Regulation of Large Conductance Voltage- and Ca\(^{2+}\)-Activated K\(^+\) Channels by the Janus Kinase JAK3

Jamshed Warsi\(^a\)  Yogesh Singh\(^a\)  Bernat Elvira\(^a\)  Zohreh Hosseinzadeh\(^a,b\)
Florian Lang\(^a\)

\(^a\)Department of Physiology I, University of Tübingen, Tübingen, \(^b\)Institute for Ophthalmic Research Experimental Retinal Prosthetics, University of Tübingen, Tübingen, Germany

Key Words
Oocytes • Voltage clamp • B lymphocytes • Jak3 knockout mice

Abstract

**Background/Aims:** Janus kinase 3 (JAK3), a tyrosine kinase contributing to the regulation of cell proliferation and apoptosis of lymphocytes and tumour cells, has been shown to modify the expression and function of several ion channels and transport proteins. Channels involved in the regulation of cell proliferation include the large conductance voltage- and Ca\(^{2+}\)-activated K\(^+\) channel BK. The present study explored whether JAK3 modifies BK channel protein abundance and current.  

**Methods:** cRNA encoding Ca\(^{2+}\)-insensitive BK channel (BK\(^{M513I+Δ899–903}\)) was injected into *Xenopus* oocytes with or without additional injection of cRNA encoding wild-type JAK3, constitutively active A568V JAK3, or inactive K851A JAK3. Voltage gated K\(^+\) channel activity was measured utilizing dual electrode voltage clamp. Moreover, BK channel protein abundance was determined utilizing flow cytometry in CD19\(^+\) B lymphocyte cell membranes from mice lacking functional JAK3 (jak3\(^{-/-}\)) and corresponding wild-type mice (jak3\(^{+/+}\)).

**Results:** BK activity in BK\(^{M513I+Δ899–903}\) expressing oocytes was slightly but significantly decreased by coexpression of wild-type JAK3 and of A568V JAK3, but not by coexpression of K851A JAK3. The BK channel protein abundance in the cell membrane was significantly higher in jak3\(^{-/-}\) than in jak3\(^{+/+}\) B lymphocytes. The decline of conductance in BK and JAK3 coexpressing oocytes following inhibition of channel protein insertion by brefeldin A (5 µM) was similar in oocytes expressing BK with JAK3 and oocytes expressing BK alone, indicating that JAK3 might slow channel protein insertion into rather than accelerating channel protein retrieval from the cell membrane.  

**Conclusion:** JAK3 is a weak negative regulator of membrane BK protein abundance and activity.

Introduction

Janus kinase 3 (JAK3) is expressed in several tissues including hematopoietic cells [1-3]. The kinase is involved in the signalling of hematopoietic cell cytokine receptors [4-8]. JAK3 has been shown to stimulate cell proliferation and to inhibit apoptosis of lymphocytes and...
tumour cells [9-13]. The gain of function mutation AS72VJAK3 is found in acute megakaryoplastic leukemia cells [14, 15]. Kinase activity of JAK3 is disrupted by replacement of the ATP coordinating lysine in the catalytic subunit with alanine thus yielding the inactive K855JAK3 [16].

Ion channels implicated in the regulation of cell proliferation include the large conductance Ca$^{2+}$-activated K$^+$ channels (maxi K$^+$ channel or BK channels) [17-29]. The present study thus explored, whether JAK3 modifies BK channel activity. To this end, the Ca$^{2+}$-insensitive BK channel (BK$_{M513I+Δ899–903}$) was expressed in Xenopus oocytes without or with additional expression of wild type JAK3, constitutively active AS68VJAK3, or inactive K855JAK3. In those oocytes the voltage gated K$^+$ current was determined utilizing dual electrode voltage clamp. The Xenopus oocytes allow strong expression and functional analysis of human channels with large signal to noise ratio. In order to test the significance of the observations in Xenopus oocytes for the channel regulation in mammalian cells, BK protein abundance was quantified in B lymphocytes isolated from gene targeted mice lacking functional JAK3 (jak3$^{-/-}$) and from corresponding wild-type mice (jak3$^{+/+}$).

### Materials and Methods

#### Ethical Statement

All experiments conform to the ‘European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes’ (Council of Europe No 123, Strasbourg 1985) and were conducted according to the German law for the welfare of animals. All procedures were reviewed and approved by the respective government authority of the state Baden-Württemberg (Regierungspräsidium) prior to the start of the study.

