

COMBINATION OF FERROPTOSIS AND PHOTODYNAMIC THERAPY IS AN EFFECTIVE STRATEGY FOR CANCER TREATMENT

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Abstract

This review examines in detail the theoretical foundations and practical aspects of using a combination of ferroptosis inducers and photosensitizers in experimental cancer therapy. Particular attention is given to comprehensive studies focusing on the combined use of these two therapeutic approaches. The results confirm the promise of further development in this research area.

Based on a combination of theoretical data and experimental studies, the effectiveness of a combined approach combining ferroptosis and photodynamic therapy (PDT) as an antitumor treatment strategy is convincingly demonstrated. A key factor determining the effectiveness of this combination is the synergistic antitumor effect, driven by interconnected biochemical processes, primarily the Fenton reaction. Ferroptosis involves a biochemical transformation capable of providing an additional source of oxygen, which is essential for effective PDT. In turn, PDT generates reactive oxygen species, which potentiate the Fenton reaction, thereby enhancing the processes leading to ferroptotic cell death in tumor cells. This creates a vicious cycle that greatly enhances the cytotoxic effect on malignant cells.

An analysis of experimental studies revealed that most studies used chlorin e6 and porphyrin derivatives as photosensitizers – compounds with proven photophysical properties. Erastin and its derivatives, as well as various iron compounds capable of effectively triggering and maintaining iron-dependent cell death, were most frequently used as ferroptosis inducers.

These data demonstrate the high potential of a combined strategy based on the coupling of ferroptosis and PDT and substantiate the need for further research in this area to develop new approaches to cancer treatment.

Key words: ferroptosis, photodynamic therapy, ferroptosis inducer, photosensitizer, antitumor activity.

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КОМБИНАЦИЯ ФЕРРОПТОЗА И ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ – ЭФФЕКТИВНАЯ СТРАТЕГИЯ ДЛЯ ЛЕЧЕНИЯ РАКА

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Резюме

В рамках проведенного обзора детально рассмотрены теоретические основы и практические аспекты применения комбинации индукторов ферроптоза и фотосенсибилизаторов в экспериментальной терапии злокачественных опухолей. Особое внимание в работе уделено комплексным исследованиям, фокусирующимся на совместном использовании двух терапевтических подходов. Полученные результаты подтверждают перспективность дальнейшего развития данного научного направления.

На основании совокупности теоретических данных и экспериментальных исследований убедительно продемонстрирована эффективность комбинированного подхода, объединяющего ферроптоз и фотодинамическую терапию (ФДТ), в качестве стратегии противоопухолевого лечения. Ключевым фактором, определяющим результативность такой комбинации, выступает синергетический противоопухолевый эффект, обусловленный взаимосвязанными биохимическими процессами, в первую очередь реакцией Фентона. В ходе ферроптоза реализуется биохимическое превращение, способное обеспечивать дополнительный источник кислорода,

необходимого для эффективного протекания ФДТ. В свою очередь, ФДТ генерирует активные формы кислорода, которые потенцируют реакцию Фентона, тем самым усиливая процессы, ведущие к ферроптотической гибели опухолевых клеток. В результате формируется замкнутый цикл, многократно повышающий цитотоксическое воздействие на злокачественные клетки.

Анализ экспериментальных работ показал, что в большинстве исследований в качестве фотосенсибилизатора используют хлорин еб и производные порфирина – соединения, хорошо зарекомендовавшие себя в ФДТ благодаря оптимальным фотофизическим характеристикам. В роли индукторов ферроптоза наиболее часто применяют эрастин и его производные, а также различные соединения железа, способные эффективно запускать и поддерживать процессы железозависимой клеточной гибели.

Представленные данные свидетельствуют о высоком потенциале комбинированной стратегии, основанной на сопряжении ферроптоза и ФДТ, и обосновывают необходимость дальнейших исследований в этой области для разработки новых подходов к лечению онкологических заболеваний.

Ключевые слова: ферроптоз, фотодинамическая терапия, индуктор ферроптоза, фотосенсибилизатор, противоопухолевая активность.

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Introduction

Modern oncology has achieved significant success in developing comprehensive treatment regimens that combine surgery, chemotherapy, and radiotherapy. However, problems such as recurrence, metastasis, the development of drug resistance, and the high toxicity of existing methods continue to have a negative impact on the prognosis and quality of life of cancer patients. This necessitates the search for and implementation of new therapeutic strategies characterized by high selectivity and lower toxicity.

