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Sodium-glucose cotransporters: new targets of cancer therapy?

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Glucose, the key source of metabolic energy, is imported into cells by two categories of transporters: 1) facilitative glucose transporters (GLUTs) and 2) secondary active sodium-glucose cotransporters (SGLTs). Cancer cells have an increased demand for glucose uptake and utilisation compared to normal cells. Previous studies have demonstrated the overexpression of GLUTs, mainly GLUT1, in many cancer types. As the current standard positron emission tomography (PET) tracer 2-deoxy-2-(^{18}F)fluoro-D-glucose (2-FDG) for imaging tumour cells *via* GLUT1 lacks in sensitivity and specificity, it may soon be replaced by the newly designed, highly sensitive and specific SGLT tracer α-methyl-4-(F-18)fluoro-4-deoxy-D-glucopyranoside (Me-4FDG) in clinical detection and tumour staging. This tracer has recently demonstrated the functional activity of SGLT in pancreatic, prostate, and brain cancers. The mRNA and protein expression of SGLTs have also been reported in colon/colorectal, lung, ovarian, head, neck, and oral squamous carcinomas. So far, SGLTs have been poorly investigated in cancer, and their protein expression and localisation are often controversial due to a lack of specific SGLT antibodies. In this review, we describe current knowledge concerning SGLT1 and SGLT2 (over)expression in various cancer types. The findings of SGLTs in malignant cells may help in developing novel cancer therapies with SGLT2 or SGLT1/SGLT2 inhibitors already used in diabetes mellitus treatment.

KEY WORDS: *brain cancer; Na$^+$-dependent glucose transporters; pancreatic cancer; positron emission tomography; prostate cancer; SGLT inhibitors*

Glucose is the key source of metabolic energy for mammalian cells. Its cell uptake has two pathways: one is sodium-independent, facilitated by glucose transporters (GLUTs) and the other is secondary active by sodium-glucose cotransporters (SGLTs). Up to date, 14 GLUTs and 12 SGLTs have been identified (1–5). GLUTs, encoded by the *SLC2* genes, have sequence and structure similarities but differ in their affinity for glucose and other hexoses, as well as in tissue-specific distribution and hormonal regulation. As for SGLTs, encoded by the *SLC5* genes, their exact atomic structure has not yet been defined. SGLTs have different affinities, capacities, and specificities for glucose. Some of them can also transport fructose, galactose, mannose, or inositol (3, 6). While GLUTs facilitate transport of glucose across the membrane and equilibrate its concentration on both sides of the membrane (7), SGLTs use transmembrane sodium gradient as a driving force to transport glucose against concentration gradient thus concentrating glucose inside the cells (4, 8).

All cancer cells require high amounts of glucose to proliferate uncontrollably. This phenomenon, called the Warburg effect, indicates that cancer cells exhibit altered metabolism, characterised by a transition from oxidative phosphorylation to glycolysis (9). Cancer cells maintain high glycolysis even in conditions of sufficient oxygen supply (10). The Warburg effect is not completely understood, but it is used in determining cancer tissue with positron emission tomography (PET), which tracks the radioactively labelled glucose analogue, 2-deoxy-2-(^{18}F)fluoro-D-glucose (2-FDG) (11, 12). Many studies have reported an increased expression of several GLUT proteins in cancer (13, 14). GLUT1 is not only widely distributed in normal tissues (brain, blood-brain barrier, and kidneys) but is also overexpressed in hepatic, pancreatic, breast, oesophageal, brain, renal, lung, cutaneous, colorectal, endometrial, ovarian, and cervical cancers (14). The overexpression of GLUT1 is associated with tumour progression and poor survival prognosis. Another well-established cause of GLUT upregulation is hypoxia (10). It induces cellular glucose uptake and is responsible for the upregulation of several glucose transporters, including GLUT1, GLUT3, and GLUT4 (15–17).