#### Constructs

Constructs encoding mouse Ca$^{2+}$-insensitive BK channel (BK$_{M513I+Δ899–903}$) [29, 30] (kindly provided by J Lingle), and/or mouse wild-type JAK3, inactive K855JAK3 mutant and gain of function AS68VJAK3 mutant [31], were used for generation of the respective cRNA as described previously [32-34].

#### Voltage clamp in Xenopus oocytes

Xenopus oocytes were prepared as previously described [35]. 20 ng cRNA encoding BK and 10 ng of cRNA encoding wild-type JAK3, constitutively active AS68VJAK3 or inactive K855JAK3 kinase were injected on the same day after preparation of the oocytes [36-38]. The oocytes were maintained at 17°C in ND96, a solution containing (in mM): 88.5 NaCl, 2 KCl, 1 MgCl$_2$, 1.8 CaCl$_2$, 5 HEPES, 5 Sodium pyruvate (C$_3$H$_4$NAO$_2$). Gentamicin (100 mg/l), Tetracycline (50 mg/l), Ciprofloxacin (1.6 mg/l), and Theophylline (90 mg/l) were added and pH adjusted to 7.4 [39-41]. Where indicated, brefeldin A (5µM) was added to the respective solutions. The voltage clamp experiments were performed at room temperature 3 days after the first injection. BK channel currents were elicited every 1 s with 1 s pulses from -150 to +190 mV in 2 s increments of 20 mV steps from a holding potential of -60 mV. The data were filtered at 2 kHz and recorded with a Digidata A/D-D/A converter (1322A Axon Instruments) and Clampex 9.2 software for data acquisition and analysis (Axon Instruments) [42-44]. The control superfusate (ND96) contained (in mM): 93.5 NaCl, 2 KCl, 1.8 CaCl$_2$, 1 MgCl$_2$, 2.5 NaOH and 5 HEPES (pH 7.4). The flow rate of the superfusion was approx. 20 ml/min, and a complete exchange of the bath solution was reached within about 10 s [45-47].

#### Mice

CD19$^+$ B cells were used for the BK channel protein expression experiments from 8-12 weeks old female gene-targeted mice lacking functional JAK3 (jak3$^{-/-}$) and in age- and sex-matched wild type mice (jak3$^{+/+}$) [48]. The mice were obtained from the Jackson laboratory (Bar Harbor; ME, USA) and had free access to water and control food (SSniff, Soest, Germany).

#### Flow cytometry of BK channel surface protein abundance in lymphocytes

To stain the CD19$^+$ B cells, spleen and lymph nodes were collected from the mice and macerated using syringe plunger. Cell suspension was centrifuged at 600 x g at 4°C for 5 minutes and cells pellet was...
treated with RBC lysis buffer for 1 minute and then washed for three times with 10% RPMI1640 media. After washing, 1 x 10⁶ cells were stained with 0.5 µg antibodies per sample [original concentrations; 0.2 µg/µl anti-CD4-APC (eBioscience, Germany), anti-CD19-PE (eBioscience, Germany) and BK rabbit anti-mouse antibodies (alomone labs, Israel)] in 50 µl 1 x DPBS (Sigma, Germany) for 30 minutes in dark and washed the cells. After washing the cells 0.2 µl Goat anti-Rabbit IgG-FITC (eBioscience Germany) in 50 µl of 1 x DPBS was added and incubated for another 30 minutes in the dark. Finally, the cells were washed twice with 1 x DPBS and added 200 µl of DPBS. All the washing steps were performed at 600 x g for 5 minutes and at room temperature. Cells were immediately acquired using BD FACSCalibre™ (BD Bioscience, Heidelberg, Germany) flow cytometry and data were analysed by Flowjo (Treestar, USA).

Statistical analysis

Data are provided as means ± SEM, n represents the number of oocytes or of cell preparations investigated. As different batches of oocytes may yield different results, comparisons were always made within a given oocyte batch. All voltage clamp experiments were repeated with at least 3 batches of oocytes; in all repetitions qualitatively similar data were obtained. Data were tested for significance using ANOVA (Tukey test or Kruskal-Wallis test) or t-test, as appropriate. Results with p < 0.05 were considered statistically significant.

