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Stimulation of the Na^+-coupled glucose transporter SGLT1 by B-RAF

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ABSTRACT

Gain of function mutations of B-RAF, a serine/threonine protein kinase may lead to development of tumor cells. As tumor cells mainly utilize glucose as fuel, their survival critically depends on their ability to accumulate glucose from extracellular space. The Na^+-coupled glucose transporter SGLT1 accomplishes concentrative cellular glucose uptake against a chemical glucose gradient and thus even at low extracellular glucose concentrations. SGLT1 contributes to glucose uptake in several tumor cells. The present study thus explored whether B-RAF activates SGLT1. To this end, SGLT1 was expressed in *Xenopus* oocytes with or without additional coexpression of B-RAF and electrogenic glucose transport was determined by dual electrode voltage clamp. In SGLT1-expressing oocytes but not in oocytes injected with water the addition of glucose to the extracellular bath generated a current (I_g), which was significantly increased following coexpression of wild-type B-RAF. According to kinetic analysis, coexpression of B-RAF enhanced the maximal transport rate without significantly modifying the affinity of the carrier. According to chemiluminescence and confocal microscopy experiments, B-RAF enhanced the Na^+-coupled glucose transporter SGLT1 protein abundance in the cell membrane. Exposure of the *Xenopus* oocytes to Brefeldin A (5 μM), an inhibitor of vesicle insertion, was followed by a decline of I_g, which was higher in oocytes expressing SGLT1 together with B-RAF than in oocytes expressing SGLT1 alone. In conclusion, B-RAF upregulates SGLT1 activity, an effect requiring vesicle insertion into the cell membrane.

1. Introduction

Cellular glucose uptake is accomplished either by carriers from the GLUT family, which mediate passive transport of glucose driven by a glucose gradient from extracellular space into the cell [1,2], or by the Na^+-glucose cotransporters from the SGLT family, which mediate secondary active transport driven by the electrochemical Na^+ gradient [3]. The Na^+ coupled glucose carriers SGLT1 and SGLT2 are primarily expressed in epithelial cells and responsible for the concentrative cellular uptake of glucose from the lumen across the apical cell membrane [3]. Several studies indicate a functional role of SGLT1 in malignant tumors [4–11]. Those cells fuel their excessive energy demand mainly by the degradation of glucose [6]. The avid cellular glucose uptake in tumor tissue may result in decreased extracellular glucose concentrations, which compromises cellular glucose uptake by facilitative glucose carriers. In contrast, Na^+-coupled glucose transport could accomplish cellular glucose uptake even at low extracellular glucose concentrations [3].

The mechanisms accounting for the function and protein expression of SGLT1 in tumor cells have remained poorly understood. Previous observations revealed that the EGF receptor stabilizes SGLT1 [5,11], and that the Janus kinase JAK2 stimulates SGLT1 [12]. Moreover, SGLT1 is up-regulated by the human papilloma virus protein HPV18 E6 [13], which causes cervical cancer, other anogenital cancers and a subset of head and neck carcinomas [14–16].

Another potential regulator of SGLT1 activity in tumor cells is B-RAF [17–19], a serine/threonine kinase up-regulated in a variety of tumor cells [20–23]. As a matter of fact, B-RAF is the most frequently mutated protein kinase gene in human tumors [20]. The kinase plays a crucial role in the activation of the Ras/Raf/MEK/ERK pathway, which controls cell proliferation, differentiation and survival [24]. B-RAF has been considered an attractive target in cancer therapy [20,25–28].

The present study explored the possibility that B-RAF regulates protein abundance and/or activity of SGLT1. SGLT1 was expressed in *Xenopus* oocytes with or without additional coexpression of B-RAF and the glucose-induced current, reflecting electrogenic glucose transport across the cell membrane, determined utilizing dual electrode voltage clamp.

2. Materials and methods

2.1. Constructs

For generation of cRNA, constructs were used encoding wild-type human SGLT1 (SLC5A1) [29,30] and wild-type human B-RAF

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(Imagenes, Berlin, Germany) inserted into the appropriate vector [31]. The constructs were used for generation of cRNA as described previously [32].

