THE ROLE OF MEMBRANE TRANSPORT PROTEINS IN 5-ALK-INDUCED ACCUMULATION OF PROTOPORPHYRIN IX IN TUMOR CELLS

Ivanova-Radkevich V.I.[1], Kuznetsova O.M.[1], Filonenko E.V.[2]
[1]Peoples' Friendship University of Russia (RUDN University), Moscow, Russia
[2]P.A. Herzen Moscow Oncology Research Center – branch of FSBI NMRRC of the Ministry of Health of the Russian Federation, Moscow, Russia

Abstract

Features of the expression of membrane importers of 5-ALA, as well as transporters involved in the removal of photoactive precursors of protoporphyrin IX (PPIX) (uro-, copro- and protoporphyrinogens), may cause differences in the effectiveness of photodynamic therapy of malignant neoplasms using 5-aminolevulinic acid (5-ALA). Increased expression of ALA transporters is associated with an increase in the intensity of PPIX synthesis. When the expression of PPIX exporters increases, there is a decrease in PPIX concentration. The review describes the main transporters of 5-ALA, uro-, copro- and protoporphyrinogens, provides data on their expression in various tissues, and discusses the possibility of predicting the effectiveness of photodynamic therapy considering the expression of the corresponding transport proteins in malignant tissues.

Key words: photodynamic therapy, 5-aminolevulinic acid, protoporphyrin IX, transmembrane transporters.

Contacts: Ivanova-Radkevich V.I., e-mail: ivanova-radkevich-vi@rudn.ru

For citations: Ivanova-Radkevich V.I., Kuznetsova O.M., Filonenko E.V. The role of membrane transport proteins in 5-ALA-induced accumulation of protoporphyrin iX in tumor cells, *Biomedical Photonics*, 2024, vol. 13, no. 2, pp. 43–48. doi: 10.24931/2413–9432–2024–13–2 –43–48.

РОЛЬ МЕМБРАННЫХ ПЕРЕНОСЧИКОВ В НАКОПЛЕНИИ 5-АЛК-ИНДУЦИРОВАННОГО ПРОТОПОРФИРИНА IX В ОПУХОЛЕВЫХ КЛЕТКАХ

В.И. Иванова-Радкевич[1], О.М. Кузнецова[1], Е.В. Филоненко[2]
[1]Российский Университет дружбы народов, Москва, Россия
[2]«Московский научно-исследовательский онкологический институт им. П.А. Герцена – филиал ФГБУ «Национальный медицинский исследовательский центр радиологии» Министерства здравоохранения Российской Федерации, Москва, Россия

Резюме

Одной из причин различий в эффективности фотодинамической терапии с применением 5-аминолевулиновой кислоты (5-АЛК) при различных типах злокачественных новообразований могут быть особенности экспрессии в этих тканях мембранных транспортеров, участвующих в переносе самой 5-АЛК в опухолевые и нормальные клетки, а также в выведении из клеток предшественников фотоактивного протопорфирина IX (ППIX) – уро-, копро- и протопорфириногенов. Повышенная экспрессия первых связана с увеличением интенсивности синтеза ППIX. При повышении экспрессии вторых наблюдается снижение скорости синтеза ППIX. В настоящем обзоре описаны основные транспортеры 5-АЛК, уро-, копро- и протопорфириногенов, приведены данные об их экспрессии в различных тканях, обсуждены возможности прогнозирования эффективности фотодинамической терапии с учетом экспрессии указанных транспортеров в злокачественных тканях.

Ключевые слова: фотодинамическая терапия, 5-аминолевулиновая кислота, протопорфирин IX, трансмембранные переносчики.

Контакты: Иванова-Радкевич В.И., e-mail: ivanova-radkevich-vi@rudn.ru

Для цитирования: Иванова-Радкевич В.И., Кузнецова О.М., Филоненко Е.В. Роль трансмембранных переносчиков в накоплении 5-АЛК-индуцированного протопорфирина IX в опухолевых клетках // Biomedical Photonics. – 2024. – Т. 13, № 2. – С. 43–48. doi: 10.24931/2413–9432–2024–13–2–43–48.

