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Механизм запуска противоопухолевого иммунитета: от фотодинамического эффекта к иммуногенной клеточной смерти

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АННОТАЦИЯ

Развитие подходов к иммунотерапии рака даёт миллионам пациентов надежду на улучшение клинического исхода после лечения опухоли. Актуальной задачей является изучение фундаментальных механизмов активации противоопухолевого иммунитета. Об индукции иммуногенной гибели клеток рассказывают многие авторы, хотя сам процесс изящен и прост. К иммуногенной клеточной смерти (ICD) могут привести различные стимулы, но фотодинамическая терапия (ФДТ) показала себя эффективным индуктором запрограммированной смерти наравне с радиотерапией. В экспериментальных работах недостаточно описана связь между запуском ответа раковыми клетками на фотоиндукцию и запуском иммуногенной клеточной гибели. Немаловажен и вопрос о том, какие молекулярные каскады активируются после ФДТ и как они приводят к высвобождению молекулярных паттернов, ассоциированных с повреждением (DAMPs). Наиболее полно описаны механизмы генерации активных форм кислорода и стресс эндоплазматического ретикулума, при этом редко учитывается аппарат Гольджи. Фотосенсибилизаторы различной природы могут приводить к разным эффектам, в том числе совершенно неиммуногенным.

В этом обзоре описаны каскады, которые связывают индукцию гибели клеток при фотодинамическом воздействии и иммуногенный паттерн высвобождения DAMP. Обсуждаются те фотосенсибилизаторы, которые продемонстрировали потенциал в качестве индукторов ICD, и говорится о различных типах запрограммированной смерти, возникающей как следствие ФДТ.

Ключевые слова: иммуногенная клеточная смерть; фотодинамическое воздействие; молекулярные паттерны, ассоциированные с повреждением; стресс эндоплазматического ретикулума; АФК; аппарат Гольджи.

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Mechanisms of triggering antitumor immunity: from photodynamic effects to immunogenic cell death

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ABSTRACT

The development of cancer immunotherapies provides hope to millions of patients for better clinical outcomes after tumor treatment. Thus, investigating the fundamental mechanisms of antitumor immunity activation is an urgent task. Numerous studies have outlined the effect of immunogenic cell death (ICD) on cancer cells, and this outcome is both sophisticated and simple. Different stimuli can cause ICD; however, photodynamic exposure has been proven to be an effective inducer of programed death on par with radiotherapy. The link between triggering a photodynamic response in cancer cells and triggering ICD has been poorly described in experimental works. The question of which molecular cascades are activated after photodynamic therapy (PDT) irradiation and the way damage-associated molecular patterns (DAMPs) are released is intriguing. Much is known about reactive oxygen species generation and endoplasmic reticulum stress but little about the Golgi apparatus. Photosensitizers of different types can exert different effects, including completely nonimmunogenic ones.

This review describes the cascades that link the induction of cell death by photodynamic exposure and the immunogenic pattern of DAMP release. The photosensitizers that have shown potential as ICD inducers and the different pathways of programed death that occur during PDT exposure are also discussed.

Keywords: immunogenic cell death; photodynamic exposure; DAMPs; ER-stress; ROS; Golgi apparatus.

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INTRODUCTION

The treatment of cancer is a significant biomedical challenge. Despite therapeutic strategies and clinical studies [1–5], cancer remains a severe illness that necessitates the creation of innovative, patient-specific therapies. Disease manifestations arise from the uncontrolled replication of tumor stem cells that exhibit unlimited self-renewal potential, insensitivity to growth inhibitory signals and high heterogeneity, and ability to invade and evade apoptosis [6]. These acquired characteristics confer invincibility upon cancerous cells and enable them to commandeer immune components of the organism to shield the tumor site from physiological immune assault [7, 8]. This leads to the wasting away of the patient; thus, the discovery of cancer immunotherapy has become a crucial breakthrough in cancer treatment [9].