Sodium-glucose cotransporters

Specific membrane cotransporters of sodium and glucose SGLT1 and SGLT2 complement insulin and glucagon in regulating glucose homeostasis in mammals (3, 4). In the intestine, SGLT1 is located in the brush-border membrane of absorptive epithelial cells (enterocytes), where

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it mediates >80 % of glucose absorption (18). The absorbed glucose is then transferred from the enterocytes into the intracellular space by facilitated diffusion *via* GLUT2, which is located in the basolateral membrane, and then released into the bloodstream. In the kidneys, glucose is freely filtered in the glomeruli and then fully reabsorbed along the proximal tubules via SGLT1 and SGLT2 located in the brush-border membrane (Figure 1). In the mouse kidneys ~97 % of glucose is reabsorbed by SGLT2 in the S1/S2 segments of proximal tubules in the kidney cortex, and the rest (~3 %) is reabsorbed by SGLT1 in the S3 segment of proximal tubules in the medullary rays and outer stripe (5, 19). Both SGLTs play a key role in maintaining the normoglycaemia, since absorption in the small intestine ensures glucose supply from food, and renal reabsorption prevents urinary glucose loss (3, 4, 18, 20). In addition to transporting glucose, SGLT1 also acts as a water and urea channel (4, 6, 21).

In healthy experimental animals and humans, SGLT2 is expressed exclusively in the kidneys, whereas SGLT1 is expressed in the intestine, kidneys, and was recently localised in heart, liver, pancreas, lungs, eyes, tongue, prostate, uterus, and salivary glands (22–27) (Table 1).

Overexpression of SGLT1 and SGLT2 has been detected in pancreatic, prostate, brain, colon/colorectal, lung, ovarian, head, neck, and oral squamous cell carcinomas (28–39) (Table 1). However, documented SGLT expression has been evaluated mainly by reverse transcription polymerase chain reaction (RT-PCR) or real-time PCR, western blotting, and immunohistochemistry and less often by activity (functional studies).

