.
- 14 Sutendra G, Dromparis P, Bonnet S, Haromy A, McMurtry MS, Bleackley RC, Michelakis ED: Pyruvate dehydrogenase inhibition by the inflammatory cytokine TNF α contributes to the pathogenesis of pulmonary arterial hypertension. *J Mol Med (Berl)* 2011;89:771-783.
- 15 Overturf KE, Russell SN, Carl A, Vogalis F, Hart PJ, Hume JR, Sanders KM, Horowitz B: Cloning and characterization of a Kv1.5 delayed rectifier K⁺ channel from vascular and visceral smooth muscles. *Am J Physiol* 1994;267:C1231-C1238.
- 16 Adda S, Fleischmann BK, Freedman BD, Yu M, Hay DW, Kotlikoff MI: Expression and function of voltage-dependent potassium channel genes in human airway smooth muscle. *J Biol Chem* 1996;271:13239-13243.
- 17 Feng J, Wible B, Li GR, Wang Z, Nattel S: Antisense oligodeoxynucleotides directed against Kv1.5 mRNA specifically inhibit ultrarapid delayed rectifier K⁺ current in cultured adult human atrial myocytes. *Circ Res* 1997;80:572-579.
- 18 Brunner M, Kodirov SA, Mitchell GF, Buckett PD, Shibata K, Folco EJ, Baker L, Salama G, Chan DP, Zhou J, Koren G: In vivo gene transfer of Kv1.5 normalizes action potential duration and shortens QT interval in mice with long QT phenotype. *Am J Physiol Heart Circ Physiol* 2003;285:H194-H203.
- 19 Fedida D, Wible B, Wang Z, Fermini B, Faust F, Nattel S, Brown AM: Identity of a novel delayed rectifier current from human heart with a cloned K⁺ channel current. *Circ Res* 1993;73:210-216.
- 20 Snyders DJ, Tamkun MM, Bennett PB: A rapidly activating and slowly inactivating potassium channel cloned from human heart. Functional analysis after stable mammalian cell culture expression. *J Gen Physiol* 1993;101:513-543.
- 21 Nattel S, Yue L, Wang Z: Cardiac ultrarapid delayed rectifiers: a novel potassium current family of functional similarity and molecular diversity. *Cell Physiol Biochem* 1999;9:217-226.
- 22 Olson TM, Alekseev AE, Liu XK, Park S, Zingman LV, Bienengraeber M, Sattiraju S, Ballew JD, Jahangir A, Terzic A: Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation. *Hum Mol Genet* 2006;15:2185-2191.
- 23 Billman GE: Vernakalant, a mixed sodium and potassium ion channel antagonist that blocks K(v)1.5 channels, for the potential treatment of atrial fibrillation. *Curr Opin Investig Drugs* 2010;11:1048-1058.
- 24 Eun JS, Kim KS, Kim HN, Park SA, Ma TZ, Lee KA, Kim DK, Kim HK, Kim IS, Jung YH, Zee OP, Yoo DJ, Kwak YG: Synthesis of psoralen derivatives and their blocking effect of hKv1.5 channel. *Arch Pharm Res* 2007;30:155-160.
- 25 Friederich P, Pfizenmayer H: The novel Kv1.5 channel blocker vernakalant for successful treatment of new-onset atrial fibrillation in a critically ill abdominal surgical patient. *Br J Anaesth* 2011;107:644-645.
- 26 Lagrutta A, Wang J, Fermini B, Salata JJ: Novel, potent inhibitors of human Kv1.5 K⁺ channels and ultrarapidly activating delayed rectifier potassium current. *J Pharmacol Exp Ther* 2006;317:1054-1063.
- 27 Peukert S, Brendel J, Pirard B, Strubing C, Kleemann HW, Bohme T, Hemmerle H: Pharmacophore-based search, synthesis, and biological evaluation of anthranilic amides as novel blockers of the Kv1.5 channel. *Bioorg Med Chem Lett* 2004;14:2823-2827.