2.2. Voltage clamp in Xenopus oocytes

Xenopus oocytes were prepared as previously described [33]. The cRNA (10 ng) encoding wild type B-RAF was injected on the first day and cRNA (10 ng) encoding SGLT1 on the same day after preparation of the oocytes. The oocytes were maintained at 17 °C in ND96 solution containing in mM: 96 NaCl, 4 KCl, 1.8 $MgCl_2$, 0.1 $CaCl_2$, 5 HEPES, pH 7.6, Tretracycline (Sigma, 0.11 mM), Ciprofloxacin (Sigma, 4 μM), Gentamycin (Refobacin © 0.2 mM) and Theophyllin (Euphylong ©, 0.5 mM) as well as sodium pyruvate (Sigma, 5 mM). The pH was adjusted to 7.5 by addition of NaOH. The voltage clamp experiments were performed at room temperature 3 days after injection. Two-electrode voltage-clamp recordings [34] were performed at a holding potential of −70 mV. The data were filtered at 10 Hz and recorded with a Digidata A/D-D/A converter and Clampex V.9 software for data acquisition and analysis (Axon Instruments). The control superfusate (ND96) contained 96 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$ and 5 mM HEPES, pH 7.4. Glucose was added to the solutions at a concentration of 10 mM unless otherwise stated. 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.

2.3. Detection of SGLT1 cell surface expression by chemiluminescence

Defolliculated oocytes were incubated with rabbit polyclonal anti-SGLT1 antibody (1:1000, Millipore, USA) and subsequently with secondary, HRP-conjugated anti-rabbit antibody (1:1000, Cell Signaling Technology, MA, USA). 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 Elmer, Juegesheim, Germany) by integrating the signal over a period of 1 s. Results display normalized relative light units [35].

2.4. Immunofluorescence in Xenopus oocytes

Oocytes were fixed in 4% paraformaldehyde at room temperature for 2 h [36]. After washing with phosphate buffered saline (PBS), the oocytes were permeabilized and blocked at room temperature for 1 h in TBS containing 0.1% TritonX-100 and 10% normal goat serum. Then, the oocytes were incubated overnight at 4 °C with primary rabbit polyclonal anti-SGLT1 antibody (1:1000, Millipore,USA) followed by 30 min incubation at 37 °C with FITC-Goat anti-rabbit IgG (diluted 1:1000, Invitrogen, Molecular Probes, Eugene, OR, USA). Next, oocytes were analyzed by a fluorescence laser scanning microscope (LSM 510, Zeiss, Germany) with A-Plan 10×/0.25. Brightness and contrast settings were kept constant during imaging of all oocytes in each injection series. The quantification of the fluorescence intensity reflecting SGLT1 protein abundance was achieved by using ZEN2009 software (Zeiss, Germany).

2.5. Statistical analysis

Data are provided as means ± SEM, *n* represents the number of oocytes investigated. All experiments were repeated with at least 2–3 batches of oocytes; in all repetitions qualitatively similar data were obtained. Data were tested for significance using ANOVA. Results with $p < 0.05$ were considered statistically significant.

3. Results

In order to possibly disclose a role of B-RAF on the function of Na^+ coupled glucose transporter SGLT1 (SLC5A1), the carrier was expressed in *Xenopus* oocytes with or without additional expression of the kinase. Glucose transport was estimated from the current generated following addition of substrate to the bath solution. The current was determined utilizing dual electrode voltage clamp. The addition of glucose (10 mM) to the extracellular

