Clinical Significance of Taurine and Creatine Transporters

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Cancer cells are characterized by uncontrolled growth, proliferation, and impaired apoptosis. Tumour progression could be related to poor prognosis and due to this fact, researchers have been working on novel therapeutic strategies and antineoplastic agents. It is known that altered expression and function of solute carrier proteins from the solute carrier 6 (SLC6) family (taurine (SLC6A6) and creatine (SLC6A8)) could be associated with severe diseases, including cancers. These proteins were noticed to play important physiological roles through transferring nutrient amino acids, osmolytes, neurotransmitters, and ions, and many of them are necessary for survival of the cells.

taurine transporter TauT creatine transporter CT-1 cancer

1. Introduction

The International Agency for Research on Cancer in 2020 published that three of the most common types of cancers were breast, lung, and colon cancers. Among them, lung and colon cancers were the most frequent causes of death in both males and females. The third reason of death was liver cancer [1]. Killing neoplasm cells without damaging normal tissues seems to be a crucial issue in antitumour therapies. The cancer therapeutic strategies could be divided into a few groups: chemotherapy, radiotherapy, immunotherapy, targeted therapy, and surgery. Therapies could also be concentrated on the specific cancer proteins or signalling pathways [2]. In the literature, it was proposed that proteins which transport some nutrients could be a promising target for cancer therapy [3][4]. It is known that transporter SLC6A14 ($ATB^{0,+}$), which carries neutral and basic amino acids, is considered as a potential biological target for the treatment of colon, breast, and pancreas cancers [5][6][7].

2. Clinical Significance of SLC6A6 and SLC6A8 Transporters

Transporters from the solute carrier 6 (SLC6) family could play multiple physiological roles. They take a part in neurotransmission, cell nutrition, and help in the maintenance of homeostasis. Impairment of their function can be associated with severe disorders [8]. In the literature, there were described diseases connected with mutations of taurine (TauT, SLC6A6), such as Gly399Val and Ala78Glu which are connected with childhood progressive retinal degeneration and cardiomyopathy [9][10]. Studies published in 2021 showed that taurine transporter potentially could be involved in myocardial dysfunction and dilated cardiomyopathy (DCM) [11]. This analysis was connected with the identification of DCM-associated locus on chromosome 3p25.1 which encoded taurine (SLC6A6) gene,

expressed among others in the heart [11]. The studies on animals showed that mice with TauT knockout displayed dilated cardiomyopathy [12]. Lack of the taurine transporter also may increase sensitivity to stress and be responsible for accelerated aging [12]. In other studies, the administration of taurine in mice with Duchenne muscular dystrophy was useful in preventing late heart dysfunction [13]. On the other hand, one of the most severe diseases connected with creatine (CT-1, SLC6A8) transporter mutation is X-linked creatine transporter deficiency (CTD) [14], which leads to cerebral creatine deficiency syndrome (CCDS). Creatine is necessary for brain functioning, and its deficiency could be associated with intellectual disorders, behavioural changes (ADHD, autism, social anxiety), language and walking development delay, problems with coordination, and dystonia. Additionally, patients with CTD suffer from gastrointestinal problems (ulcers, vomiting, constipation) as well as cardiomyopathy, ophthalmologic problems, and bladder dysfunction [14][15]. There were noticed about 80 mutations which cause creatine transporter deficiency syndrome [14]. Interestingly, Ala404Pro substitution is connected with mild CTD, whereas Pro382Leu leads to severe symptoms [14]. In rats' CTD model with Tyr389Cys mutation, the transporter is completely inactive [16]. Many creatine (SLC6A8) mutations cause folding defects [14]. In the case of impaired transport of creatine in the brain, the treatment strategy could be supplying creatine analogues which penetrate the blood–brain barrier, for example cyclocreatine, which is also CT-1 substrate [17]. Another disease, where a low level of CT-1 was noticed is inflammatory bowel disease (IBD) [18]. It was studied that CT-1 takes a part in wound healing and barrier formation in the intestinal epithelial cells. Patients with IBD have a lower concentration of CT-1 mRNA in the colon tissues, in comparison with the control, healthy patients. It may suggest that a lower level of CT-1 leads to the weaker barrier function of intestinal cells [18]. As it was described, severe diseases can be caused by transporters mutation and decreased function. On the other hand, overexpression and increased activity of SLC6A6 or SLC6A8 proteins were described in several types of cancer [19][20][21][22].