- 28 Schumacher SM, McEwen DP, Zhang L, Arendt KL, Van Genderen KM, Martens JR: Antiarrhythmic drug-induced internalization of the atrial-specific K⁺ channel kv1.5. *Circ Res* 2009;104:1390-1398.
- 29 Strutz-Seeböhm N, Gutcher I, Decher N, Steinmeyer K, Lang F, Seeböhm G: Comparison of potent Kv1.5 potassium channel inhibitors reveals the molecular basis for blocking kinetics and binding mode. *Cell Physiol Biochem* 2007;20:791-800.
- 30 Tamargo J, Caballero R, Gomez R, Delpon E: I(Kur)/Kv1.5 channel blockers for the treatment of atrial fibrillation. *Expert Opin Investig Drugs* 2009;18:399-416.
- 31 Tian D, Frishman WH: Vernakalant: a new drug to treat patients with acute onset atrial fibrillation. *Cardiol Rev* 2011;19:41-44.
- 32 Yang Q, Wang X, Du L, Li M, You Q: Drug discoveries towards Kv1.5 potassium channel. *Curr Top Med Chem* 2009;9:339-347.
- 33 Archer SL, Gomberg-Maitland M, Maitland ML, Rich S, Garcia JG, Weir EK: Mitochondrial metabolism, redox signaling, and fusion: a mitochondria-ROS-HIF-1 α -Kv1.5 O₂-sensing pathway at the intersection of pulmonary hypertension and cancer. *Am J Physiol Heart Circ Physiol* 2008;294:H570-H578.

- 34 Arvind S, Arivazhagan A, Santosh V, Chandramouli BA: Differential expression of a novel voltage gated potassium channel - Kv 1.5 in astrocytomas and its impact on prognosis in glioblastoma. *Br J Neurosurg* 2012;26:16-20.
- 35 Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, Lee CT, Lopaschuk GD, Puttagunta L, Bonnet S, Harry G, Hashimoto K, Porter CJ, Andrade MA, Thebaud B, Michelakis ED: A mitochondria-K⁺ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. *Cancer Cell* 2007;11:37-51.
- 36 Han Y, Shi Y, Han Z, Sun L, Fan D: Detection of potassium currents and regulation of multidrug resistance by potassium channels in human gastric cancer cells. *Cell Biol Int* 2007;31:741-747.
- 37 Ousingsawat J, Spitzner M, Puntheeranurak S, Terracciano L, Tornillo L, Bubendorf L, Kunzelmann K, Schreiber R: Expression of voltage-gated potassium channels in human and mouse colonic carcinoma. *Clin Cancer Res* 2007;13:824-831.
- 38 Preussat K, Beetz C, Schrey M, Kraft R, Wolf S, Kalff R, Patt S: Expression of voltage-gated potassium channels Kv1.3 and Kv1.5 in human gliomas. *Neurosci Lett* 2003;346:33-36.
- 39 Zhou Q, Kwan HY, Chan HC, Jiang JL, Tam SC, Yao X: Blockage of voltage-gated K⁺ channels inhibits adhesion and proliferation of hepatocarcinoma cells. *Int J Mol Med* 2003;11:261-266.
- 40 Felipe A, Bielanska J, Comes N, Vallejo A, Roig S, Ramon YC, Condom E, Hernandez-Losa J, Ferreres JC: Targeting the Voltage-Dependent K⁺ Channels Kv1.3 and Kv1.5 as Tumor Biomarkers for Cancer Detection and Prevention. *Curr Med Chem* 2012;19:661-674.
- 41 Chu X, Tang X, Guo L, Bao H, Zhang S, Zhang J, Zhu D: Hypoxia suppresses KV1.5 channel expression through endogenous 15-HETE in rat pulmonary artery. *Prostaglandins Other Lipid Mediat* 2009;88:42-50.
- 42 Towler MC, Hardie DG: AMP-activated protein kinase in metabolic control and insulin signaling. *Circ Res* 2007;100:328-341.
- 43 Winder WW, Thomson DM: Cellular energy sensing and signaling by AMP-activated protein kinase. *Cell Biochem Biophys* 2007;47:332-347.