Among promising approaches, photodynamic therapy (PDT) occupies a special place. It is based on the selective accumulation of a photosensitizer (PS) in tumor tissue followed by its activation with laser radiation of an appropriate wavelength. The photochemical reaction results in the generation of reactive oxygen species (ROS), which lead to tumor cell death through several mechanisms and also activate the immune response. An important advantage of PDT is the possibility of preserving the anatomical and functional integrity of organs, which is particularly valuable in clinical practice [1–2].

At the same time, the practical application of PDT is limited by a number of factors, including insufficient PS selectivity, limited depth of light penetration into tissues, and the need for high-tech equipment. To overcome these limitations, PS delivery systems based on nanocarriers are being actively developed; these systems make it possible to increase the drug concentration in the tumor and minimize its effect on healthy tissues [3–5].

Of particular interest in the context of enhancing PDT efficacy is ferroptosis, a type of iron-dependent programmed cell death characterized by excessive ROS generation and lipid peroxidation of cell membranes. Currently, the induction of ferroptosis is regarded as

a promising antitumor strategy, and the identified molecular intersections between PDT and ferroptosis open up opportunities for creating combined therapeutic approaches [6–8]. It is assumed that the combined use of PDT and ferroptosis inducers can provide a synergistic antitumor effect by enhancing oxidative stress in tumor cells [9–10].

This review systematizes current data on the combined use of PDT and ferroptosis induction. Particular attention is paid to research results obtained by scientific teams both abroad and in the Russian Federation. The work identifies certain trends characteristic of the current stage of development of this research area: the predominant use of already known photosensitizers and ferroptosis inducers, as well as a focus on traditional therapeutic targets such as breast cancer, gliomas, and glioblastomas. These patterns necessitate the development of new vectors for improving the method, in particular through the introduction of promising substances and the expansion of its therapeutic application.

Mechanism of the synergistic effect of photodynamic therapy and ferroptosis in cancer treatment

The mechanism of the synergistic effect of PDT and ferroptosis is very interesting but still insufficiently studied, due to the relatively recent discovery of the phenomenon of ferroptosis itself. Ferroptosis is a complex form of cell death associated with iron metabolism and characterized by the development of oxidative stress due to increasing lipid peroxidation of cellular lipids. The involvement of ferroptosis has been noted in the development of many pathological processes, such as fibrosis, inflammation, and tumors. The most important characteristics of ferroptosis, which have recently received considerable attention,

include the accumulation of ROS, an imbalance of the antioxidant system, disturbances in lipid peroxidation (LPO) metabolism, and iron homeostasis [11]. Ferroptosis is regulated by the fine interplay of three molecular pathways involving glutathione depletion, iron metabolism, and LPO. A number of substances are currently known to be ferroptosis inducers, some of which have previously been used as medicinal agents [12–14].

In turn, the cytotoxic mechanism of PDT is based on the use of PSs—dyes activated by laser light in the visible or near-infrared range. Their excitation by photons triggers, as in ferroptosis, the production of ROS and subsequently tumor cell death. The targeted nature and high efficacy of this therapy are due to the targeted delivery of the PS to the tumor area and the provision of a sufficient amount of oxygen for ROS generation.

Recent studies have changed the view of the PDT mechanism from a simple induction of oxidative stress leading to necrosis or apoptosis, adding to this already complex mechanism ferroptosis, pyroptosis, and other types of cell death [15]. For example, in GL261 glioblastoma cells subjected to PDT with the well-known and clinically used second-generation PS Photosens (aluminum hydroxide trisulfophthalocyanine), an interesting phenomenon was discovered: cell death induced by irradiation is blocked by the ferroptosis inhibitors ferrostatin-1 and deferoxamine (DFO), which indirectly indicates that this PS induces ferroptosis in GL261 cells upon photoactivation [16]. In Japan, ferroptotic activity was demonstrated for the widely known and clinically used sodium talaporfin (a second-generation PS), which was found to induce

