EXPRESSION OF JAK3 SENSITIVE NA^+ COUPLED GLUCOSE CARRIER SGLT1 IN ACTIVATED CYTOTOXIC T LYMPHOCYTES

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Similar to tumor cells, activated T-lymphocytes generate ATP mainly by glycolytic degradation of glucose. Lymphocyte glucose uptake involves non-concentrative glucose carriers of the GLUT family. In contrast to GLUT isoforms, Na^+-coupled glucose-carrier SGLT1 accumulates glucose against glucose gradients and is effective at low extra-cellular glucose concentrations. The present study explored expression, function and regulation of SGLT1 in activated murine splenic cytotoxic T cells (CTLs) and Jurkat-cells. According to FACS analysis, immunofluorescence and confocal microscopy as well as Western blotting, SGLT1 is expressed in CTLs and Jurkat-cells. 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose uptake was significantly decreased by SGLT1-blocker phloridzin and by pharmacological inhibition of janus kinase JAK3 with WHI-P131 (156µM), WHI-P154 (11.2µM) and JAK3 inhibitor VI (0.5µM). Electrogenic glucose transport ($I_{glucose}$) in *Xenopus* oocytes expressing SGLT1 was increased by additional expression of wild type JAK3, active ^{A568V}JAK3 but not inactive ^{K851A}JAK3. Coexpression of JAK3 enhanced the maximal transport rate without significantly modifying affinity of the carrier. $I_{glucose}$ in SGLT1+JAK3 expressing oocytes was significantly decreased by WHI-P154 (11.2µM). According to chemiluminescence JAK3 increased the SGLT1 protein abundance in the cell membrane. Inhibition of carrier insertion by brefeldin A (5 µM) in SGLT1+JAK3 expressing oocytes resulted in a decline of I_g, which was similar in presence and absence of JAK3. In conclusion, SGLT1 is expressed in murine cytotoxic T cells and Jurkat cells and significantly contributes to glucose uptake in those cells. JAK3 up-regulates SGLT1 activity by increasing the carrier protein abundance in the cell membrane, an effect enforcing cellular glucose uptake into activated lymphocytes and tumor cells. Inhibition of glucose uptake in CTLs by JAK3 inhibitors provides a further explanation for the immunosuppressive effect of JAK3 deficiency and apoptosis inducing effect of JAK3 inhibitors in T cells.

Janus Kinase 2: Unravelling Novel Functions- Regulation of Transporters and Ion Channels

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The Janus kinase-2 (JAK2) contributes to the intracellular signalling triggered by leptin and erythropoietin, hormones known to exert protective effects during cell injury, such as ischemia, hypoxia and energy depletion. In addition, JAK2 is activated by cell shrinkage and may thus participate in cell volume regulation. Inappropriate activation of JAK2 signalling underlies cell proliferation and survival in a variety of solid tumours and haematological neoplasm and the ^{V617F}JAK2 mutant is found in the majority of the Philadelphia chromosome-negative myeloproliferative neoplasm, polycythemia vera, essential thrombocythaemia and myelofibrosis. However, little is known about the molecular mechanisms required for expansion of ^{V617F}JAK2-transformed cells. My group has recently published several interesting findings on regulation of several Na^+ coupled transporters including glucose transporter SGLT1, amino acid transporters (SLC6A19, EAATs, ASCT) and ion-channels (ClC-2, KCNQ4, HERG) by JAK2 and the active mutant ^{V617F}JAK2. These findings for the first time demonstrates regulation of transporters and ion-channels directly by JAK2 and adds significant information to the mechanisms by which hyper-activation of JAK2 in cancer and the active mutant ^{V617F}JAK2 drives cell proliferation in progression of myeloproliferative neoplasms.