Results

The present study addressed a putative influence of Janus activated kinase JAK3 on large conductance voltage- and Ca²⁺-activated K⁺ channel BK. In a first series of experiments cRNA encoding Ca²⁺-insensitive BK channel (BK⁰⁵¹⁳+Δ⁸⁹⁹–⁹⁰³) was injected into Xenopus oocytes with or without additional injection of cRNA encoding JAK3. The voltage gated K⁺ current was determined by dual electrode voltage clamp experiments. As shown in Fig. 1, voltage gated current was negligible in water injected oocytes indicating that oocytes did not express BK alone (b) or expressing BK with additional co-expression of wild-type JAK3 (c). The voltage protocol is shown (not to scale). Currents were activated by depolarization from -150 to +190 mV from a holding potential of -60 mV. (B) Arithmetic means ± SEM (n = 44-57) of the current (I) as a function of the potential difference across the cell membrane (V) in Xenopus oocytes injected with water (white circles) or expressing BK without (white squares) or with (white triangles) additional co-expression of wild-type JAK3. C: Arithmetic means ± SEM (n = 44-57) of the conductance calculated by linear fit of I/V-curves shown in B between 130 mV and 190 mV in Xenopus oocytes injected with water (striped bar), or expressing BK without (white bar) or with (black bar) additional co-expression of wild-type JAK3. * (p<0.05) indicates statistically significant difference from oocytes expressing BK alone.
endogenous voltage gated K⁺ channels. In contrast, large voltage gated K⁺ currents were observed in oocytes injected with cRNA encoding BK<sub>M513I+Δ899–903</sub>. The additional injection of cRNA encoding wild-type JAK3 was followed by a slight but significant decrease of the voltage gated current.

As illustrated in Fig. 2, the effect of wild-type JAK3 was mimicked by the constitutively active <sub>568</sub>A568V JAK3. The additional injection of cRNA encoding wild-type JAK3 was followed by a slight but significant decrease of the voltage gated current. In contrast, coexpression of the inactive JAK3 mutant <sub>511</sub>K851A JAK3 did not significantly modify voltage gated current in BK<sub>M513I+Δ899–903</sub> expressing oocytes.

An additional series of experiments addressed whether JAK3 impacts on BK protein abundance in mammalian hematopoietic cells. To this end, BK channel protein abundance was determined utilizing flow cytometry in the cell membrane of B lymphocytes from mice lacking functional JAK3 (jak3<sup>−/−</sup>) and from corresponding wild-type mice (jak3<sup>+/+</sup>). As illustrated in Fig. 3, the BK channel protein abundance was significantly higher in B lymphocytes from jak3<sup>−/−</sup> mice than in B lymphocytes isolated from jak3<sup>+/+</sup> mice.

JAK3 could decrease BK protein abundance in the cell membrane either by impeding channel protein insertion or by accelerating channel protein retrieval. In order to discriminate between these two possibilities, BK and JAK3 expressing Xenopus oocytes were treated with 5 μM brefeldin A, a substance disrupting insertion of new channel protein into the cell.
membrane. As illustrated in Fig. 4, the decline of conductance in the presence of brefeldin A was similar in oocytes expressing BK together with JAK3 and oocytes expressing BK alone.

**Discussion**

The present study identifies a novel effect of Janus activated kinase JAK3, i.e. the slight but statistically significant down-regulation of the large conductance voltage- and Ca$$^{2+}$$-
activated K+ channel BK. Coexpression of wild type JAK3 or of the gain of function mutant A568V JAK3 decreased the voltage gated current in Xenopus oocytes expressing Ca2+-insensitive BK channel (BK\textsubscript{M513I+Δ899–903}). Moreover, BK channel protein abundance was significantly higher in B lymphocytes from jak3\textsuperscript{-/-} mice than in B lymphocytes from jak3\textsuperscript{+/+} mice. Thus, JAK3 sensitive regulation of BK in oocytes presumably reflects a similar regulation of BK channels in mammalian cells. Apparently, JAK3 is at least in part effective by decreasing the channel protein abundance in the cell membrane.

It must be kept in mind, though, that the effect of JAK3 on BK surface expression and activity does not necessarily reflect a direct phosphorylation of the BK channel protein. Instead, JAK3 may modify BK channel expression and activity indirectly. For instance, JAK3 may phosphorylate regulators of the channel protein thus indirectly modifying its regulation. Moreover, JAK3 is a powerful inhibitor of the Na+/K+ ATPase activity [49]. JAK3 expression is up-regulated [50] and activated [51] upon hypoxia and JAK3 is activated by energy depletion [52]. The isoform JAK2 has similarly been shown to be a powerful negative regulator of Na+/K+ ATPase [53]. Inhibition of Na+/K+ ATPase activity is in turn known to down-regulate K+ channels [54-56].