ferroptosis in gastric and esophageal cancer cells [17]. Ferroptotic activity is also found in newly synthesized PSs with enhanced photodynamic efficiency, good biocompatibility, and lysosomal targeting [18]. There are studies demonstrating the contribution of ferroptosis to antitumor PDT using an activatable, adaptable nanocarrier based on a metal-organic framework. Thus, a group of Chinese scientists formed a metal-organic framework based on an imidazole ligand coordinated with zinc, into which chlorin e6 (Ce6, a second-generation PS) was encapsulated. The high antitumor efficacy of the nanocarrier in vivo was confirmed in mice with murine breast carcinoma in terms of suppression of tumor growth and prolongation of animal survival. Simultaneous administration of an iron chelator weakened the antitumor activity of the nanocarrier due to suppression of ferroptosis, as evidenced by enhanced tumor growth and restoration of glutathione peroxidase 4 (GPX4) activity [19].

Hypoxia in the tumor microenvironment, caused by high intracellular oxygen consumption and deformation of tumor blood vessels, hinders PDT. In this regard, increasing oxygen production in the tumor microenvironment is a promising direction for enhancing PDT efficacy [20, 21]. Recently, a number of researchers have shifted their focus to an updated concept of ferroptosis-stimulated PDT. This advantageous combination is based on the biochemical characteristics of ferroptosis, which is expected to enhance the antitumor efficacy of PDT through ROS generation and sustained oxygen supply via the Fenton reaction (Fig. 1). Practical confirmation of this is the synergistic effect of ferroptosis inducers and PDT in experiments on tumor cells [22].

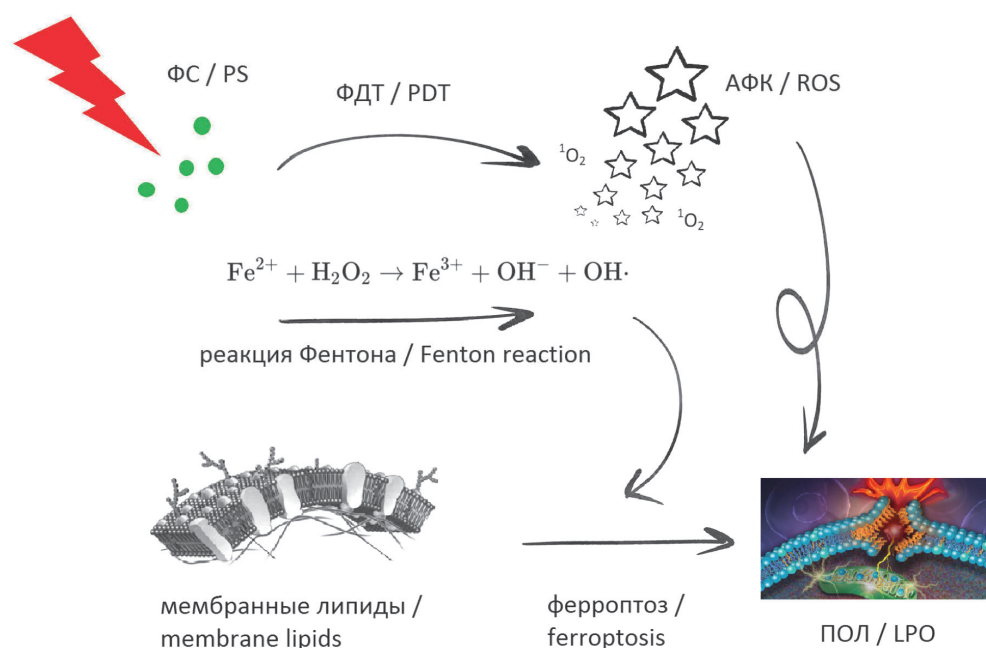


Рис. 1. Схематическое изображение взаимосвязи процессов, происходящих при ФДТ и ферроптозе в опухолевой клетке (АФК – активные формы кислорода, ФС – фотосенсибилизатор, ФДТ – фотодинамическая терапия, ПОЛ – перекисное окисление липидов).

Fig. 1. Schematic representation of the interconnection processes occurring during PDT and ferroptosis in a tumor cell (ROS – reactive oxygen species, PS – photosensitizer, PDT – photodynamic therapy, LPO – lipid peroxidation).