2.1. Taurine Transporter Overexpression in Cancer

Overexpression of the taurine transporter was noticed in a few types of cancers such as gastric and colorectal cancer [19][20]. The connection between taurine transporter and gastric cancer was evaluated using clinical outcomes and expression datasets, such as Gene Expression Omnibus, The Cancer Genome Atlas, and Human Protein Atlas [19]. It was found that expression of TauT was higher in gastric cancer tissue in comparison to the normal tissues. Based on immunochemistry data, it was also noticed that the intensity of SLC6A6 staining with anti-SLC6A6 antibodies was mostly stronger in cancer tissue in comparison to the normal cells [19]. High expression of TauT was found to be connected with poor prognosis and the factors such as advanced tumour stage, aggressive, especially invasive cancer. It was suggested that taurine transporter could be a diagnostic marker or potential biological target for anticancer agents [19].

Overexpression of taurine transporter was connected with colorectal cancer (CRC) progression [20]. As noticed before, this type of cancer is one of the most common neoplasms in the world [1]. It was detected that overexpression of the SLC6A6 increases survival and anti-apoptotic effects of CRC cells but does not influence their proliferation [20]. DNA microarray analysis showed that the SLC6A6 gene was highly expressed in five CRC cell lines (SW480, LoVo, DLD1, HT-29, and HCT116). This effect was not observed in healthy colonocytes [20]. Analysis of qPCR and ISH (in situ hybridization) was performed to validate the candidate colorectal cancer

markers. These studies indicated TauT (SLC6A6 gene) as a novel CRC-specific surface marker [20]. Further, to develop the pathological role of the transporter in CRC, knockdown (KD) of the SLC6A6 gene in DLD1, HT-29, and HCT-15 cell lines was performed. As a result, it was observed that taurine uptake was significantly less effective in comparison to the control cell lines. The growth of tested KD cells was significantly lower, but the cell cycle showed no clear differences. Authors suggested that TauT takes a part in the regulation of the survival of CRC cells [20]. It was tested how SLC6A6 signalling could influence the side population (SP) cells and their cancer stem cell (CSC)-like properties [20]. It is known that treatment failure of CRC may be associated with the appearance of chemotherapy-resistant CSC which could present some anti-apoptotic properties [23]. In SLC6A6-KD cells, SP cells, which are characterized by higher survival rates than other cells, as well as CSC markers (LGR5, ALDHI) were diminished in comparison to the control. Additionally, the expression of colorectal cancer markers was decreased in SLC6A6-KD lines. To evaluate the prosurvival role of the TauT, Colo320DM cells were transfected with the SLC6A6 gene. The CRC cell line with high expression (Hi) of the transporter presented increased taurine uptake in comparison to the control. It was noticed that, in the late log phase, SLC6A6-Hi cells were growing, whereas control cells did not survive [20]. In numbers, about 90% of CRC Hi cells lived, when about 80% of control cells died. Additionally, in contrast to the transporter KD cells, percentage of SP cells was higher in the tested Hi lines [20]. TauT has an important role in the survival, keeping of the CSC population and their properties. These findings suggest that taurine transporter plays an important role in cancer development and could be a promising target in novel CRC therapies [20].

TauT showed higher expression in cervical cancer (CC) tissue compared to normal cervical samples [24]. Reduced miRNA level (miR-3156-3p) was identified in HPV-positive CC tissue. Downregulation of miRNA was potentially involved in cell growth promotion and lower apoptosis in HPV18-positive Hela cells, HPV16-positive SiHa, and Caski cells [24]. The bioinformatic studies proposed that the SLC6A6 gene is a possible target for miR-3156-3p. Western blot analysis showed that CC cells with over- or underexpression of this miRNA exhibited a negative correlation with SLC6A6 level. Results suggest that miR-3156-3p regulates the expression of the SLC6A6 at the post-transcriptional level. Additionally, it was found that SLC6A6 mRNA level was significantly higher in HPV-positive CC samples, in comparison to the normal cells [24]. Therefore, TauT could play a significant role in the development of cervical carcinoma. However, its exact role in this process requires future studies [24].

As noticed above, taurine transporter possibly makes a contribution to colon cancer development through its prosurvival and anti-apoptotic properties [20]. Overexpression of SLC6A6 was found also in gastric cancer, which was connected with poor prognosis, advanced tumour stage, and aggressiveness of cancer [19]. The role of TauT in the development and progression of tumours needs further studies, although the application of its inhibitors seems to be a novel potential therapeutic strategy, especially in colon cancer. An invention with monoclonal antibodies was also proposed, possibly conjugated with anticancer agents, which could recognize the extracellular domain of SLC6A6 [25].