- 44 Carling D: The role of the AMP-activated protein kinase in the regulation of energy homeostasis. *Novartis Found Symp* 2007;286:72-81.
- 45 McGee SL, Hargreaves M: AMPK and transcriptional regulation. *Front Biosci* 2008;13:3022-3033.
- 46 Breen DM, Sanli T, Giacca A, Tsiani E: Stimulation of muscle cell glucose uptake by resveratrol through sirtuins and AMPK. *Biochem Biophys Res Commun* 2008;374:117-122.
- 47 Guan F, Yu B, Qi GX, Hu J, Zeng DY, Luo J: Chemical hypoxia-induced glucose transporter-4 translocation in neonatal rat cardiomyocytes. *Arch Med Res* 2008;39:52-60.
- 48 Horie T, Ono K, Nagao K, Nishi H, Kinoshita M, Kawamura T, Wada H, Shimatsu A, Kita T, Hasegawa K: Oxidative stress induces GLUT4 translocation by activation of PI3-K/Akt and dual AMPK kinase in cardiac myocytes. *J Cell Physiol* 2008;215:733-742.
- 49 Jensen TE, Rose AJ, Hellsten Y, Wojtaszewski JF, Richter EA: Caffeine-induced Ca²⁺ release increases AMPK-dependent glucose uptake in rodent soleus muscle. *Am J Physiol Endocrinol Metab* 2007;293:E286-E292.
- 50 Jessen N, Pold R, Buhl ES, Jensen LS, Schmitz O, Lund S: Effects of AICAR and exercise on insulin-stimulated glucose uptake, signaling, and GLUT-4 content in rat muscles. *J Appl Physiol* 2003;94:1373-1379.
- 51 Kim T, Davis J, Zhang AJ, He X, Mathews ST: Curcumin activates AMPK and suppresses gluconeogenic gene expression in hepatoma cells. *Biochem Biophys Res Commun* 2009;388:377-382.
- 52 Kohan AB, Talukdar I, Walsh CM, Salati LM: A role for AMPK in the inhibition of glucose-6-phosphate dehydrogenase by polyunsaturated fatty acids. *Biochem Biophys Res Commun* 2009;388:117-121.
- 53 Lei B, Matsuo K, Labinskyy V, Sharma N, Chandler MP, Ahn A, Hintze TH, Stanley WC, Recchia FA: Exogenous nitric oxide reduces glucose transporters translocation and lactate production in ischemic myocardium in vivo. *Proc Natl Acad Sci U S A* 2005;102:6966-6971.
- 54 Li J, Hu X, Selvakumar P, Russell RR, III, Cushman SW, Holman GD, Young LH: Role of the nitric oxide pathway in AMPK-mediated glucose uptake and GLUT4 translocation in heart muscle. *Am J Physiol Endocrinol Metab* 2004;287:E834-E841.
- 55 Luiken JJ, Coort SL, Koonen DP, van der Horst DJ, Bonen A, Zorzano A, Glatz JF: Regulation of cardiac long-chain fatty acid and glucose uptake by translocation of substrate transporters. *Pflugers Arch* 2004;448:1-15.
- 56 MacLean PS, Zheng D, Jones JP, Olson AL, Dohm GL: Exercise-induced transcription of the muscle glucose transporter (GLUT 4) gene. *Biochem Biophys Res Commun* 2002;292:409-414.

- 57 Natsuzaka M, Ozasa M, Darmanin S, Miyamoto M, Kondo S, Kamada S, Shindoh M, Higashino F, Suhara W, Koide H, Aita K, Nakagawa K, Kondo T, Asaka M, Okada F, Kobayashi M: Synergistic up-regulation of Hexokinase-2, glucose transporters and angiogenic factors in pancreatic cancer cells by glucose deprivation and hypoxia. *Exp Cell Res* 2007;313:3337-3348.