Cancer immunotherapy is a method of treating cancer using the host immune system to control and eliminate cancer cells. The idea of training the immune system to recognize and combat cancer is sophisticated and straightforward. Nevertheless, researchers encounter challenges in reprograming immune cells because they have already attained the endpoint of proliferation and differentiation, and manipulating stem cell components may result in uncontrolled autoimmune reactivity. Therefore, the process of altering immune cell function can be arduous [10, 11]. In 2005, G. Kroemer et al. introduced a novel mode of cell death, called immunogenic apoptosis, which was later referred to as immunogenic cell death (ICD). This discovery sparked a new research field that aims to develop anticancer treatments based on the ICD concept, which involves inducing tumor cell death by enabling the immune system to recognize and respond to them [12]. The functions and properties of immune cells do not require alteration. However, modifying the modes of tumor cell death is a relatively straightforward task.

Immunogenic cell death is a regulated cell death modality characterized by the release of damage-associated molecular patterns (DAMPs), followed by the release of different cellular molecules, stress-related reactions, and a strong adaptive immunity response. The immunogenicity of such death is caused by the adjuvant signal formed by DAMP molecules and tumor antigens. DAMP profiles include extracellular ATP, calreticulin (CRT), heat shock proteins, nuclear high mobility group box 1 (HMGB1), annexin 1, and some members of the interleukin family [13–17]. In the last few decades, researchers have attempted to determine the usage of ICD in fundamental and clinical studies for cancer treatment [18–27]. Photodynamic therapy (PDT) along with several immunogenic dyes can be used as an ICD inducer [28–36]. These are produced by cell death during PDT, with PDT-treated cells breaking down into antigens that are easily taken up by antigen-presenting cells. Thus, this photoinduced tumor death facilitates the resetting of the immune system components to combat the tumor.

PDT-related immunogenicity is considered more potent when it generates concentrated endoplasmic reticulum (ER) stress by reactive oxygen species (ROS) rather than as an incidental or additional effect of ER stress, such as with some ICD inducers, for example, mitoxantrone and oxaliplatin. Specifically, PDT has fewer molecular elements that mediate danger signaling pathways and consequently aids in DAMP turnover [13, 37]. As a result, PDT has higher effectiveness and stability in inducing tumor immunogenicity than other ICD inducers. However, no molecular mechanism has been described to establish a connection between photodynamic damage and immunogenic release of DAMPs [34, 38]. Most research groups commonly describe ICD without specifying the type of apoptosis or other ICD pathways that it undergoes at the molecular level.

This review offers a succinct overview of the molecular pathways responsible for ICD development by photodynamic effects. The traditional effects of photodynamics are described, and which photosensitizers are more likely to produce immunogenicity are investigated. This review also discusses the activation cascades in diverse cellular structures. Furthermore, the mechanisms underlying the oxidative stress caused by PDT at the subcellular and molecular levels are elucidated. Finally, we postulated that photodynamic exposure can induce a range of regulated and ICD modalities.

POTENTIAL OF PHOTOSENSITIZERS FROM VARIOUS GENERATIONS TO INDUCE IMMUNOGENIC CELL DEATH

Photodynamic therapy relies on the use of a photosensitive compound, known as a photosensitizer, which accumulates specifically in cancerous tissues. Photosensitizer molecules absorb light of a specific wavelength, initiating a process that destroys proteins, lipids, and other cell components. This selective destruction leads to the elimination of pathological cells.

Currently, one of the commonly used photosensitizer classifications encompasses the physical and chemical properties of three photoactive dye generations [39, 40]. First-generation photosensitizers are dyes based on the porphyrin framework: a hematoporphyrin derivative (HpD) and photofrin II (a purified form of HpD) [39, 41]. These agents exhibit a marked response following PDT; however, they impose considerable restrictions for clinical acceptance as effective antitumor therapy. Limitations include hydrophobicity, limited penetration depth, aggregation in water, low singlet oxygen emission, low tumor selectivity, high therapeutic dosage, prolonged half-life, and skin photosensitivity [42, 43].