An important study by Weihua et al. (35) has demonstrated overexpression of the SGLT1 protein and epidermal growth factor receptor (EGFR) in various human cancer cell lines (prostate, breast, skin, and colon). In epithelial cancers, EGFR is often overexpressed (i.e. activated) and associated with metastasis, resistance to chemotherapy, and poor prognosis. Beside its kinase activity, EGFR also maintains the basal intracellular glucose level to prevent cells from undergoing autophagic cell death. EGFR also stabilises SGLT1, preventing its proteasomal degradation. This research resulted recently in a patent that targets EGFR-SGLT1 interaction in cancer therapy and may be a promising alternative to EGFR tyrosine kinase inhibitors, which were not as efficient as hoped for in cancer therapy clinical trials.
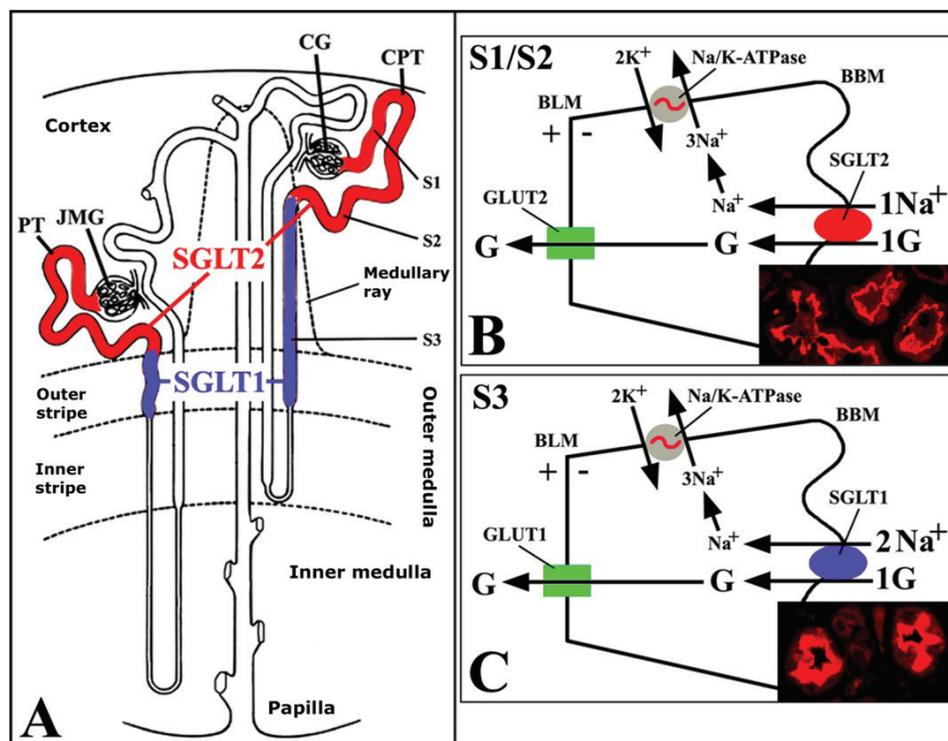
Figure 1 *A – The localisation of SGLT2 and SGLT1 along the human nephron; **B** – SGLT2 is localised in the brush-border membrane (BBM) of epithelial cells in the S1/S2 (convoluted) segments of proximal tubules (CPT) (inserted immunohistochemical image). SGLT2 mediates glucose (G) transport uphill coupled to Na⁺ transport downhill in a stoichiometric ratio 1:1 (low-affinity, high-capacity transport). The exit of internalised glucose into the intercellular space (downhill gradient) occurs by GLUT2-mediated facilitative diffusion localised in the basolateral membrane (BLM); **C** – SGLT1 is localised in the BBM of epithelial cells in the S3 (straight) segments of PT (inserted immunohistochemical image). This cotransport of Na⁺ and glucose exhibits stoichiometry of 2:1, respectively (high-affinity, low-capacity transport). The internalised glucose exits the cell at the BLM by GLUT1-mediated facilitated transport. In both cases, glucose transport is driven by the inward Na⁺ gradient maintained by the Na/K-ATPase in the BLM that moves 3 Na⁺ out in exchange for 2 K⁺ into the cell. G – glucose; CG – cortical glomerulus; CPT – convoluted proximal tubules; JMG – juxtamedullary glomerulus; PT – proximal tubule. The detailed immunohistochemical localization of SGLT2 and SGLT1 in the human kidney was described in our previous publication (23)*

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Table 1 *mRNA and protein expression of SGLTs in normal and cancer human tissues*

Transporter	Normal tissues	Cancer tissues
SGLT1	Intestine (23), kidneys (23), liver (23), lungs (23), heart (23), uterus (54), pancreas (29), prostate (29)	Pancreas (29), prostate (29, 39), ovaries (53), head (38), neck (38), brain (28)
SGLT2	Kidneys (23), pancreas (29)	Pancreas* (29, 36), prostate* (29), lungs (30), brain* (28)