Moreover, the difference between B lymphocytes from jak3\textsuperscript{-/-} mice and jak3\textsuperscript{+/+} mice may be affected by an influence of JAK3 deficiency on the abundance of inflammatory cells and the release of inflammatory mediators modifying BK channel activity. Along those lines enhanced serum calcitriol and FGF23 levels have been observed in jak3\textsuperscript{-/-} mice [57]: Moreover, JAK3-deficient mice are volume depleted [48].

To which extent the slight effect of JAK3 on BK channel protein abundance and BK channel activity modifies BK channel sensitive cellular functions, remains to be determined. In theory, inhibition of K+ channels could counteract cell shrinkage and apoptosis by counteracting cellular loss of K+ ions [58]. However, activation rather than inhibition of K+ channels fosters cell proliferation [59-61]. Stimulation of large conductance Ca2+-activated K+ channels (maxi K+ channel or BK channels) has thus been observed in proliferating cells [17-29]. The stimulating effect of JAK3 on cell proliferation [9-13] is thus hardly supported by inhibition of BK channels. Clearly, additional experimental effort is needed to clarify the functional significance of JAK3 sensitive BK channel abundance and activity.

In conclusion, wild-type JAK3 and constitutively active A568V JAK3 slightly but significantly down-regulate the large conductance voltage- and Ca2+-activated K+ channel BK.

Acknowledgements

The authors acknowledge the meticulous preparation of the manuscript by Lejla Subasic and technical support by Elfriede Faber. This study was supported by the Deutsche Forschungsgemeinschaft and Open Access Publishing Fund of Tuebingen University, GRK 1302, SFB 773 B4/A1, La 315/13-3.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