The abovementioned restrictions on first-generation photosensitizers have led to wide-ranging studies to improve the efficacy of photosensitizer molecules by

altering the peripheral functionality of porphyrin [44] or by direct modification of the porphyrin core [45]. The addition of hydrophilic radicals [46–50] to pyrrole rings resulted in increased water solubility and overall molecular stability. Nonetheless, better water solubility increases renal clearance, followed by lower bioavailability and assimilability of the photosensitizer. Skin photosensitivity persists when second-generation photosensitizers are used [43]. Only several second-generation photosensitizers are under clinical trials or approved for clinical use in cancer treatment [51–54].

Finding an appropriate photosensitizer is a protracted process. Advanced third-generation photosensitizers unify the conjugation of second-generation photosensitizers with targeting agents (e.g., carbohydrates, antibodies, amino acids, and peptides) or a combination of delivery carriers (nanocapsules, nanoparticles, liposomes, protein dots, and micelles) with encapsulated derivatives of second-generation photosensitizers [55]. Third-generation photosensitizer research aims to improve the physical and chemical characteristics of photoactive drugs, resulting in higher tumor affinity, ROS generation, and reduced adverse effects on the surrounding normal tissue. Nanoparticle delivery vehicles can play a role in multiple steps of immune system activation to suppress cancer. Nanoparticle-based therapeutics can induce tumor cell death and, in turn, increase neoantigen release from the tumor. Nanoparticles can be used to improve antigen presentation and T-cell activation [55–59].

Investigation into ICD, stimulated in cancer cells by PDT, represents a nascent subfield of ICD research. The application of this field is presently broadening the possibilities of cancer therapy. Interestingly, all three generations of photosensitizers can induce ICD, opening up a new area of research and potentially providing a new avenue for evaluating previously described photosensitizers for ICD-PDT. Thus, we provide a comprehensive table containing details regarding photosensitizers that can induce ICD in vitro, supported by an in vivo demonstration of activating specific antitumor immune responses (Supplement 1, Table 1) [60–122].

In photodynamic treatment-induced ICD, recent scientific studies have primarily described second- and third-generation photosensitizers [34, 67, 84]. However, the immunogenicity of certain first-generation photosensitizers remains under investigation [91, 109]. Elaborating on a photoactive drug is a complex and multistage process that requires a thorough understanding of the chemical and physical properties of photosensitizers, their interaction with target tumor cells, and their potential for clinical use in cancer control [43, 123].

Numerous research teams have focused on developing third-generation photosensitizers, which are first- or second-generation photosensitizers that have been augmented with nanocarriers such as nanoparticles, liposomes, and nanocapsules. This trend is primarily explained by the enhancement of critical features, including increased tumor affinity and improved photoactive agent stability [55, 100, 123]. All three generations can induce cell death, which activates dendritic cells in vitro and produces specific immune responses in vivo following different treatment modalities. Consequently, these photosensitizers have the potential for further research into patient-specific cancer treatment [73, 93, 104].

Definitively determining the most efficient generation of photosensitizers or selecting a single drug is impossible, given the evidence of comparable activation of dendritic cells or the emergence of antitumor immunity in each documented case. However, not only the in vitro and in vivo efficacy on animal models but also the requirements for an accepted photosensitizer, such as high water solubility, tumor specificity, and low or absence of cytotoxicity to healthy tissue, must be considered [124–126]. This presents prospects for further investigation into the identification of photoactive drugs that are both immunogenic and meet the requirements for clinical use.

PHOTOSENSITIZER ACCUMULATION IS A CRUCIAL STEP IN THE INITIATION OF CELL DEATH

Photosensitizers can percolate into cells by endocytosis or diffusion. Penetration and localization types depend on the size of the molecules, polarity, total charge, distribution of charged groups, and ability to form hydrogen bonds. Hydrophobic photosensitizers mainly accumulate in the plasma membrane and the membranes of cellular organelles because they easily penetrate the lipid phase of the membranes; however, the reverse process is impeded. Hydrophilic photosensitizers enter the cell mainly through endocytosis. Amphiphilic substances best enter the cell, are distributed in it, and photosensitize [127]. These terms define further the localization of photosensitizers and the way they accumulate in the intracellular space. The accumulation in the body critically indicates the place of ROS formation as a photodynamic irritation effect.