A key role in the processes occurring during ferroptosis activation and the photodynamic reaction is played by ROS, which are by-products of aerobic respiration under physiological conditions and cause DNA damage and genomic instability, thereby leading to the accumulation of genetic alterations in tumors and promoting cancer progression [23]. Tumor cells require a significant amount of ROS to maintain their invasive development [24]. However, excessive amounts of ROS cannot be *давя* and cause tumor cell death due to DNA damage and increasing LPO. This phenomenon is widely known as "oxidative stress" [25]. To overcome and modify these adverse conditions, the cell's antioxidant system maintains redox homeostasis. One of the important components of the intracellular antioxidant system is glutathione (a tripeptide consisting of the three amino acids cysteine, glycine, and glutamine), which participates in many metabolic and physiological processes in the human body. One of the functions of this substance is antioxidant. Glutathione suppresses the excess of ROS generated in the cell by oxidation to glutathione disulfide either directly or via an enzymatic reaction [26].

Tumor tissue contains four times more glutathione than normal tissue. This is necessary to adapt to rapid cell growth and survive under conditions of oxidative stress [27]. Another function of this tripeptide is the detoxification of drugs, which creates obstacles both for chemotherapy and for the implementation of photodynamic activity. It is reliably known that glutathione mediates the detoxification of doxorubicin, cisplatin, and other antitumor agents, which largely determines tumor resistance [28]. Although PDT stimulates an increase in intracellular ROS, intracellular glutathione has a direct suppressive effect on the development of oxidative stress, thereby reducing the efficacy of this therapy [29]. Cancer treatment methods aimed at suppressing glutathione metabolism are being studied, modified, and are extremely relevant.

It has already been proven that the mechanisms of ferroptosis and photodynamic action can work in fine synergy with each other; therefore, it is reasonable to assume that the induction of ferroptosis during PDT is a powerful alternative strategy for increasing the efficacy of antitumor therapy, in particular for tumors resistant to apoptosis and necrosis.

In scientific publications, ferroptosis is mentioned in connection with such nosologies as melanoma, colon cancer, breast carcinoma, glioblastoma, and prostate cancer [30–35]. Most of the presented studies are devoted to melanoma. Thus, Tsoi J. et al. demonstrated that ferroptosis-inducing agents (erastin, RSL3, ML162, and ML210) represent an alternative therapeutic approach aimed at the plasticity of melanoma cell differentiation to enhance the efficacy of targeted

therapy and immunotherapy [36]. A group of Chinese scientists obtained an expression profile of microRNA (miR-21-3p) in melanoma cells during ferroptosis induced by interferon- γ and proved that increased miR-21-3p expression promotes interferon- γ -mediated ferroptosis by enhancing LPO. In addition, this microRNA increased sensitivity to ferroptosis by directly targeting thioredoxin reductase 1 and enhancing ROS production. In turn, elevated miR-21-3p expression in the tumor enhanced the effect of anti-PD-1 antibodies by promoting ferroptosis of tumor cells [37]. Another study examined the combined use of sorafenib and vemurafenib. Vemurafenib is a BRAF kinase inhibitor approved for the treatment of melanoma; it suppresses kinase activity through competitive binding to the ATP-binding site, but resistance to it develops rather quickly. Tang F. et al. discovered an interesting fact: sorafenib (which exhibits ferroptotic activity) increases the sensitivity of melanoma cells to vemurafenib. Treatment with sorafenib alone did not significantly affect iron content, glutathione, malondialdehyde, or ROS production in vemurafenib-resistant cells, but the combined use of sorafenib and vemurafenib significantly increased ROS production, malondialdehyde and iron content, while decreasing glutathione levels. Interestingly, sorafenib significantly enhanced vemurafenib-induced cell death, which was blocked by the LPO inhibitor ferrostatin-1 but not by necrosulfonamide [38]. A study by Turubanova V.D. et al. showed that PDT with Photosens, which localizes in lysosomes, induces a type of regulated cell death combining features of apoptosis and ferroptosis. This phenomenon is explained by the release of hydrolytic enzymes and ionic iron upon photodynamic damage to the lysosomal membrane [39].

In 2020, a joint international study by scientists from the Institute of Biology and Biomedicine of Lobachevsky State University of Nizhny Novgorod (Russia), Ghent University (Belgium), and the University of Bologna (Italy) under the leadership of Prof. D. Krysko established that ferroptosis has immunogenic properties. In the course of this work, it turned out that PDT with Photosens induces a mixed type of cell death in GL261 glioma cells, with features characteristic of both apoptotic and ferroptotic death; in addition, a pronounced immunogenic effect of the therapy was detected [40]. The results obtained allowed the team of authors to create a model dendritic cell vaccine based on glioma cells induced by Photosens-PDT [40].