Introduction

Photodynamic therapy (PDT) is widely used in Russia and around the world for the treatment of tumor and other diseases [1,2,3,4,5]. Antitumor PDT is based on the selective accumulation of a photosensitizer in pathological tissue. When irradiated with light of a certain wavelength, the photosensitizer causes the formation of singlet oxygen and other cytotoxic compounds that damage the structural elements of tumor tissue [1,6]. A photosensitizer as part of a drug can be introduced into the patient's body, or it can be synthesized inside target cells from an exogenous precursor. Such precursors (pro-photosensitizers) include 5-aminolevulinic acid (5-ALA). 5-ALA is an endogenous non-photoactive compound, an intermediate metabolite of heme biosynthesis. 5-ALA enters tumor cells and is included in heme synthesis after administration into the patient's body. 5-ALA is quickly converted into heme and is used to build hemoproteins in normal cells. While in tumor cells the synthesis is inhibited at the last stage due to a deficiency of the enzyme ferrochelatase, which catalyzes the last reaction of heme synthesis. An intermediate product, photoactive protoporphyrin IX (PPIX) accumulates in the cell as a result [1,6].

The ability of exogenous 5-ALA to induce the synthesis of photoactive PPIX depends on the tissue type (in particular, how well the tissue is vascularized) and the cell type. One possible explanation for the different intensity of PPIX accumulation in different cells may be the difference in the rate of uptake of 5-ALA by cells and elimination of intermediate products of heme synthesis (uroporphyrinogens, coproporphyrinogens, protoporphyrinogens) by cells [7].

Exogenous 5-ALA can enter the cell by active transport through several transporters, including the peptide transporters PEPT1 and PEPT2, the amino acid transporter PAT1, as well as TauT and GAT2 [7]. The question arises: does increased expression of these transporters affect the uptake of 5-ALA by tumor cells compared to normal cells? Will this affect the intensity of PPIX accumulation? In addition, the role of transporters that remove intermediate metabolites of heme synthesis from cells cannot be neglected [7]. In our review, we would like to discuss the role of various transmembrane transporters in the accumulation of photoactive PPIX.

PEPT1 (SLC15A1)

The peptide transporter PEPT1 is most widely known as the transporter of dipeptides and tripeptides formed during the digestion of proteins through the apical membrane into enterocytes [8]. Theoretically, all chemical compounds that have sufficient steric similarity to dipeptides or tripeptides are potential substrates for PEPT1 [8]. As a result, PEPT1 may be involved in the transmembrane transport of many drugs. As a result, PEPT1 may be involved in the transmembrane transport of many drugs. 5-ALA does not have a peptide bond but is a high-affinity substrate for PEPT1/2 due to its ketomethylene group [8].

A direct transfer of 5-ALA across the membrane of Xenopus laevis oocytes and Pichia pastoris yeast cells expressing PEPT1 was demonstrated by Döring et al. in 1998 [9].

PEPT1 is thought to be the largest contributor to the transport of 5-ALA across the intestinal epithelium [10]. In 2016, studies on wild-type mice with the *Pept1* gene showed significant permeability of cells in the duodenum, jejunum and ileum to 5-ALA when taken orally. Moreover, in mice with Pept1 knockout, the permeability of small intestinal cells was reduced by 10 times, and the peak concentration of 5-ALA in plasma was reduced by 2 times compared to wild-type animals [11]. The study authors noted that the transport of 5-ALA into small intestinal cells occurred without apparent contributions from other transporters, including proton-associated amino acid transporter 1 (PAT1). However, PEPT1 had a slight effect on the distribution of 5-ALA along the periphery tissue [11]. This may indicate that in peripheral tissues the contribution of other transporters to the supply of 5-ALA may be more significant.

Interestingly, in wild-type mice, the rate of 5-ALA membrane transport in the duodenum, jejunum and ileum was 9-14 times lower than in the colon, and this difference is consistent with the PEPT1 protein expression pattern observed in mice [11,12].