After photosensitizers accumulate in cells, it is irritated by the light of the visible spectrum. After light absorption, the photosensitizer in its ground state is activated to the short-lived excited singlet state, after which it loses its energy. This occurs by emitting light during PDT or by generating heat during photothermal therapy. The excited singlet state may also undergo intersystem crossing to form the relatively long-lived excited triplet state. The excited triplet state can then undergo two types of reactions with surrounding molecules. Type I and II photochemical reactions can be simultaneously performed, and the ratio between them depends mainly on the type of photosensitizers used, substrate concentrations, and availability of oxygen. Because of the photodynamic reaction, various molecular mechanisms are activated, leading to different cell death modalities [36]. Although these primary

ROS are short-lived, sample evidence shows that PDT induces prolonged oxidative stress in PDT-treated cells. PostPDT oxidative stress stems from (per)oxidized reaction products such as lipids and proteins that have a longer lifetime and, in addition to acutely generated ROS, depletion of intracellular antioxidants and, hence, further exacerbation of already perturbed intracellular redox homeostasis [128]. The first type of reaction often leads to the formation of superoxide ions by transferring one electron to an oxygen molecule. These ions do not act as active ions in biological systems but can produce H_2O_2, which is easily absorbed by cell membranes. At high concentrations, H_2O_2 can react with superoxide molecules through the formation of hydroxyl radicals, which can ionize molecules with low activation energy. In reaction II, the photosensitizer molecule transforms into excited singlet oxygen by transitioning from the triplet state to the ground state and transferring energy to the oxygen molecule. Singlet oxygen as a molecule without charge can spread into the cytoplasm and biological membranes. Type I and type II reactions, as direct effects of PDT, occur in parallel, depending on the photosensitizer type and oxygen concentration. For more commonly used photosensitizers, the type II reaction is the dominant process [129].

The localization of the photosensitizer is significant for PDT-based ICD. Moreover, its localization during irradiation in cellular compartments largely determines where oxidative damage will occur because of the short lifetime and limited diffusion capacity of ROS ($^1O_2$) [130, 131]. If the photosensitizer accumulates in membranes, the cell dies from the rupture of membranes because of necrosis [132]. If the photosensitizer accumulates in the nucleus, the main consequence of PDT is DNA damage [133]. In this case, ICD can be initiated; however, it will mostly depend on p53, BAX, and caspase-8. As mentioned above, this makes the immunogenic pathway difficult for tumors with p53 mutations, which are present in the cells of several human tumors [134]. Photodamage of the mitochondria releases the products they contain, for example, the release of cytochrome c into the cytoplasm, which triggers apoptosis (Fig. 1) [135]. The most optimal localizations of photosensitizers are ER, AG, lysosomes, and mitochondria. In this case, oxidative stress occurs, which quickly leads to an internal pathway that triggers apoptosis [136–138]. Today, PDT-based ICDs, which directly cause growth stress in these cell organoids, are hypericin PDT [139], photosens PDT, photoditazine PDT [34], and methylene blue PDT [140].

ROLE OF REACTIVE OXYGEN SPECIES IN OXIDATIVE AND ENDOPLASMIC RETICULUM STRESS

Reactive oxygen species are produced in each aerobic cell and are involved in some metabolic processes [141]. ROS generation depends on several enzymes, such as nicotinamide adenine dinucleotide phosphate oxidase (NADPH, which converts electrons into molecular oxygen), xanthine oxidoreductase, and peroxidases, as well as mitochondria containing electron transport systems [141]. However, cells have antioxidant defense systems, including catalase, superoxide dismutase (SOD), glutathione (GSH) peroxidase, and other exogenous substances with antioxidant properties that can significantly prevent ROS production by direct action on radical chain reactions and detoxification enzymes [141, 142]. However, under prolonged and powerful oxidative stress, the balance between ROS and the oxidative system is disrupted, homeostasis/proteostasis may not be restored, and cell death mechanisms, such as apoptosis, are activated [143].