- 58 Ojuka EO, Nolte LA, Holloszy JO: Increased expression of GLUT-4 and hexokinase in rat epitrochlearis muscles exposed to AICAR in vitro. *J Appl Physiol* 2000;88:1072-1075.
- 59 Ota S, Horigome K, Ishii T, Nakai M, Hayashi K, Kawamura T, Kishino A, Taiji M, Kimura T: Metformin suppresses glucose-6-phosphatase expression by a complex I inhibition and AMPK activation-independent mechanism. *Biochem Biophys Res Commun* 2009;388:311-316.
- 60 Park S, Scheffler TL, Gunawan AM, Shi H, Zeng C, Hannon KM, Grant AL, Gerrard DE: Chronic elevated calcium blocks AMPK-induced GLUT-4 expression in skeletal muscle. *Am J Physiol Cell Physiol* 2009;296:C106-C115.
- 61 Song H, Guan Y, Zhang L, Li K, Dong C: SPARC interacts with AMPK and regulates GLUT4 expression. *Biochem Biophys Res Commun* 2010;396:961-966.
- 62 Sopjani M, Bhavsar SK, Fraser S, Kemp BE, Föller M, Lang F: Regulation of Na⁺-coupled glucose carrier SGLT1 by AMP-activated protein kinase. *Mol Membr Biol* 2010;27:137-144.
- 63 Walker J, Jijon HB, Diaz H, Salehi P, Churchill T, Madsen KL: 5-aminoimidazole-4-carboxamide riboside (AICAR) enhances GLUT2-dependent jejunal glucose transport: a possible role for AMPK. *Biochem J* 2005;385:485-491.
- 64 Winder WW, Holmes BF, Rubink DS, Jensen EB, Chen M, Holloszy JO: Activation of AMP-activated protein kinase increases mitochondrial enzymes in skeletal muscle. *J Appl Physiol* 2000;88:2219-2226.
- 65 Zheng D, MacLean PS, Pohnert SC, Knight JB, Olson AL, Winder WW, Dohm GL: Regulation of muscle GLUT-4 transcription by AMP-activated protein kinase. *J Appl Physiol* 2001;91:1073-1083.
- 66 Zygmunt K, Faubert B, MacNeil J, Tsiani E: Naringenin, a citrus flavonoid, increases muscle cell glucose uptake via AMPK. *Biochem Biophys Res Commun* 2010;398:178-183.
- 67 Foller M, Sopjani M, Koka S, Gu S, Mahmud H, Wang K, Floride E, Schleicher E, Schulz E, Munzel T, Lang F: Regulation of erythrocyte survival by AMP-activated protein kinase. *FASEB J* 2009;23:1072-1080.
- 68 Hardie DG: The AMP-activated protein kinase pathway--new players upstream and downstream. *J Cell Sci* 2004;117:5479-5487.
- 69 Almaca J, Kongsuphol P, Hieke B, Ousingsawat J, Viollet B, Schreiber R, Amaral MD, Kunzelmann K: AMPK controls epithelial Na⁺ channels through Nedd4-2 and causes an epithelial phenotype when mutated. *Pflugers Arch* 2009;458:713-721.
- 70 Bhalla V, Oyster NM, Fitch AC, Wijngaarden MA, Neumann D, Schlattner U, Pearce D, Hallows KR: AMP-activated kinase inhibits the epithelial Na⁺ channel through functional regulation of the ubiquitin ligase Nedd4-2. *J Biol Chem* 2006;281:26159-26169.
- 71 Carattino MD, Edinger RS, Grieser HJ, Wise R, Neumann D, Schlattner U, Johnson JP, Kleyman TR, Hallows KR: Epithelial sodium channel inhibition by AMP-activated protein kinase in oocytes and polarized renal epithelial cells. *J Biol Chem* 2005;280:17608-17616.
- 72 Hallows KR, Kobinger GP, Wilson JM, Witters LA, Foskett JK: Physiological modulation of CFTR activity by AMP-activated protein kinase in polarized T84 cells. *Am J Physiol Cell Physiol* 2003;284:C1297-C1308.