*demonstrated functional activity
Numbers in parentheses indicate references

SGLT inhibitors

The use of gliflozins, new anti-diabetic SGLT2 inhibitors, has also emerged as a possibility in cancer treatment, considering that SGLTs are functionally active in pancreatic, prostate, and brain cancers (28, 29, 40). These inhibitors are nowadays in the centre of pharmaceutical and clinical investigations for treatment of diabetes mellitus type 2 aiming to lower blood glucose by inhibiting glucose reabsorption in the kidneys *via* SGLT2-induced glucosuria and lowering body weight. Also, they have beneficial effects on the cardiovascular system (41, 42). SGLT2 inhibitors can be combined with other antidiabetic agents because their mechanism of action is independent of insulin secretion. The US Food and Drug Administration has recently approved three SGLT2 inhibitors, empagliflozin (Jardiance), dapagliflozin (Forxiga) and canagliflozin (Invokana) (Figure 2) for the treatment of type 2 diabetes mellitus, but their underlying mechanism is still unknown. However, recent research has demonstrated that SGLT2 inhibitors inhibit only 50 % of the renal glucose reabsorption because of a significant compensatory role of SGLT1 in the late proximal tubule (42). This issue could be overcome by the use of an additional, selective SGLT1 inhibitor and/or a dual SGLT1/SGLT2 inhibitor. There are many knowledge gaps about the functions of SGLTs in normal and pathophysiological conditions. Findings about SGLT activity in malignant cells are opening a new chapter in cancer research, but we still need to understand its precise mechanism. Here we summarise current knowledge about the expression and localisation of SGLTs which could help in discerning their functions in various types of cancer.
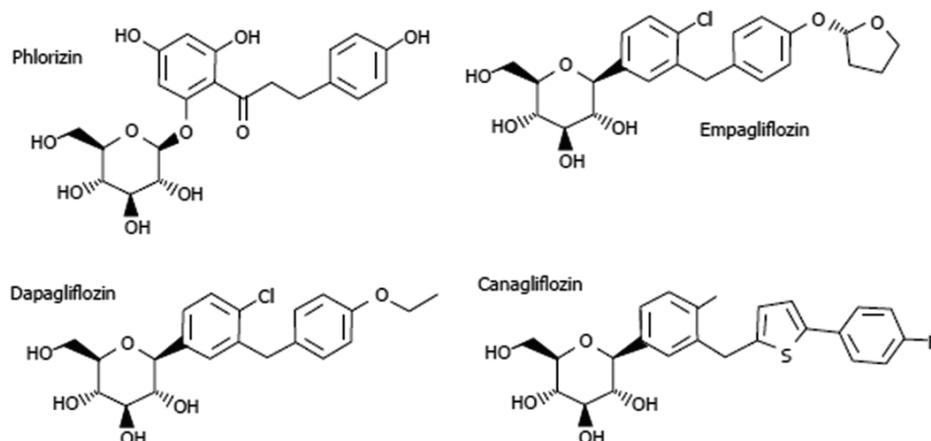
SGLTs IN CANCERS

SGLT1 in colon/colorectal cancer

In physiological conditions, SGLT1 is expressed in the jejunum, duodenum, and ileum (lowest expression) but not in the colon (24). In her pioneer study, Blais (32) reported sodium-dependent α-methyl-D-glucopyranoside (AMG) uptake in colon carcinoma HT-29D4 cells. Delezay at al. (33) identified three protein bands in HT-29D4 cells, two of which (64 kDa and 71 kDa) were specific for SGLT1. In healthy humans, rats, and mice the SGLT1 protein was associated with the ~85 kDa and ~75 kDa bands in small intestinal and renal total cell membranes, respectively (18,

23, 24, 43). This difference in the molecular weights of SGLT1 could be explained by cell line/tissue-specific pattern or protein glycosylation and/or phosphorylation. Guo et al. (31) reported that overexpression of SGLT1 and EGFR was related to higher clinical stages in patients diagnosed with colorectal cancer (CRC), but other authors reported no differences between healthy and cancer tissues for lung and pancreatic cancer (30, 36). These contradictory findings may be related to varying glucose demand in different cancer types but also in the methods used for SGLT expression analysis. Immunohistochemistry, which was used by Guo et al. (31) and Casneuf et al. (36), is a semi-quantitative method for measuring staining intensity, and more diverse methodology and larger cohorts of patients are required to clarify SGLT1 expression and function in CRC.