In tumor cells, high levels of intracellular ROS are a frequent phenomenon, which may be caused by their increased metabolic activity, mitochondrial dysfunction due to constant hypoxic conditions, peroxisome activity, constant presence of growth factors, and oncogene activity. In addition, the activities of NADPH oxidase, cyclooxygenase, and lipoxygenase, which are ROS sources, are increased in tumor cells. ROS can promote tumor proliferation and mutagenic transformation by affecting intracellular signaling pathways that control proliferation, survival, and stimulation [144].

Reactive oxygen species formation is an important feature of PDT-induced cell death, particularly ICD. ROS release in this situation is the standard defense mechanism [145–147], which some authors call mitochondrial DAMPs [17, 148, 149]. Oxidative stress emerges not only after PDT; it is also caused by chemotherapy [150], radiotherapy [151], oncolytic viruses [152], and other anticancer treatments [153–156]. In this case, ROS are formed as in the case of specially stimulated exposure (Hyp-PDT), so it is synthesized by the cell itself in response to stress (anthracyclines) [133]. Primary ROS are formed when a photosensitizer is irradiated. These primary ROS are short-lived. Oxidative stress after PDT occurs because of (re)oxidized reaction products, such as lipids and proteins, which have a longer lifetime. In addition to ROS accumulation, intracellular antioxidants are depleted, which further exacerbates the already disturbed intracellular redox homeostasis [128].

The ER is one of the key centers of oxidative stress during the induction of ICD-based PDT [157]. The ER is highly sensitive to stresses that perturb cellular energy levels, the redox state, or Ca^{2+} concentration. ER disturbance reduces the protein-folding capacity in the ER, which results in the accumulation and aggregation of unfolded proteins, a condition referred to as ER stress [158]. To avert the harmful effects of ER stress, cells have evolved various protective strategies, collectively termed unfolded protein response (UPR) (See Fig. 1). This concerted and complex cellular cascade is mediated through three ER transmembrane receptors: pancreatic ER kinase (PKR)-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1). Normally, all three