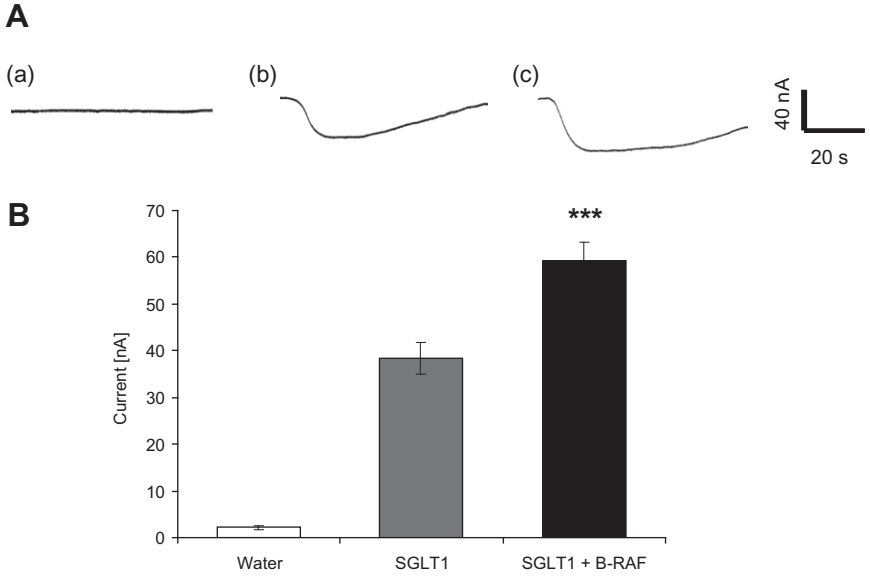

Fig. 1. Coexpression of B-RAF increases electrogenic glucose transport in SGLT1-expressing *Xenopus* oocytes. (A) Representative original tracings showing glucose-induced current (10 mM) (I_g) in *Xenopus* oocytes injected with water (a), expressing SGLT1 without (b) or with additional coexpression of wild-type B-RAF (c). (B) Arithmetic means ± SEM (n = 11–14) of glucose (10 mM)-induced current (I_g) in *Xenopus* oocytes injected with water (water, white bar), expressing SGLT1 without (SGLT1, grey bar) or with additional coexpression of wild-type B-RAF (SGLT1 + B-RAF, black bar). *** ($p < 0.001$) indicates statistically significant difference from *Xenopus* oocytes expressing SGLT1 alone.

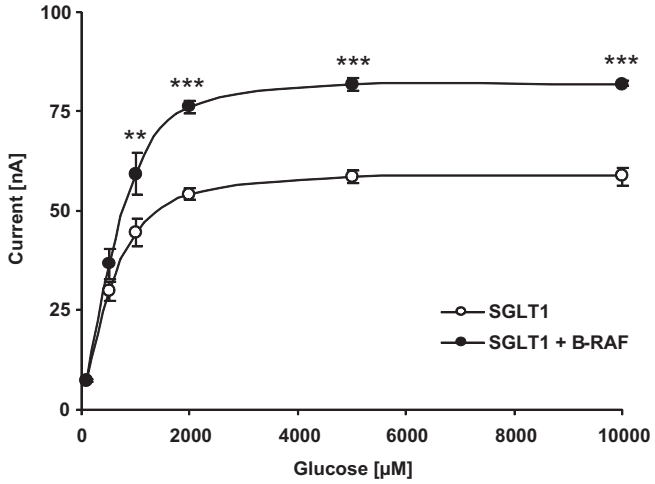

Fig. 2. Coexpression of B-RAF increases maximal glucose transport rate in SGLT1-expressing *Xenopus* oocytes. Arithmetic means ± SEM ($n = 6$) of glucose induced current (I_g) as a function of glucose concentration in *Xenopus* oocytes expressing SGLT1 without (open circles) and with additional coexpression of wild-type B-RAF (closed cirsxcles). ** ($p < 0.01$) and *** ($p < 0.001$) indicate statistically significant difference from *Xenopus* oocytes expressing SGLT1 alone at the respective glucose concentration.

fluid did not induce an appreciable inward current in water-injected *Xenopus* oocytes, indicating that *Xenopus* oocytes do not express appreciable endogenous electrogenic glucose transport (Fig. 1). In *Xenopus* oocytes expressing SGLT1, however, glucose (10 mM) induced an inward current (I_g) reflecting electrogenic entry of Na^+ and glucose. As illustrated in Fig. 1B, I_g was significantly enhanced by additional coexpression of B-RAF.

Kinetic analysis of the glucose-induced currents in SGLT1-expressing *Xenopus* oocytes (Fig. 2) yielded a maximal I_g of 58.8 ± 2.3 nA ($n = 8$). Coexpression of B-RAF significantly enhanced the maximal I_g to 82.0 ± 0.6 nA ($n = 8$). Calculation of the glucose concentration required for half maximal I_g (K_M) yielded values of 425 ± 77 µM ($n = 8$) in oocytes expressing SGLT1 alone and of 288 ± 88 µM ($n = 8$) in oocytes expressing SGLT1 together with B-RAF, values not significantly different. Accordingly, coexpression of B-RAF enhanced SGLT1 activity at least in part by increasing the maximal current.

In theory, enhanced SGLT1 activity could result from increased carrier protein abundance in the plasma membrane. Accordingly, immunocytochemistry and confocal microscopy were employed to quantify the SGLT1 protein abundance in the cell membrane. As illustrated in Fig. 3A, the coexpression of B-RAF was followed by an increase of SGLT1 protein abundance within the oocyte cell membrane. The protein abundance was quantified utilizing chemiluminescence. As shown in Fig. 3B, the coexpression of B-RAF was again followed by a significant increase of cell membrane SGLT1 protein abundance.

