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Up-regulation of Kv1.3 Channels by Janus Kinase 2

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Abstract The janus-activated kinase 2 JAK2 participates in the signalling of several hormones including interferon, a powerful regulator of lymphocyte function. Lymphocyte activity and survival depend on the activity of the voltage-gated K^+ channel KCNA3 (Kv1.3). The present study thus explored whether JAK2 modifies the activity of voltage-gated K^+ channel KCNA3. To this end, cRNA encoding KCNA3 was injected in *Xenopus* oocytes with or without additional injection of cRNA encoding wild-type human JAK2, human inactive ^{K882E}JAK2 mutant, or human gain-of-function ^{V617F}JAK2 mutant. KCNA3-dependent depolarization-induced current was determined utilizing dual-electrode voltage clamp, and protein KCNA3 abundance in the cell membrane was quantified by chemiluminescence. Moreover, the effect of interferon-γ on voltage-gated K^+ current was determined by patch clamp in mainly KCNA3-expressing Jurkat T cells with or without prior treatment with JAK2 inhibitor AG490 (40 μM). As a result, KCNA3 channel activity and protein abundance were up-regulated by coexpression of JAK2 or ^{V617F}JAK2 but not ^{K882E}JAK2. The effect of JAK2 coexpression was reversed by AG490 treatment. In human Jurkat T lymphoma cells, voltage-gated K^+ current was up-regulated by interferon-γ and down-regulated by AG490 (40 μM). In conclusion, JAK2 participates in the signalling, regulating the voltage-gated K^+ channel KCNA3.

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Introduction

The janus-activated kinase 2 (JAK2) contributes to the signalling of a variety of hormones and cytokines (Lopez et al. 2010; Noon-Song et al. 2011; Spivak 2010), including leptin (Morris and Rui 2009; Schmid et al. 2012), growth hormone (Brooks and Waters 2010; Xia et al. 2002; Yang et al. 2010), erythropoietin (Spivak 2010), thrombopoietin (Spivak 2010), granulocyte colony-stimulating factor (Spivak 2010), and interferon (Johnson and Ahmed 2006).

The gain-of-function mutation ^{V617F}JAK2 is associated with (Mahfouz et al. 2011; Shen et al. 2010; Venkitachalam et al. 2012; Yao et al. 2010), and JAK2 inhibitors are considered for the treatment of (Comes et al. 2013; Ho et al. 2010; Oh and Gotlib 2010; Pardanani et al. 2011; Santos and Verstovsek 2011; Tefferi 2010) myeloproliferative disease. JAK2 is thus part of the signalling, stimulating cell proliferation.

Cell proliferation requires timely activation of K^+ channels (Arcangeli et al. 2012; Lang et al. 2007; Ouadid-Ahidouch and Ahidouch 2008; Villalonga et al. 2007; Wallace et al. 2011), which are involved in the machinery of tumour cell migration (Sontheimer 2008). K^+ channels involved in triggering of cell proliferation and migration include the voltage-gated K^+ channel Kv1.3 (KCNA3) (Comes et al. 2013). KCNA3-expressing cells include the Jurkat lymphoma cells (Szabo et al. 2010).

The present study explored whether JAK2 participates in the regulation of Kv1.3. To this end, KCNA3 was expressed in *Xenopus laevis* oocytes with or without wild-type JAK2, gain-of-function ^{V617F}JAK2, or inactive ^{K882E}JAK2. KCNA3 channel-mediated current was

determined utilizing dual-electrode voltage clamp, and KCNA3 protein abundance in the cell membrane was quantified by chemiluminescence. Moreover, voltage-gated K^+ current was measured by whole-cell patch clamp recording in Jurkat T cells without or with prior exposure to JAK2 inhibitor AG490.

Materials and Methods

Oocyte Preparation

Xenopus oocytes were explanted from adult *X. laevis* (NASCO) as previously described (Munoz et al. 2013; Pakladok et al. 2014; Warsi et al. 2013, 2014). The frogs were anaesthetized by a 0.1 % tricain (ethyl 3-aminobenzoate methanesulfonate salt) solution. After confirmation of anaesthesia and disinfection of the skin, a small abdominal incision was made and oocytes were removed, followed by closure of the skin by sutures. All animal experiments were conducted in accordance with the Helsinki Declaration of 1975 and according to the German law for the welfare of animals.

Constructs

For generation of cRNA, constructs were used encoding wild-type mouse KCNA3 (Kv1.3) (Henke et al. 2004), wild-type human JAK2, human inactive ^{K882E}JAK2 mutant, and human gain-of-function ^{V617F}JAK2 mutant (Hosseinzadeh et al. 2012b, 2013b, 2014). The constructs were used for the generation of cRNA as described previously (Alesutan et al. 2012).