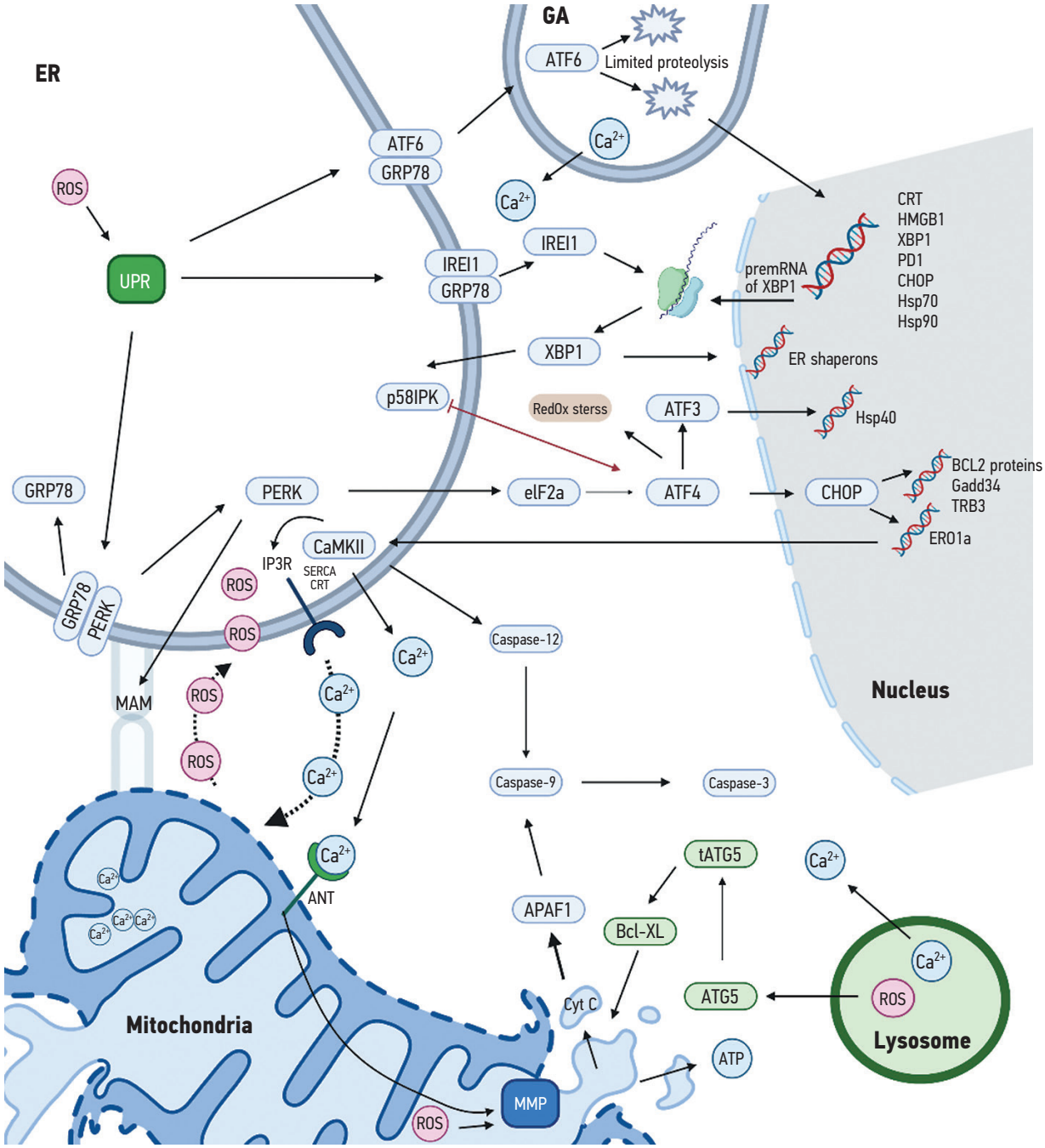

Fig. 1. Main mechanisms triggering immunogenic cell death under photodynamic exposure The localization of the photosensitizer in the endoplasmic reticulum leads to misfolding of proteins, which triggers three pathways of endoplasmic reticulum stress. The accumulation of reactive oxygen species in the ER during photodynamic therapy also leads to the loss of calcium homeostasis and its outflow into the cytosol or mitochondria, including through mitochondria-associated membranes. When a photosensitizer is localized in the mitochondria, large amounts of reactive oxygen species accumulate in organelles, and their integrity is subsequently lost, accompanied by the release of numerous apoptotic factors. The accumulation of photosensitizers and reactive oxygen species formation in lysosomes lead to the loss of lysosomal calcium and the convergence of ATG5 to tATG5, followed by the triggering of mitochondrial apoptosis. MMP — mitochondrial membrane potential; Bsl-XL — B-cell lymphoma-extra large. See text for designations.

Рис. 1. Основной механизм запуска иммуногенной клеточной смерти вследствие фотодинамического воздействия. Локализация фотосенсибилизатора в эндоплазматическом ретикулуме приводит к неправильному сворачиванию белков, что запускает три пути стресса эндоплазматического ретикулума. Накопление активных форм кислорода при фотодинамической терапии в эндоплазматическом ретикулуме также приводит к снижению гомеостаза кальция и его выходу в цитозоль или митохондрии, в том числе через ассоциированные с митахондриями мембраны. При локализации фотосенсибилизатора в митохондриях в органеллах накапливается большое количество активных форм кислорода и впоследствии происходит нарушение их целостности, сопровождающееся высвобождением ряда апоптотических факторов. При накоплении фотосенсибилизаторов и появлении активных форм кислорода в лизосомах происходит потеря лизосомального кальция и конверсия ATG5 в tATG5, после чего запускается митохондриальный апоптоз. MMP — мембранный потенциал митохондрий; Bsl-XL — B-клеточная лимфома экстракрупного размера. Обозначения см. в тексте.