SGLT1 and SGLT2 in lung cancer

Lung cancer is the most common malignancy and the leading cause of cancer-related death worldwide (44). It is also associated with the expression of GLUT1, GLUT3, and GLUT4 (45). In 2001, Ishikawa et al. (30) examined *SGLT* gene expression levels in primary lung cancer and its metastases in 96 autopsy samples (primary lung cancers, normal lung tissues, metastatic liver lesions, metastatic lymph nodes) taken from 35 deceased patients. The mRNA expression of either *SGLT1* or *SGLT2* did not differ between primary lung cancer and normal lung tissue. *SGLT1* mRNA expression was also similar between primary lung cancer and metastatic lesions, but *SGLT2* mRNA expression was significantly higher in the metastatic lesions and lymph nodes. These findings suggest that SGLT2 may play a role in glucose uptake by lung cancer metastases. The reason for the difference in the expression of these two SGLT isoforms in lung cancer (primary and metastatic lesions) could be explained by their different physiological properties; SGLT1 is a high-affinity but low-capacity Na^+/glucose cotransporter, and SGLT2 is a low-affinity, high-capacity Na^+/glucose cotransporter. Earlier in 1999, the same group of authors described higher expression of *GLUT1* mRNA in the same lung cancer samples than in normal tissue, indicating that *GLUT1* may also play a role in cancer glucose uptake. The expression of *GLUT3* mRNA and *GLUT5* mRNA in primary tumours was similar to the expression in normal tissue, whereas their expression in the metastases was higher (46).

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Figure 2 *Chemical structures of new antidiabetic drugs that inhibit SGLTs*

The overexpression of *GLUTs* has been related with aggressive tumour behaviour and poor survival prognosis (47). It implies that tumours with increased glucose uptake are more metabolically active and therefore more aggressive.

Our group has recently localised the SGLT1 protein in the lungs of healthy humans, more specifically in the Clara cells of bronchioles and in the alveolar type II cells. This finding suggests that SGLT1 may have several roles in fluid absorption and energy supply to Clara cells (23). Furthermore, it is important to elucidate the function of SGLT1 in Clara cells, as they consist of several cell subtypes, including stem cells capable of transforming into cancer cells.

Although SGLT2 inhibitors may promise a more effective lung cancer therapy, dual SGLT1/SGLT2 inhibitors, which are under development by the pharmaceutical industry, could interfere with the specific functions of SGLT1. Functional studies of SGLTs in lung cancer patients are therefore needed.

SGLT1 in head and neck cancers

One study (38) reported *SGLT1* mRNA in only 17 of 36 short-term cultures of head and neck squamous cell carcinomas (HNSCC), whereas *SGLT2* mRNA was not detected. The SGLT1 protein, however, was detected in 27 of 30 HNSCC tissues with heterogeneous staining restricted to differentiated tumour cells. The reason for such discrepancy between SGLT1 expression in cell culture and tissues could be in the fact that fewer differentiated tumour cells proliferate under *in vitro* conditions (38).

At the protein level Hanabata et al. (37) demonstrated a correlation between SGLT1 and EGFR expression in six cell lines of oral squamous carcinoma (Ca-9-22, HOC313, HO-1-N-1, HSC2, NA, and ZA) as well as in 52 patients with tongue cancer. As evidenced by immunoblotting, all cell lines exhibited the SGLT1-related protein band of 73 kDa, and EGFR correlated significantly with SGLT1 expression. However, RT-PCR demonstrated that the *SGLT1* mRNA expression was not proportional to the protein expression in Ca-9-22, HOC313, and NA cells. In the squamous carcinoma tissues of the patients with tongue cancer, immunohistochemistry revealed upregulated SGLT1 and a high correlation between SGLT1 and EGFR expression.

For now, however, these two studies are the only ones to have analysed SGLT1 expression in these tumour types, and further studies of its expression and function in squamous epithelia are needed to elucidate the potential use of SGLT1 as a prognostic marker in head, neck, and oral carcinomas.