Voltage Clamp

Xenopus laevis oocytes were prepared as previously described (Bogatikov et al. 2012; Henrion et al. 2012). cRNA encoding KCNA3 (2.5 ng) was injected with or without 10 ng of cRNA encoding JAK2, ^{K882E}JAK2, or ^{V617F}JAK2 on the next day of preparation of the *X. laevis* oocytes. All experiments were performed at room temperature 3 days after injection (Pathare et al. 2012). The oocytes were maintained at 17 °C in ND96 solution containing 88.5 mM NaCl, 2 mM KCl, 1 mM $MgC1_2$, 1.8 mM $CaC1_2$, 2.5 mM NaOH,5 mM HEPES (pH7.4), 5 mM sodium pyruvate ($C_3H_3NaO_3$), 100 mg/l gentamicin, 50 mg/l tetracycline, 1.6 mg/l ciprofloxacin and 90 mg/l theophilin (Almilaji et al. 2013a; Hosseinzadeh et al. 2012a). 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). To obtain current–voltage curves, oocytes were held at a holding potential of −100 mV and current was measured following voltage steps between −80 and +50 mV. For activation and inactivation analysis, single exponential functions were fitted to the rising or decaying portions of the curves, respectively, and time constants of activation and inactivation were determined. The data were filtered at 2 kHz and recorded with a Digidata 1322A A/D–D/A converter and Clampex 9.2 software for data acquisition (Axon Instruments). The analysis of the data was performed with Clampfit 9.2 (Axon Instruments) software (Hosseinzadeh et al. 2013a).

Detection of KCNA3 Cell Surface Expression by Chemiluminescence

For detection of KCNA3 cell surface expression, the oocytes were first incubated with primary polyclonal rabbit anti-Kv1.3 (KCNA3) antibody (extracellular) (1:200, Alomone Labs) and subsequently with secondary, HRP-conjugated anti-rabbit IgG antibody (1:2,500, Cell Signaling). Individual oocytes were placed in 96-well plates with 20 µl of SuperSignal ELISA Femto Maximum Sensitivity Substrate (Pierce, Rockford, IL, USA), and chemiluminescence of single oocytes was quantified in a luminometer (Walter Wallac 2 plate reader, Perkin Juegesheim, Germany) by integrating the signal over a period of 1 s. Results display normalized relative light units (Mia et al. 2012).

Culture of Jurkat T Cells

Human Jurkat T cells were cultured in Roswell Park Memorial Institute medium RPMI 1640 (PAA-15–840) supplemented with 10 % FBS and 5 % penicillin/streptomycin at 37 °C in a humidified atmosphere with 5 % CO_2.

Patch Clamp

Patch clamp experiments were performed at room temperature in voltage-clamp, fast-whole-cell mode as described previously (Almilaji et al. 2013b; Hamill et al. 1981). The cells were continuously superfused through a flow system inserted into the dish. The bath was grounded via a bridge filled with NaCl Ringer solution. Borosilicate glass pipettes (1–3 MΩ tip resistance; GC 150 TF-10, Clark Medical Instruments, Pangbourne, UK) manufactured by a microprocessor-driven DMZ puller (Zeitz, Augsburg, Germany) were used in combination with a MS314 electrical micromanipulator (MW, Märzhäuser, Wetzlar, Germany) (Pakladok et al. 2013). The currents were recorded by an EPC-9 amplifier (Heka, Lambrecht, Germany) using Pulse software (Heka) and an ITC-16 Interface (Instrutech, Port Washington, NY, USA). Whole-cell currents were elicited by 200-ms square wave voltage pulses from −80 to +100 mV in 20-mV steps delivered at 20-s intervals from a holding potential of