References

1 O'Shea JJ, Husa M, Li D, Hofmann SR, Watford W, Roberts JL, Buckley RH, Changelian P, Candotti F: Jak3 and the pathogenesis of severe combined immunodeficiency. Mol Immunol 2004;41:727-737.
2 Vijayakrishnan L, Venkataramanan R, Gullati P: Treating inflammation with the Janus kinase inhibitor CP-690,550. Trends Pharmacol Sci 2011;32:25-34.
3 Bharadwaj AS, Agrawal DK: Transcription factors in the control of dendritic cell life cycle. Immunol Res 2007;37:79-96.
4 Cornejo MG, Boggon TJ, Mercher T: JAK3: a two-faced player in hematological disorders. Int J Biochem Cell Biol 2009;41:2376-2379.
5 Ghoreschi K, Laurence A, O'Shea JJ: Janus kinases in immune cell signaling. Immunol Rev 2009;228:273-287.
6 Imada K, Leonard WJ: The Jak-STAT pathway. Mol Immunol 2000;37:1-11.
7 O'Shea JJ, Gadina M, Schreiber RD: Cytokine signaling in 2002: new surprises in the Jak/Stat pathway. Cell 2002;109 Suppl:S1 21-131.
8 Shuai K, Liu B: Regulation of JAK-STAT signalling in the immune system. Nat Rev Immunol 2003;3:900-911.
9 de Totero D, Meazza R, Capaia M, Fabbri M, Azzarone B, Balleari E, Gobbi M, Cutrona G, Ferrarini M, Ferrini S: The opposite effects of IL-15 and IL-21 on CLL B cells correlate with differential activation of the JAK/STAT and ERK1/2 pathways. Blood 2008;111:517-524.
10 Fainstein N, Vaknin I, Einstein O, Zisman P, Ben Sasson SZ, Banjashy M, Ben-Hur T: Neural precursor cells inhibit multiple inflammatory signals. Mol Cell Neurosci 2008;39:335-341.
11 Kim BH, Oh SR, Yin CH, Lee S, Kim EA, Kim MS, Sandoval C, Jayabose S, Bach EA, Lee HK, Baeg GH: MS-1020 is a novel small molecule that selectively inhibits JAK3 activity. Br J Haematol 2010;148:132-143.
12 Nakayama J, Yamamoto M, Hayashi K, Satoh H, Bundo K, Kubo M, Goitsuka R, Farrar MA, Kitamura D: BLNK suppresses pre-B-cell leukemogenesis through inhibition of JAK3. Blood 2009;113:1483-1492.
13 Uckun FM, Vassilev A, Dibirdik I, Tibbles H: Targeting JAK3 tyrosine kinase-linked signal transduction pathways with rationally-designed inhibitors. Anticancer Agents Med Chem 2007;7:612-623.
14 Malinge S, Ragu C, Della-Valle V, Pisani D, Constantinescu SN, Perez C, Villeval JL, Reinhardt D, Landman-Parker J, Michaux L, Dastugue N, Baruchel A, Vainchenker W, Bourquin JP, Penard-Lacronique V, Bernard OA: Activating mutations in human acute megakaryoblastic leukemia. Blood 2008;112:4220-4226.
15 Walters DK, Mercher T, Gu TL, O’Hare T, Tynier JW, Loriaux M, Goss VL, Lee KA, Eide CA, Wong MJ, Stoffregen EP, McGreevey L, Nardone J, Moore SA, Crispino J, Boggon TJ, Heinrich MC, Deininger MW, Polakiewicz RD, Gilliland DG, Druker BJ: Activating alleles of JAK3 in acute megakaryoblastic leukemia. Cancer Cell 2006;10:65-75.
16 Haan C, Rolvering C, Rauf F, Kapp M, Druckes P, Thoma G, Behrmann I, Zerwes HG: Jak1 has a dominant role over Jak3 in signal transduction through gammac-containing cytokine receptors. Chem Biol 2011;18:314-323.
17 Dal-Cim T, Molz S, Egea J, Parada E, Romero A, Budni J, Martin de Saavedra MD, del Barrio L, Tasca CL, Lopez MG: Guanosine protects human neuroblastoma SH-SY5Y cells against mitochondrial oxidative stress by inducing heme oxygenase-1 via PI3K/Akt/GSK-3β pathway. Neurochem Int 2012;61:397-404.
18 Ge L, Hoa NT, Cornforth AN, Bota DA, Mai A, Kim DJ, Chiu SK, Hickey MJ, Kruse CA, Jadus MR: Glioma big potassium channel expression in human cancers and possible T cell epitopes for their immunotherapy. J Immunol 2012;189:2625-2634.
19 Handlechner AG, Hermann A, Fuchs R, Weiger TM: Acetaldehyde-ethanol interactions on calcium-activated potassium (BK) channels in pituitary tumor (GH3) cells. Front Behav Neurosci 2013;7:58.
20 Ma YG, Liu WC, Dong S, Du C, Wang XJ, Li JS, Xie XP, Wu L, Ma DC, Yu ZB, Xie MJ: Activation of BK(Ca) channels in zoledronic acid-induced apoptosis of MDA-MB-231 breast cancer cells. PLoS One 2012;7:e37451.
21 McFerrin MB, Turner KL, Cuddapah VA, Sontheimer H: Differential role of IK and BK potassium channels as mediators of intrinsic and extrinsic apoptotic cell death. J Physiol Cell Physiol 2012;303:C1070-1078.
22 Oegerl ML, Tian Y, Ruiz C, Wijker B, Sauter G, Obermann E, Guth U, Zlobec I, Saubier M, Kunzelmann K, Bubendorf L: Role of KCNMA1 in breast cancer. PLoS One 2012;7:e41664.
23 Singh H, Stefani E, Toro L: Intracellular BK(Ca) (IbK(Ca)) channels. J Physiol 2012;590:5937-5947.
24 So EC, Wu KC, Liang CH, Chen JY, Wu SN: Evidence for activation of BK Ca channels by a known inhibitor of focal adhesion kinase, PF573228. Life Sci 2011;89:691-701.
25 Sontheimer H: An unexpected role for ion channels in brain tumor metastasis. Exp Biol Med (Maywood) 2008;233:779-791.
26 Tajima N, Itozku Y, Korpi ER, Somerharju P, Kakela R: Activity of BK(Ca) channel is modulated by membrane cholesterol content and association with Na+/K+-ATPase in human melanoma IGR39 cells. J Biol Chem 2011;286:5624-5638.