In addition to enterocytes, PEPT1 is also expressed in other tissues: the stomach, bladder, and extrahepatic bile ducts.

In 2003, 5-ALA was shown to enter cells in human cholangiocarcinoma SK-ChA-1 cells via the PEPT1 transporter [13]. Ten years later, Chung et al. confirmed the transmembrane transfer of 5-ALA with the participation of PEPT1 in cholangiocyte cell lines derived from bile duct carcinoma [14].

In studies on human gastric cancer cells KKLS, NKPS and TMK-1, the effectiveness of 5-ALA-induced PDT was also associated with high expression of PEPT1 and simultaneously low expression of the ATP-binding cassette transporter ABCG2 (involved in the clearance of PPIX through the membrane). The expression of these transporters together determines the efficient formation and accumulation of PPIX after exogenous administration of 5-ALA [15]. Similar results were obtained in a study of bladder tumor samples: the accumulation of PPIX was due to increased expression of PEPT1 and decreased expression of ABCG2 [10].

An interesting observation was made by Lai et al. [16]: while PEPT1 was highly expressed in normal lung cells WI38, PEPT1 was not expressed in non-small cell lung cancer cells A549.

PEPT2 (SLC15A2)

PEPT2 is widely expressed in the tissues, especially kidney, brain and lung [11]. PEPT2 has been shown to play a central role in the reabsorption of 5-ALA from the glomeru-

lar filtrate in human renal proximal tubular cells [17] and is also involved in the uptake of 5-ALA by astrocytes in newborn mice [18].

PAT1 (SLC36A1)

The amino acid transporter PAT1 is involved in the membrane transport of small neutral amino acids such as proline and γ-aminobutyric acid (GABA). In its chemical structure, 5-ALA is like GABA. This is the basis for the possibility of 5-ALA transport through the GABA membrane transporters [19]. Several experimental studies provide evidence for the involvement of PAT1 in 5-ALA transport. Thus, Xenopus laevis oocytes expressing PAT1 more actively absorb 5-ALA [20].

In a study by Lai et al. [16], as well as for PEPT1, showed a difference in the expression of PAT1 in normal and malignant cells originating from the same organ: expression was quite high in healthy prostate cells PrEC, while it was almost absent in prostate cancer cells DU145.

TauT (SLC6A6) and GAT2 (SLC6A13)

In addition to PAT1, GABA is also a substrate for the TauT and GAT2 transporters, raising questions about whether they are involved in the transmembrane transport of 5-ALA [7]. According to some data, both transporters are highly expressed in many human tissues, especially in brain and liver cells [21]. Studies by others show that the highest levels of GAT2 mRNA are found in the liver and kidneys, whereas levels in the cerebellum and cerebral cortex are low [22]. In addition, high levels of the transporters are found in the stomach and retina [23].

In their study, Tran et al. assessed 5-ALA-induced protoporphyrin accumulation in DLD-1 colon cancer cells, HeLa cells, and HEK293. PPIX was not synthesized in the absence of exogenous 5-ALA. The authors used GABA homologs to evaluate the efficiency of 5-ALA transfer. The inhibitory effect of GABA homologs on 5-ALA-induced PPIX accumulation in HeLa cells was less than that observed in DLD-1 cells. Knockdown of GAT2 in HeLa cells resulted in a slight decrease in PPIX levels, suggesting the presence of alternative transporters in these cells. Simultaneous knockdown of TauT and GAT2 in HeLa cells resulted in a significant decrease in PPIX levels, indicating an important role of TauT in 5-ALA transport in these cells [24]. The authors also note that HEK293 renal adenocarcinoma cells, when overexpressed with either TauT or GAT2, induced a significant increase in PPIX production. The results of the described experiments confirm the significant contribution of the TauT and GAT2 transporters to the penetration of 5-ALA into the cell [24,25].