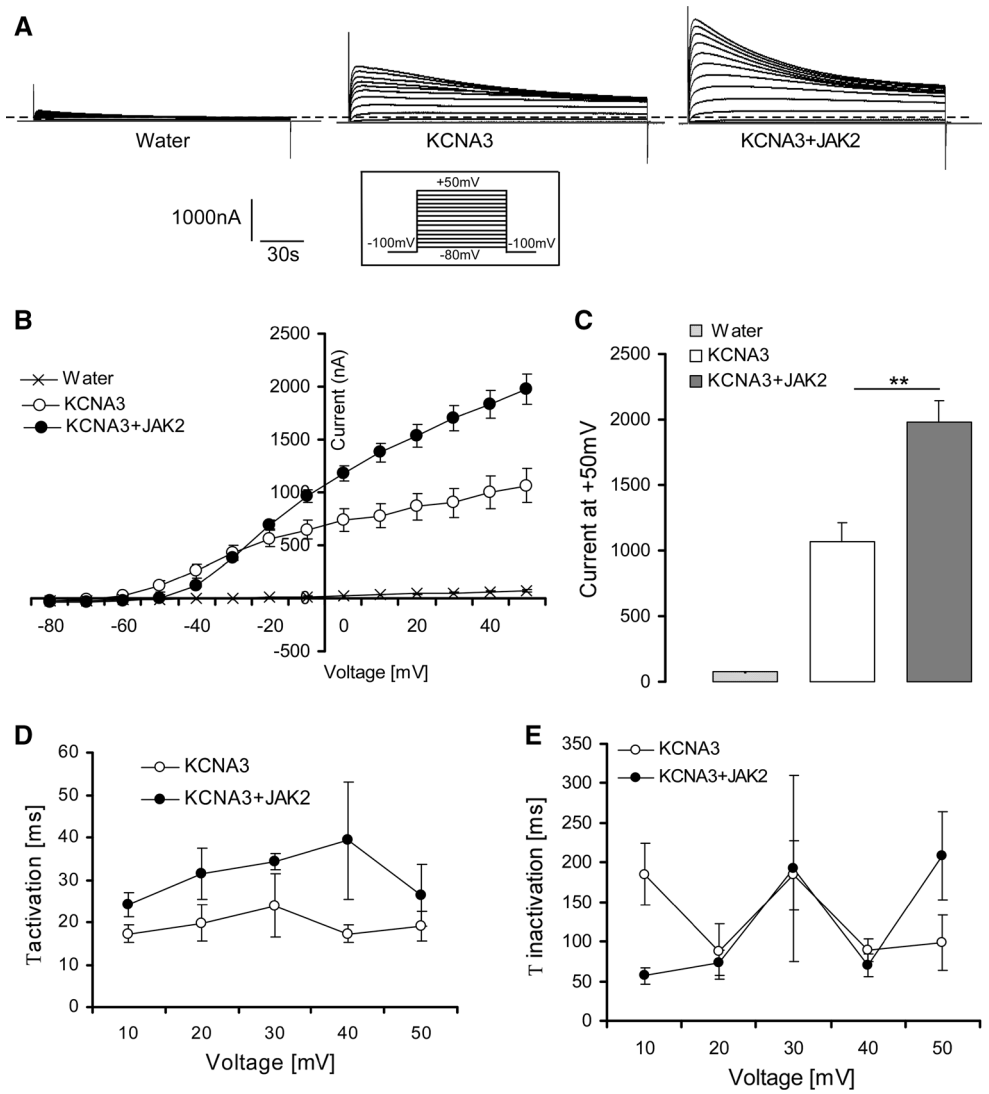

Fig. 1 Coexpression of wild-type JAK2 up-regulates voltage-gated K^+ current in KCNA3 (Kv1.3)-expressing *X. laevis* oocytes. **a** Original tracings of the voltage-gated K^+ current from −80 to +50 mV in *X. laevis* oocytes injected with water or expressing KCNA3 channels alone or coexpressing KCNA3 channels with wild-type JAK2. The dotted line indicates the zero current value. **b** Arithmetic mean ± SEM ($n = 12$) of the voltage-gated K^+ current as a function of voltage in *X. laevis* oocytes injected with water (*open diamonds*) or expressing KCNA3 channels alone (KCNA3, *white circles*), or expressing KCNA3 channels and JAK2 (KCNA3 + JAK2, *black circles*). **c** Arithmetic mean ± SEM ($n = 12$) of the normalized voltage-gated K^+ current at +50 mV in *X. laevis* oocytes injected with water (*grey bar*) or expressing KCNA3 channels alone (KCNA3, white bar) or expressing KCNA3 channels and JAK2 (KCNA3 + JAK2) (*dark grey bar*). **($p < 0.01$) indicates significant difference, ANOVA. **d** Activation time constants determined by fitting single exponential functions to the rising phase of currents at voltages from +10 to +50 mV in oocytes expressing KCNA3 alone (KCNA3) or in oocytes expressing KCNA3 together with JAK2 (KCNA3 + JAK2). **e** Inactivation time constants determined by fitting single exponential functions to the decaying phase of currents at voltages from +10 to +50 mV in oocytes expressing KCNA3 alone (KCNA3) or in oocytes expressing KCNA3 together with JAK2 (KCNA3 + JAK2)

−70 mV. Kv currents in Jurkat T cells were shown to recover from their use-dependent inactivation within 20 s. The currents were recorded with an acquisition frequency of 10 and 3 kHz low-pass filter. Since the time constant of activation decreased with the applied depolarizing voltage step and inactivation occurred especially during strong depolarization, the current was analysed at its maximal amplitude (peak current).