27 Tao J, Shi J, Yan L, Chen Y, Duan YH, Ye P, Feng Q, Zhang JW, Shu XQ, Ji YH: Enhancement effects of martentoxin on glioma BK channel and BK channel (alpha+beta1) subtypes. PLoS One 2011;6:e15896.
28 Yin LT, Fu YJ, Xu QL, Yang J, Liu ZL, Liang AH, Fan XJ, Xu CG: Potential biochemical therapy of glioma cancer. Biochem Biophys Res Commun 2007;362:225-229.
29 Sausbier M, Hu H, Arntz C, Feil S, Kamm S, Adelsberger H, Sausbier U, Sailer CA, Feil R, Hofmann F, Korth M, Shipston MJ, Knues HG, Wolfer DP, Pedroarena CM, Storm JE, Ruth P: Cerbellar ataxia and Purkinje cell dysfunction caused by Ca2+-activated K+ channel deficiency. Proc Natl Acad Sci U S A 2004;101:9474-9478.
30 Xia XM, Zeng X, Lingle CJ: Multiple regulatory sites in large-conductance calcium-activated potassium channels. Nature 2002;418:880-884.
31 Warsi J, Hosseinzadeh Z, Dong L, Pakladok T, Umbach AT, Bhavsar SK, Shumilina E, Lang F: Effect of Janus kinase 3 on the peptide transporters PEPT1 and PEPT2. J Membr Biol 2013;246:885-892.
32 Hosseinzadeh Z, Dong L, Bhavsar SK, Warsi J, Almilaji A, Lang F: Upregulation of peptide transporters PEPT1 and PEPT2 by Janus kinase JAK2. Cell Physiol Biochem 2013;31:673-682.
33 Almilaji A, Honisch S, Liu G, Elvira B, Ajay SS, Hosseinzadeh Z, Ahmed M, Munoz C, Sopjani M, Lang F: Regulation of the voltage gated K channel Kv1.3 by recombinant human klotho protein. Kidney Blood Press Res 2014;39:609-622.
34 Fezai M, Elvira B, Borras J, Ben-Atta M, Hosseinzadeh Z, Lang F: Negative regulation of the creatine transporter Slc6A8 by SPAK and OSR1. Kidney Blood Press Res 2014;39:546-554.
35 Almilaji A, Munoz C, Hosseinzadeh Z, Lang F: Upregulation of Na+,Cl(-)-coupled betaine/gamma-amino-butyric acid transporter BGT1 by Tau tubulin kinase 2. Cell Physiol Biochem 2013;32:334-343.
36 Pakladok T, Almilaji A, Munoz C, Alesutan I, Lang F: PIKfyve sensitivity of hERG channels. Cell Physiol Biochem 2013;31:785-794.
37 Almilaji A, Sopjani M, Elvira B, Borras J, Dermaku-Sopjani M, Munoz C, Warsi J, Lang UE, Lang F: Upregulation of the creatine transporter Slc6A8 by Klotho. Kidney Blood Press Res 2014;39:516-525.
38 Warsi J, Elvira B, Bissinger R, Shumilina E, Hosseinzadeh Z, Lang F: Downregulation of peptide transporters PEPT1 and PEPT2 by oxidative stress responsive kinase OSR1. Kidney Blood Press Res 2014;39:591-599.
39 Almilaji A, Szteyn K, Fein E, Pakladok T, Munoz C, Elvira B, Towhid ST, Alesutan I, Shumilina E, Bock CT, Kandolf R, Lang F: Down-regulation of Na/K+ atpase activity by human parvovirus B19 capsid protein VP1. Cell Physiol Biochem 2013;31:638-648.
40 Warsi J, Dong L, Elvira B, Salker MS, Shumilina E, Hosseinzadeh Z, Lang F: SPAn dependent regulation of peptide transporters PEPT1 and PEPT2. Kidney Blood Press Res 2014;39:388-398.
41 Warsi J, Hosseinzadeh Z, Elvira B, Bissinger R, Shumilina E, Lang F: Regulation of CIC-2 activity by SPAK and OSR1. Kidney Blood Press Res 2014;39:378-387.
42 Hosseinzadeh Z, Luo D, Sopjani M, Bhavsar SK, Lang F: Down-regulation of the epithelial Na(+)-channel ENaC by Janus kinase 2. J Membr Biol 2014;247:331-338.
43 Hosseinzadeh Z, Sopjani M, Pakladok T, Bhavsar SK, Lang F: Downregulation of KCNQ4 by Janus kinase 2. J Membr Biol 2013;246:335-341.
44 Munoz C, Almilaji A, Setiawan I, Foller M, Lang F: Up-regulation of the inwardly rectifying K+ channel Kir2.1 (KCNJ2) by protein kinase B (PKB/Akt) and PIKfyve. J Membr Biol 2013;246:189-197.
45 Pakladok T, Hosseinzadeh Z, Lebedeva A, Alesutan I, Lang F: Upregulation of the Na(+)-coupled phosphate cotransporters NaPi-IIa and NaPi-IIb by B-RAF. J Membr Biol 2014;247:137-145.
46 Dermaku-Sopjani M, Almilaji A, Pakladok T, Munoz C, Hosseinzadeh Z, Blecua M, Sopjani M, Lang F: Down-regulation of the Na+-coupled phosphate transporter NaPi-1la by AMP-activated protein kinase. Kidney Blood Press Res 2013;37:547-556.
47 Elvira B, Munoz C, Borras J, Chen H, Warsi J, Ajay SS, Shumilina E, Lang F: SPAK and OSR1 dependent down-regulation of murine renal outer medullary K channel ROMK1. Kidney Blood Press Res 2014;39:353-360.
48 Umbach AT, Luo D, Bhavsar SK, Hosseinzadeh Z, Lang F: Intestinal Na+ loss and volume depletion in JAK3-deficient mice. Kidney Blood Press Res 2013;37:514-520.
49 Hosseinzadeh Z, Honisch S, Schmid E, Jilani K, Szteyn K, Bhavsar SK, Singh Y, Palmada M, Umbach AT, Shumilina E, Lang F: The Role of Janus Kinase 3 in the Regulation of Na+/K(+) ATPase under Energy Depletion. Cell Physiol Biochem 2015;36:77-27-740.
50 Wang GS, Qian GS, Zhou DS, Zhao JQ: JAK-STAT signaling pathway in pulmonary arterial smooth muscle cells is activated by hypoxia. Cell Biol Int 2005;29:598-603.
51 Wang G, Qian P, Jackson FR, Qian G, Wu G: Sequential activation of JAKs, STATs and xanthine dehydrogenase/oxidase by hypoxia in lung microvascular endothelial cells. Int J Biochem Cell Biol 2008;40:461-470.