ER stress receptors are maintained in an inactive state through their association with the ER chaperone 78 kDa glucose-regulated protein (GRP78). On accumulation of unfolded proteins, GRP78 dissociates from the three receptors, which leads to their activation and triggers UPR [158]. The UPR is a prosurvival response that reduces the accumulation of unfolded proteins and restores normal ER functioning. On the aggregation of unfolded proteins, GRP78 dissociates from the three ER stress receptors, PERK, ATF6, and IRE1, allowing their activation. The receptors are activated sequentially, with PERK being the first and rapidly followed by ATF6, whereas IRE1 is activated last. Active PERK blocks general protein synthesis by phosphorylating eukaryotic initiation factor 2α (eIF2α) that enables activating transcription factor 4 (ATF4) translation, which occurs through an alternative, eIF2α-independent translation pathway. ATF4, being a transcription factor, translocates to the nucleus and induces the transcription of genes required to restore ER homeostasis [159]. Important targets driven by ATF4 are transcriptional factor C/EBP homologous protein (CHOP), growth arrest and DNA damage-inducible 34 (GADD34), and ATF3 [160]. ATF3 contemporaneously regulates Hsp40 transcription, which is a staple DAMP for ICD [128]. In addition, PERK provides effective interaction between ER and mitochondrial membranes through ROS and Ca^{2+} transportation and plays a crucial role in the mitochondria and ER contact site stabilization and MAM (mitochondria-associated membranes) integrity [138]. ATF6 is activated by limited proteolysis after its translocation from the ER to the Golgi apparatus (GA). Active ATF6 is also a transcription factor that regulates the expression of ER chaperones and X box-binding protein 1, another transcription factor (XBP1) [158]. ATF6 is also responsible for some DAMP transcription, including CRT, HMGB1, and HSP90 [128].

To achieve its active form, XBP1 must undergo mRNA splicing, which is performed by IRE1. Spliced XBP1 protein translocates to the nucleus and controls the transcription of chaperones, cochaperones, and PERK inhibitor P58IPK, and genes involved in protein degradation. This concerted action restores ER function by blocking further buildup of client proteins, enhancing the folding capacity, and initiating degradation of protein aggregates CHOP and C/EBP homologous protein. Under conditions of prolonged oxidative stress, homeostasis/proteostasis may not be restored; instead, mechanisms of cell death, such as apoptosis, are activated [159]. Interestingly, ER stress can lead not only to apoptosis but also to paraptosis [161, 162]. However, this mechanism is still poorly understood in the context of the ICD path.

An important feature of ER and GA is the presence of Ca-related proteins. Specific and limited PDI oxidation by endoplasmic reticulum disulphide oxidase 1α (ERO1α) is essential for avoiding ER hyperoxidation. Under normal physiological conditions, the ER forms an oxidizing environment, and Ca^{2+} stores are filled, allowing the proper function of the various chaperones. During ER stress, ERO1α is upregulated in a CHOP-dependent manner, leading to ER hyperoxidation. Because the conformation of the third luminal loop of inositol trisphosphate receptor (IP3R) depends on the oxidation state, hyperoxidation could disrupt the interaction between ERp44 and IP3R, causing IP3R hypersensitivity, increased calcium release, and induction of apoptosis [162].