The enhanced SGLT1 protein abundance in the cell membrane of B-RAF coexpressing oocytes could have resulted from accelerated insertion of new carriers into or delayed clearance of carriers

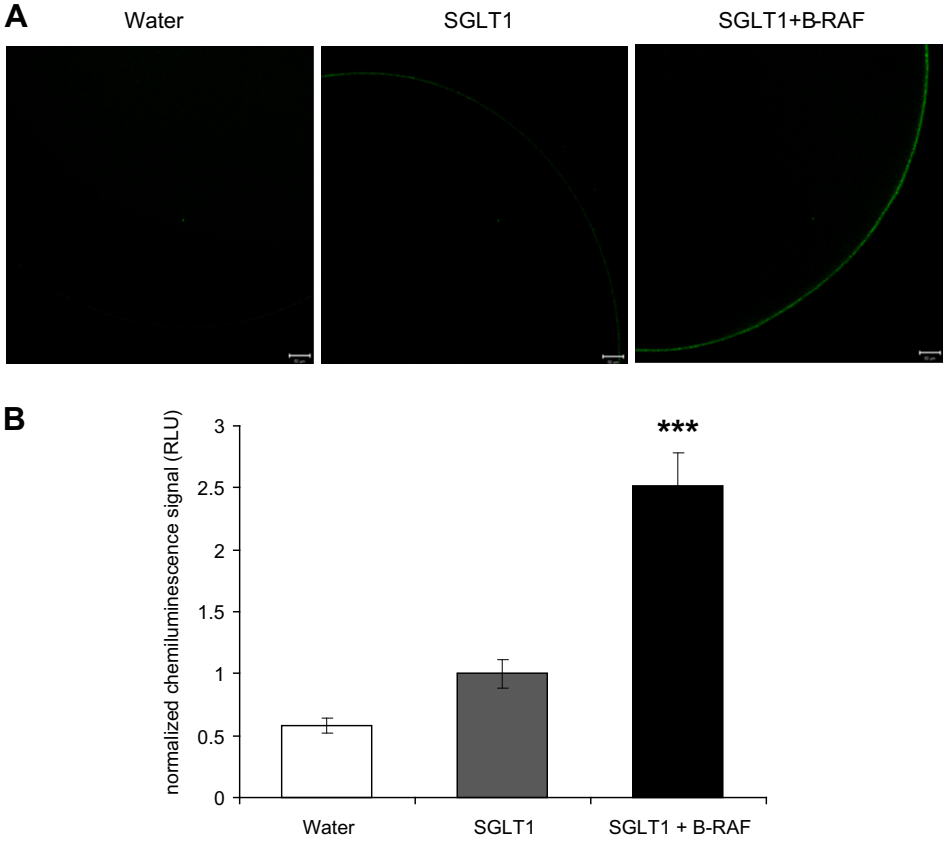

Fig. 3. Coexpression of B-RAF enhanced SGLT1 protein abundance at the cell surface in SGLT1-expressing *Xenopus* oocytes. (A) Confocal images reflecting SGLT1 membrane protein abundance in *Xenopus* oocytes injected with water (water), expressing SGLT1 without (SGLT1) or with additional coexpression of wild-type B-RAF (SGLT1 + B-RAF). The images are representative for three independent experiments. (B) Arithmetic means ± SEM ($n = 43–47$) of the chemiluminescence of SGLT1 protein abundance in *Xenopus* oocytes injected with water (water), expressing SGLT1 without (SGLT1) or with additional coexpression of wild-type B-RAF (SGLT1 + B-RAF), *** ($p < 0.001$) indicates statistically significant difference from *Xenopus* oocytes expressing SGLT1 alone.

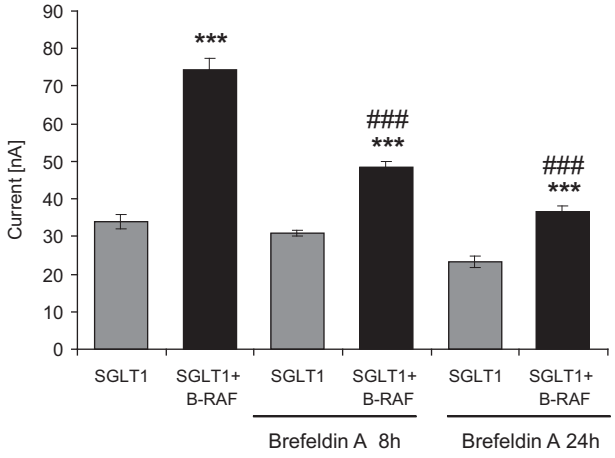

Fig. 4. Effects of Brefeldin A on SGLT1-expressing *Xenopus* oocytes with or without additional coexpression of B-RAF. Arithmetic means ± SEM (n = 10–14) of glucose (10 mM)-induced current (I_g) in *Xenopus* oocytes injected with SGLT1 without (grey bars) and with additional coexpression of B-RAF (black bars) in the presence and absence of 5 μM Brefeldin A for 8 and 24 h prior to the measurements. *** ($p < 0.001$) indicates statistically significant difference from *Xenopus* oocytes expressing SGLT1 alone at respective time point measured. ### ($p < 0.001$) indicates statistically significant difference from *Xenopus* oocytes coexpressing SGLT1 and B-RAF in the absence of Brefeldin A.