The cells were superfused with a bath solution containing (in mM): 140 NaCl, 5 KCl, 1 $MgCl_2$, 2 $CaCl_2$, 10 glucose and 10 HEPES (pH 7.4, NaOH). The patch clamp pipettes were filled with an internal solution containing (in mM): 80 KCl, 60 K^+-gluconate, 1 $MgCl_2$, 1 Mg-ATP, 1 EGTA, 10 HEPES (pH 7.2, KOH).

The offset potentials between both electrodes were zeroed before sealing. The potentials were corrected for liquid

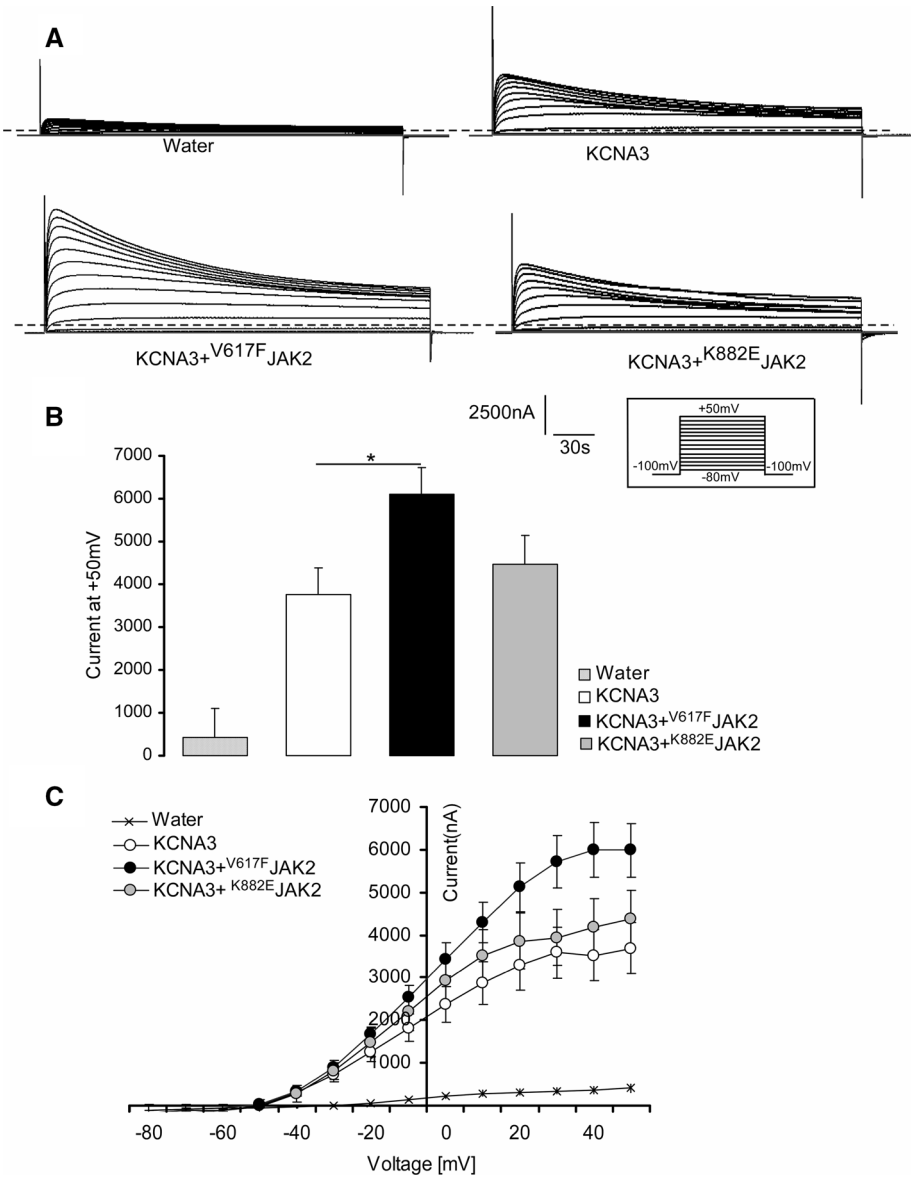

Fig. 2 Coexpression of active mutant ^{V617F}JAK2 but not of inactive ^{K882E}JAK2 increased the voltage-gated K^+ current in KCNA3-expressing *X. laevis* oocytes. **a** Original tracings of the current measured from −80 to +50 mV in *X. laevis* oocytes injected with water, expressing KCNA3 channels alone (KCNA3) or expressing KCNA3 channels with additional coexpression of active ^{V617F}JAK2 (KCNA3 + ^{V617F}JAK2) or inactive ^{K882E}JAK2 (KCNA3 + ^{K882E}JAK2). The dotted line indicates the zero current value. **b** Arithmetic mean ± SEM ($n = 27$–34) of the K^+ current at +50 mV in *X. laevis* oocytes injected with water (DEPC Water, *light grey bar*), expressing KCNA3 channels alone (KCNA3, *white bar*) or expressing KCNA3 channels with additional coexpression of active ^{V617F}JAK2 (KCNA3 + ^{V617F}JAK2, *black bar*), or of inactive ^{K882E}JAK2 mutants (KCNA3 + ^{K882E}JAK2, *grey bar*). **c** Arithmetic mean ± SEM ($n = 27$–34) of the K^+ current as a function of voltage in *Xenopus* oocytes injected with water (DEPC Water, *open diamonds*), expressing KCNA3 channels alone (KCNA3, *white circles*), or expressing KCNA3 channels with additional coexpression of active ^{V617F}JAK2 (KCNA3 + ^{V617F}JAK2, *black circles*), or of inactive ^{K882E}JAK2 mutants (KCNA3 + ^{K882E}JAK2, *grey circles*).*($p < 0.05$) indicates significant difference, ANOVA