In another study, during investigation of the efficacy of PDT based on 5-aminolevulinic acid (5-ALA) in SiHa cervical cancer cells, increased intracellular ROS generation was observed, accompanied by decreased GPX4 expression, which indicates ferroptosis induced by PDT. It was also established that the ferroptosis inducer sorafenib potentiates 5-ALA-based PDT in vitro.

The antitumor effect of the combination of ferroptosis and PDT was confirmed in vivo on cervical cancer xenografts [41].

Enhancement of ferroptosis during PDT with ferroptosis inducers

Currently, studies devoted to the combination of PDT and ferroptosis-stimulating therapy are actively emerging [42, 43], including through the creation of combined particles [44]. It is assumed that such bifunctional particles will be able to generate large amounts of ROS, which can effectively inhibit glutathione activity and thereby demonstrate high antitumor efficacy [45]. In these studies, Ce6 is most often used as the PS, along with porphyrin derivatives—protoporphyrin IX and 5,10,15,20-tetrakis(4-aminophenyl)porphyrin [46–48], among others. As for ferroptosis-stimulating therapy, most studies have focused on ferroptosis inducers, among which the most frequently used are erastin and its derivatives (piperazine erastin, imidazole ketone erastin (IKE)), sorafenib, sulfasalazine, RAS-selective lethal 3 (RSL3), and iron compounds [49] (Table 1). However, ferroptotic activity, expressed to varying degrees, has also been found in many other compounds, including metformin, curcumin, metamizole sodium, simvastatin, sunitinib, lapatinib, disulfiram, quercetin, and others [50].

The simplest way to combine PDT and ferroptosis induction is the simultaneous administration of iron compounds and a PS. For example, nanoparticles

with a PLGA framework loaded with Fe_3O_4 and Ce6 (Fe_3O_4 -PLGA-Ce6) were obtained [51]. The use of these combined particles in vitro in murine 4T1 breast cancer cells showed that when Fe_3O_4 -PLGA-Ce6 is added to cells and subsequently internalized, Ce6 and $\text{Fe}^{3+}/\text{Fe}^{2+}$ are released; ionic iron stimulates the Fenton reaction and induces ferroptosis through a decrease in glutathione and GPX4 levels and an increase in malondialdehyde levels. In addition, upon laser irradiation, the nanoparticles release free Ce6, which enhances ROS accumulation, potentiating the iron-mediated cell death pathway. In vivo experiments on the 4T1 tumor model demonstrated the biocompatibility, antitumor efficacy of the developed particles, and the presence of additional useful properties for MRI due to the magnetic properties of Fe_3O_4 .

In scientific practice, a combination of a PS with erastin—the “gold standard” in ferroptosis induction—is used. The synergy between PDT and ferroptosis is being actively studied by Chinese scientists, who discovered an interesting technical fact: Ce6 and erastin molecules are capable of self-assembling into a “nanodrug” through hydrogen bonds and π - π interactions. Compared with monotherapy, this “nanodrug” (Ce6-erastin) exhibited greater antitumor efficacy against tongue squamous cell carcinoma both in vitro and in vivo. Zhu T. et al. calculated the combination index for Ce6-erastin and mathematically proved the presence of a synergistic effect [52].

Таблица 1

Примеры совместного успешного применения ФС и индукторов ферроптоза в эксперименте

Table 1

Examples of the joint successful use of photosensitizers and inducers of ferroptosis in an experiment