from the cell membrane. To discriminate between those two possibilities the SGLT1-expressing *Xenopus* oocytes were treated with 5 μM Brefeldin A, which blocks the insertion of new carrier protein into the cell membrane. Following addition of Brefeldin A the glucose induced current declined at a similar rate in oocytes expressing SGLT1 alone and in oocytes expressing SGLT1 together with B-RAF (Fig. 4). Thus, the presence of B-RAF did not delay the decrease of SGLT1 activity, indicating that B-RAF was not effective by counteracting carrier protein retrieval from the cell membrane.

4. Discussion

The present study discloses a novel regulator of the Na^+-coupled glucose transporter SGLT1. The serine/threonine kinase B-RAF enhances the SGLT1 protein abundance in the cell membrane and thus increases the transport rate by this carrier. Accordingly, B-RAF significantly increases the maximal transport rate without significantly affecting the substrate affinity of the carrier. The impact of B-RAF on the decline of electrogenic glucose transport in SGLT1-expressing *Xenopus* oocytes suggests that B-RAF enhances carrier protein insertion into rather than delaying retrieval of carrier protein from the cell membrane. Those experiments do, however, not rule out that B-RAF has some effect on SGLT1 protein degradation.

SGLT1 is well known to accomplish Na^+-coupled glucose transport across the brush border of the small intestine and the proximal tubule within the kidney [3]. The glucose transport by SGLT1 is driven by the steep electrochemical Na^+ gradient across the plasma membrane [3]. The coupling to Na^+ thus allows almost complete (re)absorption of luminal glucose in intestine and kidney.

The present observations did not attempt to define the molecular mechanism of B-RAF dependent regulation of SGLT1. B-RAF may influence SGLT1 activity by directly phosporylating the carrier or by phosphorylating other signaling molecules, which in turn regulate SGLT1. SGLT1 is a target of several kinases including protein kinase A (PKA) [37,38], protein kinase C (PKC) [37,38], serum- and glucocorticoid-inducible kinase [30], AMP-activated protein kinase [39] and Janus kinase JAK2 [12]. Those kinases regulate SGLT1 activity by influencing the carrier protein abundance within the plasma membrane.

Besides its well established expression and functional role in epithelial transport, SGLT1 is expressed in a variety of tumor cells [4–11]. Tumor cells further take up glucose by the facilitative glucose transporter GLUT1, a carrier accomplishing non-concentrative glucose uptake [40,41]. The very high demand of tumor cells for nutrients may, however, require the additional involvement of SGLT1 [6]. Glucose uptake through passive GLUT carriers has the advantage that it does not require energy expenditure. In contrast, Na^+-coupled glucose uptake eventually requires ATP-consuming extrusion of the cotransported Na^+ by the Na^+/K^+ ATPase. The pump further replenishes the cell with K^+ as the SGLT1 induced depolarization leads to cellular K^+ loss. Without Na^+/K^+ ATPase activity, SGLT1 activity would lead to gradual dissipation of the Na^+ gradient and depolarisation eventually resulting in cell swelling [42]. SGLT1 has, however, the advantage that it is able to allow cellular accumulation of glucose even at decreased extracellular glucose concentration, which impairs the glucose uptake through the facilitative glucose carriers more profoundly than Na^+-coupled glucose uptake. In contrast to the facilitative glucose carriers, SGLT1 accomplishes cellular glucose uptake even at extracellular glucose concentrations far below the intracellular concentrations. The ATP needed for the extrusion of the cotransported Na^+ by the Na^+/K^+ ATPase is only a fraction of the ATP generated during degradation of glucose, even if glucose is utilized only for glycolysis without oxidative metabolism.

In conclusion, B-RAF upregulates the protein abundance and activity of Na^+-coupled glucose transporter SGLT1. The stimulation of SGLT1 may allow the maintenance of cellular glucose delivery and thus confer survival of tumor cells at low local extracellular glucose concentration.

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