Neoplastic cells exhibit an increased requirement for certain metabolites, including amino acids, and adapt to this requirement not only through increased expression of transporters, but also through the expression of isoforms not found in normal tissues. Based on the overlapping specificities of amino acid transporters and neurotransmitters, increased expression of these transporters may explain the greater accumulation of PPIX in various cancer cells, including HeLa cells [24].

TSPO1/2

The TSPO protein is also involved in the transmembrane transport of 5-ALA. It exists as two isoforms: TSPO1 is mainly localized in the outer membrane of mitochondria, while TSPO2 is found in the plasma membrane of red blood cells. The work of Manceau et al. [26] showed that the intensity of 5-ALA-induced accumulation of PPIX in erythroleukemia cells (UT-7 and K562) decreased when a specific competitive inhibitor TSPO1/2 was added to the medium (inhibitor code PK 11195). PK 11195 did not change the activity of heme biosynthetic enzymes. From the data obtained, the study authors concluded that the limiting factor in heme synthesis was the penetration of 5-ALA through the plasma membrane. However, PK 11195 had no effect on porphobilinogen (PBG)-induced PPIX accumulation, suggesting that TSPO2 is a selective 5-ALA transporter. Further evidence for the role of TSPO2 in membrane transport of 5-ALA is the fact that overexpression of TSPO2 on the plasma membrane of erythroleukemia cells increased 5-ALA-induced accumulation of PPIX [26]. The described patterns are rather important for determining the mechanism and the possibility of influencing the development of congenital sideroblastic anemia, however, potentially, data on the expression of TSPO2 in other tissues can be used to predict the effectiveness of PDT in tissues expressing TSPO.

ABCG2

ABCG2, a protein used to transport compounds against their concentration gradient using ATP hydrolysis as an energy source, has been identified as an exporter of PPIX and heme in mammals [27]. These data are supported by experiments with ectopically expressed ABCG2, which exports ZnMP (zinc-containing mesoporphyrin, used as a heme analog in experimental models) into K562 cells [28]. ABCG2 is expressed in a wide range of tissues, including hematopoietic stem cells and erythroid progenitor cells. High protein concentrations are found in the duodenum, small and large intestines, rectum, seminal vesicles and endometrium. The distribution of the transporter in tissues that have a predominantly secretory or barrier function leads to the idea that ABCG2 plays an essential role in controlling the distribution and tissue exposure of the different chemical compounds, such as antibiotics, sterols, immunosuppressants (including anti-HIV drugs), fluorescent dyes (for example, Hoechst 33342), photosensitizers (pheophorbide A and PPIX). Increased expression of ABCG2 has been associated with multidrug resistance in cancer [29].

The level of ABCG2 expression is especially high in the early stages of hematopoiesis [30]. Like FLVCR1-mediated heme export, ABCG2 possibly exports and transfers heme to extracellular heme-binding proteins such as albumin [31]. However, unlike FLVCR1, ABCG2 has a wide range of substrates, including porphyrin and non-porphyrin sub-

strates, suggesting that ABCG2 may not be a functional backup to FLVCR1.

The activity of ABCG2, which is used for PPIX transport, also affects the fluorescence intensity of PPIX. Thus, the combined use of 5-ALA and Ko143, a specific inhibitor of ABCG2, on a model of cultured cancer cells MCF-7 and MDA-MB 231 increased the fluorescence intensity of PPIX compared to cultured non-cancerous MCF10A cells [32]. And in the study by Hagiya et al. [10] showed that the selective accumulation of PPIX in bladder cancer cells is caused precisely by an increase in the expression of PEPT1 and a decrease in the expression of ABCG2.

ABCB6

ABCB6 is a heme-binding ATP-dependent transport protein that can interact with various tetrapyrroles, such as heme, coproporphyrin III, PPIX and plant porphyrin, pheophorbide A. ABCB6 can be localized both in the outer mitochondrial membrane and in the plasma membrane [33]. The basal level of metabolites of heme synthesis metabolites is maintained by ATP-independent transporters, this level is sufficient for the survival of the organism. But under stress conditions, the work of ATP-dependent transporters, such as ABCB6, is necessary. When the level of the transporter is low, the synthesis of zinc protoporphyrin IX occurs, so it can be assumed that this transporter is also involved in iron homeostasis [33].