junction potentials estimated as described previously (Barry and Lynch 1991; Szteyn et al. 2012). The original whole-cell current traces are depicted without filtering (acquisition frequency of 5 kHz), and currents of the individual voltage square pulses are superimposed. The applied voltages refer to the cytoplasmic face of the membrane with respect to the extracellular space. The inward currents, defined as flow of positive charge from the extracellular to the cytoplasmic membrane face, are negative currents and depicted as downward deflections of the original current traces.

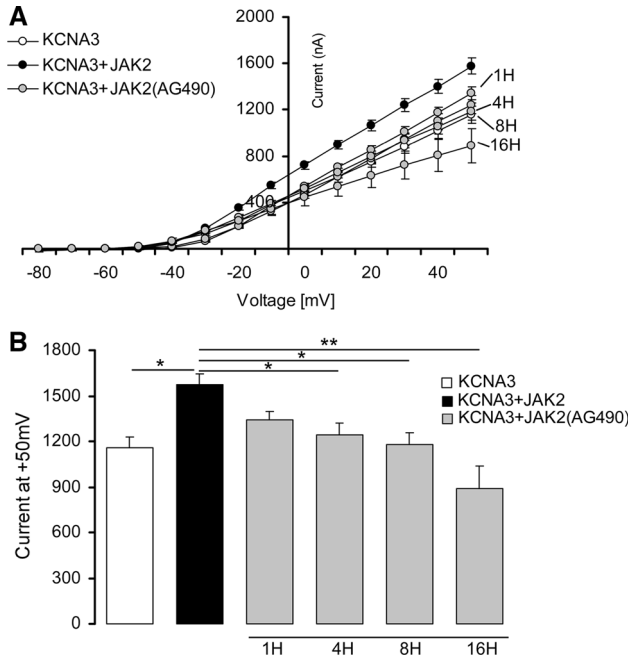

Fig. 3 Effect of JAK2 on voltage-gated K^+ current in KCNA3 is reversed by JAK2 inhibitor AG490. **a** Arithmetic mean ± SEM ($n = 35$–53) of the voltage-gated K^+ current as a function of voltage in *X. laevis* oocytes expressing KCNA3 channels alone (*white circles*) or expressing KCNA3 channels with JAK2 (*black circles*) without or with 1, 4, 8 and 16 h pretreatment with JAK2 inhibitor AG490 (40 μM) (*grey circles*) as indicated. **b** Arithmetic mean ± SEM ($n = 35$–53) of the voltage-gated K^+ current at +50 mV in *X. laevis* oocytes expressing KCNA3 channels alone (KCNA3, *white bar*) or expressing KCNA3 channels and JAK2 (KCNA3 + JAK2) without (*black bar*) or with 1, 4, 8 and 16 h (*grey bar*) pretreatment with JAK2 inhibitor AG490 (40 μM). *($p < 0.05$); **($p < 0.01$) indicate significant difference, ANOVA

Statistics

Data are provided as mean ± SEM; *n* represents the number of independent experiments. All oocyte experiments were repeated with at least three batches of oocytes; in all repetitions, qualitatively similar data were obtained. All data were tested for significance using ANOVA followed by post hoc analysis or unpaired *t* test, where appropriate. Only results with $p < 0.05$ were considered statistically significant.