Фотосенсибилизатор Photosensitizer	Индуктор ферроптоза Inducer of ferroptosis	Носитель Carrier	Источник Source
Хлорин е6 Chlorin e6	Эрастин Erastin	Без носителя Without a carrier	[52]
Бенгальский розовый Rose Bengal	Эрастин Erastin	Экзосомы с функционализацией поверхности CD47 (Exos ^{CD47}) Exosomes with CD47 surface functionalization	[53]
Талапорфин натрия	IKE или сорафениб	Без носителя Without a carrier	[17]
Хлорин е6 Chlorin e6	Fe_3O_4	PLGA-частицы PLGA particles	[51]
Хлорин е6 Chlorin e6	RSL3	Нейтрофильно-миметические гибридные липосомы Neutrophil-mimetic hybrid liposomes	[56]
Протопорфилин IX Protoporphyrin IX	Эрастин Erastin	Амфифильные полимерные наночастицы Amphiphilic polymer nanoparticles	[46]
5,10,15,20-тетракис(4-аминофенил)порфирин 5,10,15,20-tetrakis(4-aminophenyl) porphyrin	Fe^{3+}	Наноконкомплекс из ПЭГилированной полигалактуроновой кислоты Nanocomplex of PEGylated polygalacturonic acid	[48]

Some researchers seek to create platforms for delivering erastin and a PS to tumor tissues with high specificity. The use of exosomes with a CD47-functionalized surface loaded with erastin and the PS Rose Bengal allowed the resulting modified exosomes to effectively evade phagocytosis by the mononuclear phagocyte system and to induce ferroptosis in tumor cells after laser irradiation at 532 nm both in vitro and in vivo. Moreover, compared with control "empty" exosomes, the "loaded" exosomes exerted less toxic effect on the liver. The proposed exosomes may become a promising strategy for the treatment of various types of malignant tumors [53].

A study of the biochemical mechanism of PDT using the PS sodium talaporfin led to the conclusion that this therapy induces ferroptosis by inhibiting cystine uptake via system Xc⁻, and when combined with ferroptosis inducers such as IKE or RSL3, an enhancement of tumor cell death induction occurs. Combining PDT with sodium talaporfin and ferroptosis inducers (IKE or sorafenib) in vivo significantly reduced tumor volume in the experiment [17]. Sun X. et al. confirmed that sorafenib in combination with PDT exerts a synergistic antitumor effect with activation of immune mechanisms [54]. Another group of Chinese researchers demonstrated the efficacy of combining surufatinib (a novel multikinase inhibitor with ferroptotic activity) with PDT in the treatment of such an aggressive disease as cholangiocarcinoma [55].

PDT and ferroptosis therapy have become widespread in studies devoted to the treatment of breast cancer, because ROS produced by PDT can promote ferroptosis in tumor cells, and ferroptosis therapy is expected to eliminate tumor cells resistant to apoptosis. Considering that PDT is characterized by a high level of ROS production and that neutrophils have a natural tendency to generate ROS, a neutrophil-mimetic hybrid system for the co-delivery of the PS Ce6 and the ferroptosis inducer RSL3 was theoretically proposed and practically developed. This hybrid system suppressed tumor cell growth through the natural ability of neutrophils to induce LPO and the enhanced permeability and retention (EPR)

effect, and then induced both apoptosis and ferroptosis, which led to a significant increase in peroxide levels and ultimately to potentiation of the LPO cascade. Synergistic ferroptosis-PDT demonstrated significant therapeutic efficacy in mice bearing 4T1 tumors, which indicates the promise of this type of breast cancer treatment [48].

As we have already described, the use of exosomes as a combined delivery system is also applicable in ferro-PDT. There are studies on loading macrophage exosomes with the PS SR780, Fe³⁺, and the antioxidant enzyme catalase, with subsequent modification of the nanoplatform with RS17 peptides to improve tumor targeting and block the CD47 signaling regulatory protein checkpoint. Upon laser activation, the created nanoparticles demonstrated high antitumor efficacy both against a subcutaneous Lewis lung carcinoma xenograft model and against an orthotopic lung metastasis model and a liver metastasis model [57].

Conclusion

The combination of ferroptosis and PDT is a new but undoubtedly effective and promising strategy for cancer treatment. Currently, research in this area proceeds along three main directions. The first includes the study of mechanisms of ferroptosis potentiation by PDT. The second direction is associated with the search for effective combinations of PSs and ferroptosis inducers. The third and most high-tech direction is the creation of combined nanoplatforms and nanodelivery systems to increase selectivity and reduce toxicity. All these directions are interrelated and developing in parallel, which has allowed scientists to prove the efficacy of ferro-photodynamic therapy in experiments. The body of primary scientific and practical knowledge obtained will further contribute to preclinical and clinical studies using this innovative type of tumor therapy.

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The authors declare no conflict of interest.

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