2.2. Creatine Transporter Contribution in Cancer

The altered level and activity of creatine transporter can be connected with tumour development. Analysis of literature data showed that an elevated level of SLC6A8 was noticed in breast [26], non-small cell lung [21] or hepatocellular cancers [27]. In clinical trials, inhibition of CT-1 is tested for the treatment of colorectal carcinoma [28]. These findings indicate that the transporter is a suitable biological target for anticancer agents.

Creatine transporter was found to be overexpressed in the most aggressive subtype of breast cancer (BC)—triple-negative (TNBC), which is connected with poor prognosis [26]. TNBC is a neoplasm without the expression of receptors for oestrogens and progesterone and without amplification of human epidermal growth factor receptor 2 (HER2) [29]. It was observed that the level of CT-1 was associated with advanced tumour development, histological grade, and low condition of patients [26]. These effects possibly are caused by the anti-oxidant activity of the main substrate of CT-1. The fast-growing tumour often presents hypoxic regions which could be associated with the production of reactive oxygen species (ROS). A low level of ROS is related to cancer progression: angiogenesis and metastasis while a high level of ROS leads to cancer cell death [30]. Data analysis showed that the SLC6A8 gene was upregulated under hypoxia, which suggests that creatine can function as an antioxidant molecule in cancer cells [26]. In hypoxic TNBC cells, the activity of SLC6A8 mediated intracellular accumulation of creatine, which caused survival of cancer and decreased apoptosis by keeping homeostasis [26]. Creatine possibly takes a part in the protection of cells under hypoxic conditions by activating the AKT-ERK1/2 signalling pathway. It leads to upregulation of pro-survival Ki-67, Bcl-2, and downregulation of proapoptotic Bax protein [26]. Studies showed that the expression of the transporter under hypoxic conditions was regulated by p65/NF-κB. Tests on TNBC lines with silenced p65/NF-κB showed reduction of SLC6A8 expression. It was claimed that upregulation of SLC6A8 leads to higher creatine usage. Studies on cell models with inactive SLC6A8 transporter presented low intracellular creatine concentration [26]. To evaluate the cancer-promoting features of creatine, the cancer cell lines MDA-MB-231 with functional and nonfunctional SLC6A8 were orthotopically inoculated into mice. Animals before and during the procedure were supplemented by creatine solution injected intraperitoneally. These in vivo studies showed that mice injected with tumour cells with functional SLC6A8 presented severe disease and a higher amount of intratumour creatine as well as lower ROS levels [26]. Authors concluded that overexpression of SLC6A8 induced by hypoxic condition leads to intratumoral accumulation of creatine and helps in keeping redox homeostasis. These effects are connected with TNBC cell growing and survival [26]. Described studies showed that inhibition of CT-1 is a promising therapeutic option for the treatment of TNBC with high levels of SLC6A8 [26].

Interesting results were published in 2021. It was shown that therapeutic targeting of creatine transporter suppresses colon cancer progression and modulates creatine levels [28]. The studies evaluated compound RGX-202 (ompenaclid) which mimics creatine and competitively inhibits its transport by CT-1. The biological activity of RGX-202 was checked in wild-type mice and SLC6A8 knockout mice. An animal model with SLC6A8 knockout showed an undetectable level of d^3-creatine in the heart tissue, while in WT the uptake of substrate was inhibited by RGX-202 in 75%. These findings proved ligand activity [28]. Following, it was checked how the inhibitor influenced CT-1 in tumour cells. The compound suppressed tumoral transport of labelled creatine by 50% in pancreatic tumour-bearing mice. In highly metastatic colorectal cancer cell lines (LS174T Lvm3b) under hypoxia condition, the inhibitor led to the significant reduction of the amount of phosphocreatine, which is the source of high-energy phosphate [28]. A low level of intracellular creatine or its phosphate derivative was connected with a

reduced ATP level. ATP and phosphocreatine are necessary for the growth and progression of the tumour under hypoxic conditions [28]. In Lvm3b cancer cells, RGX-202 leads to the suppression of CRC growth. In animal models, the administration of the drug caused tumour growth inhibition (TGI). Lvm3b with KRAS oncogene mutation (G12D), which is a highly aggressive and metastatic cancer, were implanted subcutaneously into athymic nude mice. Oral treatment with RGX-202 began after tumours were bigger than 30 mm^3. Inhibitors led to about 50% of TGI upon obtaining by cancer size above 500 mm^3. Treatment improved survival of mice, from 23 to 48 days. In one among nine animals, cancer presented a complete regression response. Similar observations were noticed in the case of implanted HT29 cells: regression in case of large size of cancer (>900 mm^3) and prolonged mice lives. Additionally, it was noticed that drug treatment increased tumour cell apoptosis. In the PDX (patient-derived xenograft) studies, the compound showed antitumour effects against several CRC subtypes [28].