Results

The present study explored the effect of janus-activated kinase 2 (JAK2) on the voltage-gated K^+ channel KCNA3 (Kv1.3). To this end, KCNA3 was expressed in *X. laevis* oocytes with or without coexpression of JAK2 and depolarization-induced outward K^+ currents recorded by dual-electrode voltage clamp. As illustrated in Fig. 1, no appreciable voltage-gated K^+ channel activity was observed in water-injected *X. laevis* oocytes. Injection of cRNA encoding KCNA3 was followed by the appearance of the typical voltage-gated outward current. The current was significantly increased following coexpression of wild-type JAK2 (Fig. 1a–c). Analysis of activation and inactivation time constants of KCNA3 (Fig. 1d, e) revealed that JAK2 did not significantly affect τ activation and τ inactivation of KCNA3.

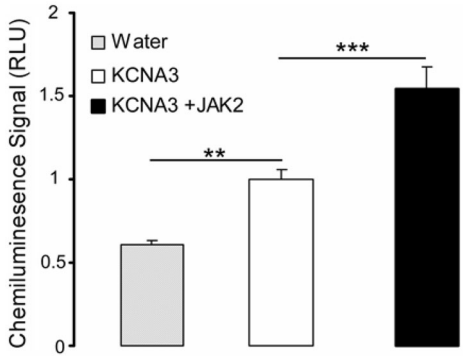

Fig. 4 Coexpression of JAK2 increased the KCNA3 abundance within the plasma membrane of oocytes. Arithmetic mean ± SEM ($n = 69$–71) of the normalized KCNA3 protein abundance assessed by chemiluminescence in oocytes injected with water (*grey bar*), or expressing KCNA3 alone (*white bar*), or together with wild-type JAK2 (*black bar*). **($p < 0.01$); ***($p < 0.001$) indicate significant difference, ANOVA

The effect of wild-type JAK2 on KCNA3 was mimicked by the active mutant ^{V617F}JAK2 but not by the inactive mutant ^{K882E}JAK2. Coexpression of ^{V617F}JAK2 but not of ^{K882E}JAK2 increased the voltage-gated K^+ current in KCNA3 channel-expressing *X. laevis* oocytes. Again, coexpression of ^{V617F}JAK2 increased the current amplitude without appreciably modifying the voltage dependence of KCNA3 (Fig. 2). The voltage-gated K^+ current in KCNA3- and JAK2-expressing *Xenopus laevis* oocytes was significantly decreased by a 4 to 16-h incubation with JAK2 inhibitor AG490 (40 μM). Neither JAK2 expression nor exposure to AG490 appreciably modified the voltage dependence of KCNA3 (Fig. 3).

The up-regulation of the voltage-gated K^+ channel KCNA3 by JAK2 could have resulted in part from an increase in protein abundance in the cell membrane. The protein abundance was thus quantified by chemiluminescence. As illustrated in Fig. 4, the cell surface expression of KCNA3 channel in oocytes was indeed increased by the coexpression of JAK2.

Whole-cell patch clamp was employed to test whether JAK2 inhibitor AG490 influenced the voltage-gated K^+ current in Jurkat cells. As illustrated in Fig. 5, the application of AG490 (40 μM) was within 4 h followed by a decline of voltage-gated K^+ current in Jurkat T cells. The