SGLT1 and SGLT2 in pancreatic cancer

Ten years ago, Casneuf et al. (36) were the first to report SGLT1 expression in 83 patients with primary pancreatic adenocarcinoma. They examined the expression of SGLT1 together with Bcl-2 and p53 in relation to patient survival. *Bcl-2* belongs to a large family of apoptosis-regulating genes, and its overexpression is related to the development of human pancreatic carcinoma (48). *p53* is a tumour suppressor gene, abnormally expressed in more than 50 % of human tumours (49). Immunohistochemical staining showed that patients with high Bcl-2 expression had significantly higher SGLT1 expression. On the other hand, no such correlation was found between p53 and SGLT1. In normal pancreatic tissue, SGLT1 expression was not detected (36). In a recent study Scafoglio et al. (29) demonstrated for the first time the functional expression of sodium-glucose cotransporters in human pancreatic cancer using a newly designed, specific PET imaging probe for SGLTs, α-methyl-4-(F-18)fluoro-4-deoxy-D-glucopyranoside (Me-4FDG). Immunohistochemical staining of SGLT1 was restricted to nuclei, while SGLT2 was detected in the cytoplasm of malignant cells in all samples of pancreatic cancer. The use of this newly designed SGLT tracer, which is not transported by GLUTs, showed that only SGLT2 was responsible for Me-4FDG uptake. Ghezzi et al. (50) suggested that SGLT2 trafficking to the plasma membrane could be regulated by an external signal, such as the one known for GLUT4 regulation by insulin.

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Scafoglio et al. (29) also reported that the treatment with the SGLT2 inhibitor dapagliflozin blocked Me-4FDG uptake by 40–50 % in mice with pancreatic cancer. Finally, this research group reported that SGLT2 inhibitors decreased cancer cell viability in a mouse xenograft model treated with SGLT inhibitors (canagliflozin and dapagliflozin) or chemotherapeutic gemcitabine for four weeks and suggested that they could potentiate anti-tumour effects of gemcitabine. Canagliflozin, they claimed, reduced tumour growth by increasing necrosis. These findings suggest that SGLT2 inhibitors bear promise for the treatment of pancreatic cancer. Furthermore, the newly designed SGLT-specific tracer Me-4FDG may improve early detection and stage determination of pancreatic cancer.

SGLT1 and SGLT2 in prostate cancer

Prostate cancer is the second leading neoplasm and cause of cancer-related death amongst men worldwide (51). It has been associated with upregulated GLUT1, GLUT3, and even insulin-dependent GLUT4 in earlier reports (47, 52). In Blessing et al. (39), immunohistochemistry and western blotting revealed a weakly expressed SGLT1 in the epithelium of normal prostate tissue, and much higher expression in the basal and stromal cells of benign prostatic hyperplasia and prostate human cancer tissue.

In the same study we referred to above, Scagoflio et al. (29) identified the expression of SGLT1 and SGLT2 in malignant prostate acini nuclei and cytoplasm, respectively. In normal tissue, SGLT1 was expressed in prostate ducts, but SGLT2 was absent. Me-4FDG uptake was found only in SGLT2-positive prostate cancers. As with pancreatic cancer, these results imply that SGLT2 inhibitors could be useful in prostate cancer therapy.

SGLT1 in ovarian cancer

So far, Lai et al. (53) have published the only research describing SGLT1 overexpression in ovarian cancer. Their analysis in 178 samples of epithelial ovarian tumour showed that it was associated with shorter patient survival. The limitation of the study however was the use of immunohistochemistry, which is a semi-quantitative method. Further research is needed to confirm whether SGLT1 has a role in the development and progression of ovarian cancer, especially because Salker et al. (54) has recently reported SGLT1 activity in normal ovary tissue (human endometrium), where it controlled glycogen accumulation essential for embryo implantation.

SGLT in brain cancer

In 2018, Kepe et al. (28) found accumulation of the SGLT-specific tracer Me-4FDG, in four patients diagnosed with WHO grade III and IV glioblastoma (astrocytoma). Immunohistochemistry of freshly frozen brain tissue samples revealed SGLT1 expression restricted to the nuclei, whereas SGLT2 was localised in the nuclei and the cytoplasm of glioblastoma cells. Surprisingly, SGLT2 was also detected in the endothelium surrounding tumour microvasculature (capillaries of proliferating micro-vessels and in microglia/macrophages). Studies in rats, in contrast, found no SGLTs in the normal endothelium of rat brain capillaries (55, 56). As in the studies with pancreatic and prostate cancer, Me-4FDG has been suggested as a highly sensitive PET tracer for clinical imaging of high-grade astrocytomas. Future studies should include a larger number of tissue/patients to establish its potential as an imaging tool. Likewise, further research should corroborate or dismiss the role of SGLT2 inhibitors in disrupting brain tumour growth and proliferation.