52 Bhavsar SK, Gu S, Bobbala D, Lang F: Janus kinase 3 is expressed in erythrocytes, phosphorylated upon energy depletion and involved in the regulation of suicidal erythrocyte death. Cell Physiol Biochem 2011;27:547-556.

53 Bhavsar SK, Hosseinzadeh Z, Brenner D, Honisch S, Jilani K, Liu G, Szteyn K, Sopjani M, Mak TW, Shumilina E, Lang F: Energy-sensitive regulation of Na+/K+-ATPase by Janus kinase 2. Am J Physiol Cell Physiol 2014;306:C374-384.

54 Lang F, Rehwald W: Potassium channels in renal epithelial transport regulation. Physiol Rev 1992;72:1-32.

55 Messner G, Wang W, Paulmichl M, Oberleithner H, Lang F: Ouabain decreases apparent potassium conductance in proximal tubules of the amphibian kidney. Pflugers Arch 1985;404:131-137.

56 Warsi J, Elvira B, Bissinger R, Hosseinzadeh Z, Lang F: Regulation of voltage gated K+ channel Kv1.5 by the Janus kinase JAK3. J Membr Biol 2015; in press.

57 Umbach AT, Zhang B, Daniel C, Fajol A, Velic A, Hosseinzadeh Z, Bhavsar SK, Bock CT, Kandolf R, Pichler BJ, Amann KU, Foller M, Lang F: Janus kinase 3 regulates renal 25-hydroxyvitamin D 1alpha-hydroxylase expression, calcitriol formation, and phosphate metabolism. Kidney Int 2014;10.1038/ki.2014.371.

58 Lang F, Hoffmann EK: Role of ion transport in control of apoptotic cell death. Compr Physiol 2012;2:2037-2061.

59 Lang F, Stournaras C: Ion channels in cancer: future perspectives and clinical potential. Philos Trans R Soc Lond B Biol Sci 2014;369:20130108.

60 Pardo LA, Stuhmer W: The roles of K(+) channels in cancer. Nat Rev Cancer 2014;14:39-48.

61 Turner KL, Sontheimer H: Cl- and K+ channels and their role in primary brain tumour biology. Philos Trans R Soc Lond B Biol Sci 2014;369:20130095.