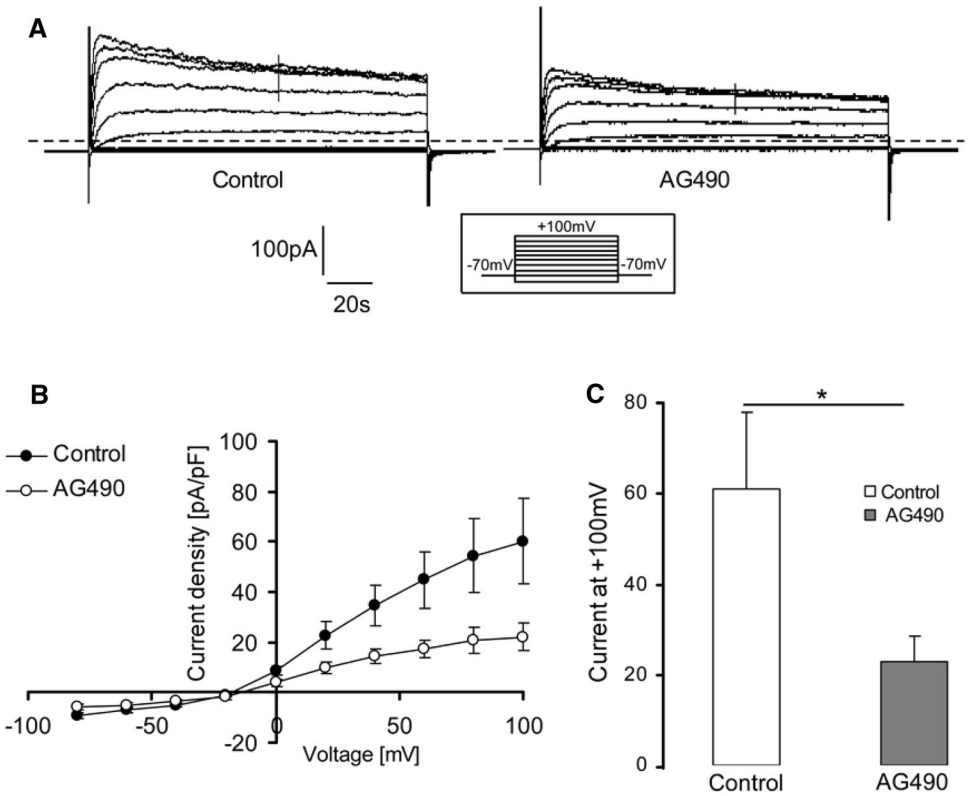

Fig. 5 Effect of JAK2 inhibitor AG490 on voltage-gated K^+ current in Jurkat T cells. **a** Representative whole-cell currents elicited by 200 ms pulses ranging from −80 to +100 mV in 20 mV increments from a holding potential of −70 mV in Jurkat T cells without (*left traces* control, $n = 6$) and with (*right traces* $n = 7$) a 4-h pretreatment with JAK2 inhibitor AG490 (40 μM). The dotted line indicates the zero current value. **b** Mean current–voltage (*I–V*) relationships (±SEM) of peak Kv current density in untreated (*white circles*) and AG490-treated (*black circles*) Jurkat T cells recorded as in **a**. *($p < 0.05$) indicate significant difference, *t* test. **c** Arithmetic mean ± SEM of voltage-gated K^+ current at +100-mV in Jurkat T cells without (*white bar*) and with a 4-h pretreatment with JAK2 inhibitor AG490 (40 μM) (*grey bar*). *($p < 0.05$) indicates significant difference, *t* test

inhibitor decreased the current amplitude without appreciably modifying the voltage dependence of the outward current (Fig. 5).

In order to explore whether the voltage-gated current is sensitive to interferon-γ (INF-γ), Jurkat T cells were exposed for 4 h to INF-γ (10 ng/ml) in the absence and presence of JAK2 inhibitor AG490 (40 μM, 4 h). As illustrated in Fig. 6, the exposure of Jurkat T cells to INF-γ was followed by a marked and significant increase in the voltage-gated current, an effect reversed by JAK2 inhibitor AG490.

Discussion

The present study reveals a novel function of janus-activated kinase 2 (JAK2), i.e. the up-regulation of the voltage-gated K^+ channel Kv1.3 (KCNA3). Apparently, JAK2 increases the amplitude of KCNA3 channel currents without appreciably affecting other properties of the channel. Furthermore, JAK2 increases protein abundance of Kv1.3. As shown in Jurkat T cells, JAK2 participates in the up-regulation of voltage-gated K^+ current by interferon-γ.

KCNA3 plays a decisive role in the regulation of lymphocyte function (Cahalan and Chandy 2009; Varga et al. 2010), and KCNA3 inhibitors have thus been considered for the treatment of autoimmune disease (Panyi et al. 2006; Wulff and Pennington 2007). A powerful regulator of lymphocyte function is interferon (Stackaruk et al. 2013; Zheng et al. 2013). Interferon is at least partially effective through JAK (Axtell and Raman 2012). To the best of our knowledge, an effect of interferon on KCNA3 activity has never been shown before.

KCNA3 is expressed in many further cell types and participates in the regulation of a wide variety of cellular functions, including excitability (Jan and Jan 2012; Ko et al. 2010; Pongs 2009; Vacher and Trimmer 2011), cell proliferation (Comes et al. 2013), apoptosis (Szabo et al. 2010), immune response (Cahalan and Chandy 2009; Wang and Xiang 2013), insulin sensitivity (Choi and Hahn 2010), and platelet function (Mahaut-Smith 2012). Future studies will be required to define JAK2 sensitivity of those functions.