- 73 Alesutan I, Munoz C, Sopjani M, Dermaku-Sopjani M, Michael D, Fraser S, Kemp BE, Seeböhm G, Foller M, Lang F: Inhibition of Kir2.1 (KCNJ2) by the AMP-activated protein kinase. *Biochem Biophys Res Commun* 2011;408:505-510.
- 74 Alesutan IS, Foller M, Sopjani M, Dermaku-Sopjani M, Zelenak C, Frohlich H, Velic A, Fraser S, Kemp BE, Seeböhm G, Volkl H, Lang F: Inhibition of the heterotetrameric K⁺ channel KCNQ1/KCNE1 by the AMP-activated protein kinase. *Molecular Membrane Biology* 2011;28:79-89.
- 75 Rotin D, Staub O: Nedd4-2 and the regulation of epithelial sodium transport. *Front Physiol* 2012;3:212.
- 76 Soundararajan R, Lu M, Pearce D: Organization of the ENaC-regulatory machinery. *Crit Rev Biochem Mol Biol* 2012;47:349-359.
- 77 Gasser A, Cheng X, Gilmore ES, Tyrrell L, Waxman SG, Dib-Hajj SD: Two Nedd4-binding motifs underlie modulation of sodium channel Nav1.6 by p38 MAPK. *J Biol Chem* 2010;285:26149-26161.
- 78 Eylonstein A, Gehring EM, Heise N, Shumilina E, Schmidt S, Sztejn K, Munzer P, Nurbaeva MK, Eichenmüller M, Tyán L, Regel I, Foller M, Kuhl D, Soboloff J, Penner R, Lang F: Stimulation of Ca²⁺-channel Orai1/STIM1 by serum- and glucocorticoid-inducible kinase 1 (SGK1). *FASEB J* 2011;25:2012-2021.

- 79 Zhang W, Na T, Wu G, Jing H, Peng JB: Down-regulation of intestinal apical calcium entry channel TRPV6 by ubiquitin E3 ligase Nedd4-2. *J Biol Chem* 2010;285:36586-36596.
- 80 Alzamora R, Gong F, Rondanino C, Lee JK, Smolak C, Pastor-Soler NM, Hallows KR: AMP-activated protein kinase inhibits KCNQ1 channels through regulation of the ubiquitin ligase Nedd4-2 in renal epithelial cells. *Am J Physiol Renal Physiol* 2010;299:F1308-F1319.
- 81 Krzystanek K, Rasmussen HB, Grunnet M, Staub O, Olesen SP, Abriel H, Jespersen T: Deubiquitylating enzyme USP2 counteracts Nedd4-2-mediated downregulation of KCNQ1 potassium channels. *Heart Rhythm* 2012;9:440-448.
- 82 Schuetz F, Kumar S, Poronnik P, Adams DJ: Regulation of the voltage-gated K⁺ channels KCNQ2/3 and KCNQ3/5 by serum- and glucocorticoid-regulated kinase-1. *Am J Physiol Cell Physiol* 2008;295:C73-C80.
- 83 Guo J, Wang T, Li X, Shallow H, Yang T, Li W, Xu J, Fridman MD, Yang X, Zhang S: Cell surface expression of hERG channels is regulated by caveolin-3 via Nedd4-2. *J Biol Chem* 2012; in press.
- 84 Baltaev R, Strutz-Seeböhm N, Korniyshuk G, Myssina S, Lang F, Seeböhm G: Regulation of cardiac shal-related potassium channel Kv 4.3 by serum- and glucocorticoid-inducible kinase isoforms in *Xenopus* oocytes. *Pflügers Arch* 2005;450:26-33.
- 85 Andersen MN, Krzystanek K, Jespersen T, Olesen SP, Rasmussen HB: AMP-activated protein kinase downregulates Kv7.1 cell surface expression. *Traffic* 2012;13:143-156.
- 86 Boehmer C, Laufer J, Jeyaraj S, Klaus F, Lindner R, Lang F, Palmada M: Modulation of the voltage-gated potassium channel Kv1.5 by the SGK1 protein kinase involves inhibition of channel ubiquitination. *Cell Physiol Biochem* 2008;22:591-600.