In further studies, it was proved that CT-1 inhibition can give synergistic effects with 5-fluorouracil or leflunomide. The combination of RGX-202/5-FU led to a 99% reduction in cancer cell growth and enhanced mice survival [28]. RGX-202 was pharmaceutically optimized and under the name RGX-202-01 is currently being investigated in the first phase of clinical trials alone and in a combination with FOLFIRI with or without bevacizumab [28][31]. It was noticed that ligand increased the level of creatine in the serum and urine in patients with gastrointestinal cancer [28]. Inhibiting CT-1 and decreasing the intracellular level of creatine lead to the suppression of the cancer cell development. These findings strongly proved that the SLC6A8 transporter is a potential biological target for colorectal cancer therapy.

During other studies, the bioinformatic analysis allowed to claim that in non-small cell lung cancer (NSCLC), the level of SLC6A8 was increased, and it was related to poor prognosis [21]. In several probes of NSCLC, high impact of the transporter was detected in comparison to the normal epithelial cells. Moreover, it was noticed that overexpression of creatine transporter promotes in vitro proliferation, migration, and invasion of NSCLC [21]. Non-small cell lung cancer lines H1299 with knockdown of SLC6A8 presented inhibited proliferation, whereas overexpression of SLC6A8 in H520 lines was connected with induced proliferation. Downregulation or upregulation of SLC6A8 activity influenced different cell cycle stages of cancer: G1 and S, respectively [21]. It was detected that H1299 cells with silenced CT-1 revealed reduced migration and invasion properties. Overexpression of SLC6A8 was correlated with high level of the invasion and migration factor—matrix metalloproteinase-9 (MMP9) [32], whereas lack of SLC6A8 gene led to downregulation of MMP9 protein [21]. Interestingly, promoting a progression could be connected with the notch signalling pathway as well as E-cadherin [21]. Therefore, blocking SLC6A8 activity in NSCLC cell lines by inhibitors seems to be an interesting field for biological studies.

The data analysis presented an abnormal SLC6A8 expression level in lung adenocarcinoma (LUAD) [22]. It was suggested that overexpression of CT-1 in LUAD is connected with poor prognosis. CT-1 possibly could be used as a cancer prognostic biomarker [22]. Creatine transporter may be a potential target in the treatment of hepatocellular cancer [27]. Study on human hepatocellular carcinoma cells (Huh-7 and Hep3B) with knockdown of the SLC6A8 gene showed that the lack of transporter leads to decrease of proliferation, induction of apoptosis, blockage of cell migration, and invasion [27]. The effect of CT-1 silencing is important in potential carcinoma therapy [27].

Literature data confirm that taurine and creatine transporter can be considered as targets in the treatment of several diseases. Diminished activity of TauT and CT-1 is mainly observed in genetic disorders [11][14][15], whereas overexpression could be associated with several types of cancers [19][20][21][22][26] (**Table 1**). The most important case to utilize both transporters as targets could be colorectal cancer, especially the one with poor prognosis [1]. Overexpression and over-activity of SLC6A6 transporter leads to survival of cancer cells. In the case of CT-1, inhibiting the transport of its substrate leads to tumour growth suppression [20][28]. Modifying activity of SLC6A8 by inhibitors may be tested in TNBC cells as well as NSCLC [21][26]. The exact roles of TauT and its overexpression in the development of cervical and gastric cancer need further studies (**Table 1**). Generally, decreasing the activity of taurine and creatine transporters could be a promising approach in antitumour therapy. As mentioned, an inhibitor of SLC6A8-RGX-202-01 is tested against gastrointestinal tract cancer, which proves the utility of such compounds [28]. There are known several groups of inhibitors, but novel compounds are expected to be developed and tested.

Table 1. Taurine and creatine transporters are associated with several types of cancer.

Gene Name	Transporter Name	Type of Cancer	Ref.
SLC6A6	Taurine transporter	Gastric cancer	[19]
		Colorectal cancer (CRC)	[20]
		Cervical cancer (CC)	[24]
		Triple-negative breast cancer (TNBC)	[26]
SLC6A8	Creatine transporter	Colorectal cancer (CRC)	[28]
		Non-small cell lung cancer (NSCLC)	[21]
		Lung adenocarcinoma (LUAD)	[22]
		Hepatocellular cancer	[27]

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