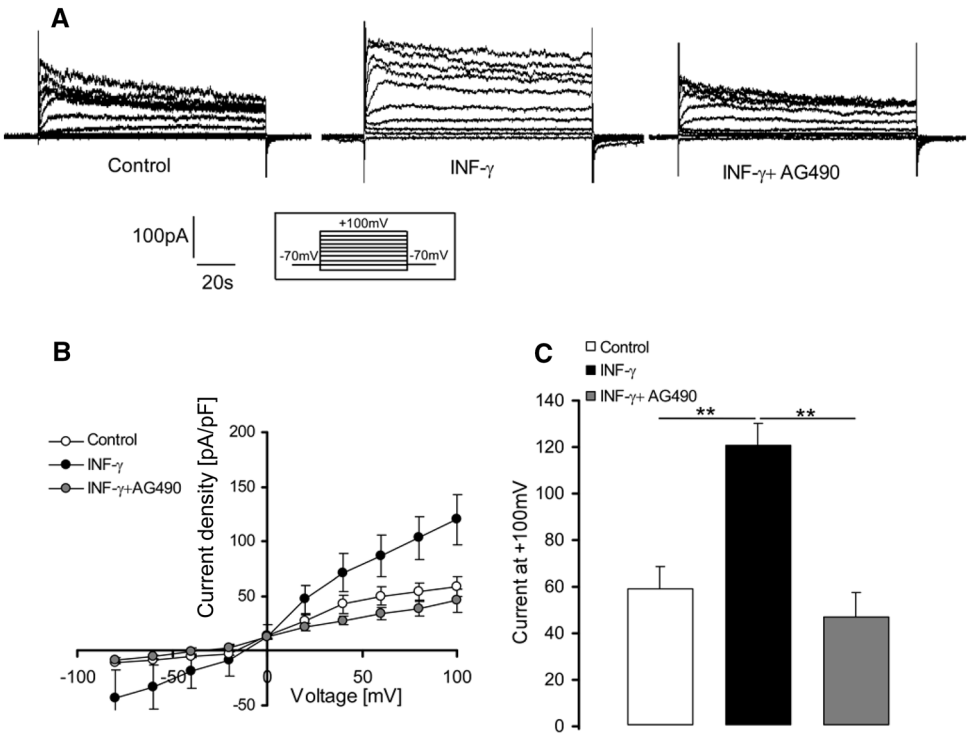

Fig. 6 Effect of interferon-γ (INF-γ) on voltage-gated K^+ current in Jurkat T cells in the absence and presence of JAK2 inhibitor AG490. **a** Representative whole-cell currents elicited by 200-ms pulses ranging from −80 to +100 mV in 20 mV increments from a holding potential of −70 mV in Jurkat T cells without (left traces, control) and with a 4-h pretreatment with INF-γ (10 ng/ml) in the absence (*middle tracing* INF-γ) and presence (*right tracing* INF-γ +AG490) of JAK2 inhibitor AG490 (40 μM, 4 h). The *dotted line* indicates the zero current value. **b** Mean current–voltage (*I–V*) relationship (±SEM) of the voltage-gated current in Jurkat T cells without treatment (*white circles*) and with a 4-h pretreatment with INF-γ in the absence (*black circles*) and presence (*grey circles*) of JAK2 inhibitor AG490 (40 μM, 4 h). **c** Arithmetic mean ± SEM of the normalized voltage-gated K^+ current at +100 mV in Jurkat T cells without (*white bar* $n = 6$) and with a 4-h pretreatment with INF-γ (10 ng/ml) in the absence (*black bar* $n = 5$) and presence (*grey bar*) of JAK2 inhibitor AG490 (40 μM). **($p < 0.01$), ANOVA

As KCNA3 is involved in the regulation of apoptosis and tumour growth (Comes et al. 2013), it is tempting to speculate that the stimulating effect of JAK2 on KCNA3 contributes to the excessive proliferation of cells carrying the gain-of-function mutation ^{V617F}JAK2 (Mahfouz et al. 2011; Shen et al. 2010; Venkitachalam et al. 2012; Yao et al. 2010) and the anti-proliferative effect of JAK2 inhibitors (Comes et al. 2013; Ho et al. 2010; Oh and Gotlib 2010; Pardanani et al. 2011; Santos and Verstovsek 2011; Tefferi 2010).

KCNA3 is not only expressed in the cell membrane but as well in mitochondria (Leanza et al. 2013; Szabo et al. 2010). Mitochondrial KCNA3 interacts with pro-apoptotic Bax and is involved in the regulation of mitochondrial potential and function as well as cytochrome c release (Szabo et al. 2010). Whether JAK2 participates in the regulation of mitochondrial KCNA3 remains to be shown.

In conclusion, the present observations reveal that JAK2 up-regulates voltage-gated K^+ channel Kv1.3 (KCNA3) and may participate in the stimulation of KCNA3 by interferon-γ.

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

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