High concentrations of the transporter are found in the gallbladder, testes and epididymis [23].

FLVCR1

FLVCR1 is an export protein and has a narrow spectrum of substrates, including heme, PPIX and coproporphyrin. FLVCR1 is localized on the surface of the plasma membrane [34]. FLVCR1 is actively expressed in various hematopoietic cells, and low-level expression is found in the fetal liver, pancreas, and kidneys [35]. Ectopic expression of FLVCR1 reduces intracellular concentrations of PPIX. This is supported by experiments using ZnMP, which mediates PPIX efflux in K562 rat kidney epithelial and hematopoietic cells [34]. FLVCR1 is predicted to normally export heme when macrophages phagocytose senescent erythrocytes. Given that PPIX is also a substrate of FLVCR1, it is possible that PPIX efflux is mediated by this transport protein. Alves et al. showed that in nucleated erythrocyte progenitors from human bone marrow, FLVCR1 expression increased during erythropoiesis and reached a maximum level at an intermediate stage of maturation under conditions in which the heme oxygenase system was defective [36]. It is possible that FLVCR1 may export excess PPIX or heme to prevent toxicity under conditions in which heme degradation is not fully induced.

In addition to full-length FLVCR1 (FLVCR1a), there is another isoform, FLVCR1b, which is a smaller protein possibly localized to mitochondria [37]. Overexpression of FLVCR1b increases cytosolic heme concentration, whereas knockdown of FLVCR1b results in heme accumulation in mitochondria, indicating that FLVCR1b is an exporter of mitochondrial heme and possibly PPIX [37].

Increased expression of FLVCR1, according to several authors, is found in hepatocellular carcinoma and is associated with a higher stage of the disease and vascular invasion. FLVCR1 also plays a key role in cell survival, growth and migration in esophageal squamous cell carcinoma [38]. Given the high degree of homology between FLVCR2 and FLVCR1 [39], it is possible that FLVCR2 also promotes PPIX and heme efflux. FLVCR2 is expressed in a wide range of human tissues, including fetal liver, brain, and kidney [40]. However, the direct physiological role of FLVCR2 in PPIX and heme transport is currently unclear.

MFRN

Mitoferrins (MFRN) are transporters involved in the transport of iron ions into mitochondria. Transported iron ions are also used for intramitochondrial heme synthesis. According to Hayashi et al. [41], the level of iron in the mitochondria of tumor cells can be significantly lower than in normal cells. This is one of the reasons (besides the low activity of ferrochelatase) why the excess PPIX formed upon exogenous administration of 5-ALA is quickly utilized in normal cells and persists for a longer period in tumor cells. This difference in iron levels can be explained by decreased expression in tumor cells of mitoferrins, which transport iron across the mitochondrial membrane. A practical application of the results of this study may be to increase the effectiveness of PDT by additionally introducing iron supplements during the treatment period: in normal cells this can lead to a decrease in PPIX induced by exogenous administration of 5-ALA, but in tumor cells (due to low expression of mitoferrins) there is no such effect will be [41].

Practical use

Assessment of the expression level of the transporter proteins genes for 5-ALA and porphyrinogens (primarily PEPT1 and ABCG2) under certain conditions can be used to predict the rate and intensity of accumulation of 5-ALA-induced PPIX [8]. And in tumor tissues this may correlate with the effectiveness of PDT.

In addition, as some studies have shown [16], the expression of 5-ALA transporters in normal cells may be higher or like that in tumor cells of similar origin. For example, normal lung cells (WI38) express much more PEPT1 than their malignant counterparts (A549) [16]. According to the authors of the study [16], for such cells PDT can be less effective and the risk of developing phototoxicity can be higher. The study authors suggest that the application of appropriate transporter inhibitors to be used with PDT may be promising. Experimental results show that this strategy leads to an increase in the fluorescent contrast between malignant and normal cells: in normal cells with high expression of the transporter, the inhibitory effect is more pronounced [16].

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