- 87 Arroyo JP, Lagnaz D, Ronzaud C, Vazquez N, Ko BS, Moddes L, Ruffieux-Daidie D, Hausel P, Koesters R, Yang B, Stokes JB, Hoover RS, Gamba G, Staub O: Nedd4-2 modulates renal Na⁺-Cl⁻ cotransporter via the aldosterone-SGK1-Nedd4-2 pathway. *J Am Soc Nephrol* 2011;22:1707-1719.
- 88 Palmada M, Dieter M, Speil A, Bohmer C, Mack AF, Wagner HJ, Klingel K, Kandolf R, Murer H, Biber J, Closs EI, Lang F: Regulation of intestinal phosphate cotransporter NaPi IIb by ubiquitin ligase Nedd4-2 and by serum- and glucocorticoid-dependent kinase 1. *Am J Physiol Gastrointest Liver Physiol* 2004;287:G143-G150.
- 89 Boehmer C, Palmada M, Rajamanickam J, Schniepp R, Amara S, Lang F: Post-translational regulation of EAAT2 function by co-expressed ubiquitin ligase Nedd4-2 is impacted by SGK kinases. *J Neurochem* 2006;97:911-921.
- 90 Dieter M, Palmada M, Rajamanickam J, Aydin A, Busjahn A, Boehmer C, Luft FC, Lang F: Regulation of glucose transporter SGLT1 by ubiquitin ligase Nedd4-2 and kinases SGK1, SGK3, and PKB. *Obes Res* 2004;12:862-870.
- 91 Klaus F, Palmada M, Lindner R, Laufer J, Jeyaraj S, Lang F, Boehmer C: Up-regulation of hypertonicity-activated myo-inositol transporter SMIT1 by the cell volume-sensitive protein kinase SGK1. *J Physiol* 2008;586:1539-1547.
- 92 Koutsouki E, Lam RS, Seeböhm G, Ureche ON, Ureche L, Baltaev R, Lang F: Modulation of human Kv1.5 channel kinetics by N-cadherin. *Biochem Biophys Res Commun* 2007;363:18-23.
- 93 Munoz C, Tovolli RH, Sopjani M, Alesutan I, Lam RS, Seeböhm G, Foller M, Lang F: Activation of voltage gated K⁺ channel Kv1.5 by beta-catenin. *Biochem Biophys Res Commun* 2012;417:692-696.
- 94 Fraser SA, Gimenez I, Cook N, Jennings I, Katerelos M, Katsis F, Levidiotis V, Kemp BE, Power DA: Regulation of the renal-specific Na⁺-K⁺-2Cl⁻ co-transporter NKCC2 by AMP-activated protein kinase (AMPK). *Biochem J* 2007;405:85-93.
- 95 Hamilton SR, Yao SY, Ingram JC, Hadden DA, Ritzel MW, Gallagher MP, Henderson PJ, Cass CE, Young JD, Baldwin SA: Subcellular distribution and membrane topology of the mammalian concentrative Na⁺-nucleoside cotransporter rCNT1. *J Biol Chem* 2001;276:27981-27988.
- 96 Mohamed MR, Alesutan I, Foller M, Sopjani M, Bress A, Baur M, Salama RH, Bakr MS, Mohamed MA, Blin N, Lang F, Pfister M: Functional analysis of a novel I71N mutation in the GJB2 gene among Southern Egyptians causing autosomal recessive hearing loss. *Cell Physiol Biochem* 2010;26:959-966.
- 97 Dermaku-Sopjani M, Sopjani M, Saxena A, Shojaiefard M, Bogatikov E, Alesutan I, Eichenmüller M, Lang F: Downregulation of NaPi-IIa and NaPi-IIb Na-coupled phosphate transporters by coexpression of Klotho. *Cell Physiol Biochem* 2011;28:251-258.