CONCLUDING REMARKS

Despite significant recent advances in cancer therapy, cancer mortality remains very high. It is, therefore, very important to identify new reliable molecular biomarkers for early tumour detection and new treatment targets that will warrant the efficacy of cancer therapy (57). Novel application of Me-4FDG as a PET probe revealed SGLT functional activity in pancreatic, prostate, and brain cancers and identified these proteins as potential targets of cancer therapy (28, 29, 58, 59), more precisely, as targets of SGLT inhibitors, which are currently used in diabetes treatment. However, there is still much to learn about the expression and the role of SGLTs in different cancers. The expression/overexpression of SGLT1 and SGLT2 has been reported in colon/colorectal, lung, ovarian, head, neck and oral squamous carcinomas, but the precise localisation and importance of these findings is questionable due to nonspecific SGLT antibodies used in the studies. Therefore, it is undoubtedly important to analyse their functional activity and investigate other SGLT isoforms in cancers. Furthermore, the SGLT-specific Me-4FDG PET imaging probe, rather than 2-FDG, may be a novel tool in diagnosing and staging cancers. The exact role of SGLTs in the development and progression of different cancer types and their contribution to new therapies remains to be elucidated.

Conflicts of interest

None to declare.

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Prijenosnici natrija i glukoze: nove mete ciljanih terapija u liječenju raka?

Glukoza, glavni izvor metaboličke energije, ulazi u stanicu na dva načina: 1) olakšanom difuzijom pomoću prijenosnika glukoze GLUT i 2) sekundarno aktivnim prijenosom pomoću prijenosnika natrija i glukoze SGLT. Stanice raka imaju povećani unos glukoze u usporedbi s normalnim stanicama. Prethodna istraživanja pokazala su povećanu ekspresiju prijenosnika GLUT, uglavnom GLUT1, u mnogim tipovima raka. Radiofarmaceutik (engl. *tracer*) 2-deoksi-2-(^{18}F) fluoro-D-glukoza (2-FDG), koji se koristi za detekciju tumorskih stanica putem GLUT1, nije dovoljno osjetljiv i specifičan. Uskoro bi mogao biti zamijenjen α-metil-4-(F-18) fluoro-4-deoksi-D-glukopiranozidom (Me-4FDG), novim i visoko osjetljivim, i specifičnim SGLT-radiofarmaceutikom u kliničkoj detekciji i određivanju stadija tumora. Tim je radiofarmaceutikom nedavno dokazana funkcionalna aktivnost prijenosnika SGLT u raku gušterače, prostate i mozga. Ekspresija mRNA i proteina SGLT također je pronađena u raku debelog crijeva, pluća, jajnika, glave, vrata i pločastih stanica usne šupljine. Prijenosnici SGLT nedovoljno su istraženi u raku, a njihova ekspresija i lokalizacija često su oprečne zbog nedostatka specifičnih SGLT-protutijela. U ovom preglednom radu opisujemo trenutačna znanja o povećanoj ekspresiji prijenosnika SGLT1 i SGLT2 u različitim tipovima raka. Spoznaje o ekspresiji i/ili lokalizaciji prijenosnika SGLT u malignim stanicama pomoći će u razvoju novih terapija u liječenju raka korištenjem već poznatih antidijabetika, SGLT2 ili SGLT1/SGLT2 inhibitora.

KLJUČNE RIJEČI: *Na$^+$-ovisni prijenosnici glukoze; pozitronska emisijska tomografija; rak gušterače; rak mozga; rak prostate; SGLT inhibitori*