- 98 Menniti M, Iuliano R, Foller M, Sopjani M, Alesutan I, Mariggio S, Nofziger C, Perri AM, Amato R, Blazer-Yost B, Corda D, Lang F, Perrotti N: 60kDa lysophospholipase, a new Sgk1 molecular partner involved in the regulation of ENaC. *Cell Physiol Biochem* 2010;26:587-596.
- 99 Bohmer C, Sopjani M, Klaus F, Lindner R, Laufer J, Jeyaraj S, Lang F, Palmada M: The serum and glucocorticoid inducible kinases SGK1-3 stimulate the neutral amino acid transporter SLC6A19. *Cell Physiol Biochem* 2010;25:723-732.
- 100 Eckey K, Strutz-Seeböhm N, Katz G, Fuhrmann G, Henrion U, Pott L, Linke WA, Arad M, Lang F, Seeböhm G: Modulation of human ether a gogo related channels by CASQ2 contributes to etiology of catecholaminergic polymorphic ventricular tachycardia (CPVT). *Cell Physiol Biochem* 2010;26:503-512.
- 101 Boiteux A, Hess B: Design of glycolysis. *Philos Trans R Soc Lond B Biol Sci* 1981;293:5-22.
- 102 Lang F, Rehwald W: Potassium channels in renal epithelial transport regulation. *Physiol Rev* 1992;72:1-32.
- 103 Rotte A, Pasham V, Eichenmüller M, Bhandaru M, Foller M, Lang F: Upregulation of Na⁺/H⁺ exchanger by the AMP-activated protein kinase. *Biochem Biophys Res Commun* 2010;398:677-682.
- 104 Becker S, Reinehr R, Graf D, vom DS, Haussinger D: Hydrophobic bile salts induce hepatocyte shrinkage via NADPH oxidase activation. *Cell Physiol Biochem* 2007;19:89-98.
- 105 Bortner CD, Cidlowski JA: The role of apoptotic volume decrease and ionic homeostasis in the activation and repression of apoptosis. *Pflugers Arch* 2004;448:313-318.
- 106 Foller M, Kasinathan RS, Duranton C, Wieder T, Huber SM, Lang F: PGE2-induced apoptotic cell death in K562 human leukaemia cells. *Cell Physiol Biochem* 2006;17:201-210.
- 107 Schneider J, Nicolay JP, Foller M, Wieder T, Lang F: Suicidal erythrocyte death following cellular K⁺ loss. *Cell Physiol Biochem* 2007;20:35-44.
- 108 Shimizu T, Wehner F, Okada Y: Inhibition of hypertonicity-induced cation channels sensitizes HeLa cells to shrinkage-induced apoptosis. *Cell Physiol Biochem* 2006;18:295-302.
- 109 Lupescu A, Geiger C, Zahir N, Aberle S, Lang PA, Kramer S, Wesselborg S, Kandolf R, Foller M, Lang F, Bock CT: Inhibition of Na⁺/H⁺ exchanger activity by parvovirus B19 protein NS1. *Cell Physiol Biochem* 2009;23:211-220.
- 110 Lang F, Messner G, Rehwald W: Electrophysiology of sodium-coupled transport in proximal renal tubules. *Am J Physiol* 1986;250:F953-F962.
- 111 Lang F, Busch GL, Ritter M, Volkl H, Waldegger S, Gulbins E, Haussinger D: Functional significance of cell volume regulatory mechanisms. *Physiol Rev* 1998;78:247-306.
- 112 Evans AM, Mustard KJ, Wyatt CN, Peers C, Dipp M, Kumar P, Kinnear NP, Hardie DG: Does AMP-activated protein kinase couple inhibition of mitochondrial oxidative phosphorylation by hypoxia to calcium signaling in O₂-sensing cells? *J Biol Chem* 2005;280:41504-41511.
- 113 Lira VA, Soltow QA, Long JH, Betters JL, Sellman JE, Criswell DS: Nitric oxide increases GLUT4 expression and regulates AMPK signaling in skeletal muscle. *Am J Physiol Endocrinol Metab* 2007;293:E1062-E1068.