Calcium from ER cisternae flows mainly through calcium release channels as IP3R. This channel is accumulated in MAM, which are associated with the mitochondrial outer membrane. Calcium ions from the cytoplasm enter the mitochondria through voltage-dependent anion channels or calcium uniporters. High levels of calcium stimulate respiratory chain activity, leading to higher ROS levels. ROS can further target ER-based calcium channels, leading to the increased release of calcium and further increased ROS levels. Increased ROS and calcium load can open mitochondrial permeability transition pores, resulting in the release of proapoptotic factors [163]. Furthermore, calcium unleashed from the ER binds and activates several MAM receptors, such as adenine nucleotide translocase (ANT), on the mitochondrial membrane. ANT activation leads to depolarization and membrane bursts followed by proapoptotic factors, cytochrome c, and other cell death-dependent molecules [164].

Calcium ions activate the calcium-dependent enzyme calpain, which then triggers caspase-12, which is located in the ER. This enzyme mobilizes to the cytosol and subsequently initiates the apoptotic cascade via interactions with caspase-9 and caspase-3 [165]. Moreover, ROS formation not only in the ER but also in the GA and lysosomes can trigger this mechanism [166]. In this case, calcium is involved in oxidative stress in both the mitochondria and EP. The constancy of the calcium current can be disrupted both at the onset of oxidative stress in the mitochondria and ER, which in total will lead to the same consequences.

In the mitochondria, ROS typically fulfill numerous crucial roles, such as contributing to glucose oxidation and synthesis of fatty acids, amino acids, and hormones. Furthermore, the mitochondria serve as a hub for ROS signaling during apoptosis and innate immune responses. Concurrently, the mitochondria produce ROS and possess an influential antioxidant mechanism to counteract ROS-mediated destruction, comprising mitochondrial superoxide dismutase (SOD2) and a thioredoxin system composed of thioredoxin-2 (Trx2), thioredoxin reductase-2, and peroxidase 3 [167]. Various methods by which prolonged opening of the pores during mitochondrial permeability transition (MPT) and the permeability of the outer mitochondrial membrane can destroy the inner and outer mitochondrial membranes. This reaction is an initial response to oxidative stress and is a crucial stage in cell death. In general, MPT pores become open and remain open after mitochondrial damage, which is linked to compromised calcium levels and oxidative stress [148]. In

PDT, oxidative stress triggers a sequence of events resulting in decreased permeability of the inner mitochondrial membrane, thereby regulating the MPT pore complex and disrupting the membrane potential. Although photosensitizers may accumulate outside the mitochondria, these events primarily occur within this cellular compartment [168]. When singlet oxygen accumulates directly in the mitochondrial membrane, cytochrome c is released. This binds to apoptotic protease activating factor 1 (APAF-1) and procaspase-9, forming a complex that activates caspase-3 [143, 169]. Furthermore, the disintegration of the mitochondrial membrane releases a crucial DAMP, ATP [148, 170].

Lysosomal photodamage results in lysosomal calcium depletion, activating the calpain protease. In addition, it facilitates ATG5 cleavage, an apoptosis-related protein, into a fragment named tATG5. Subsequently, tATG5 attaches to the mitochondrial membrane and triggers a series of events that ultimately culminate in the loss of cytochrome c, catalyst for apoptosis (See Fig. 1) [171]. When the lysosomal membrane is permeabilized, proteases such as cathepsins B and D are released. They subsequently activate Bid proteolytically, leading to mitochondrial apoptosis and release [133, 169].

NOT JUST APOPTOSIS

Apoptosis and necrosis are the predominant cell death modes triggered by PDT. Apoptosis is an energy-dependent cell death modality that is regulated. Several morphological changes characterize it, including chromatin condensation, cytoplasmic reduction, plasma membrane blebbing, and phagocytic activity [172, 173]. Necrosis is an unregulated cell death type induced by external damage [173], characterized by cellular swelling along with chromatin condensation, eventually leading to cellular and nuclear lysis with subsequent inflammation [174]. In addition, some cell death pathways such as autophagy, mitotic catastrophe, cellular senescence, and programed necrosis have been described and summarized in other reviews [175, 176]. The extent to which photodynamic treatment can induce ferroptosis remains unclear [34].

Because the tumor microenvironment is naturally poor in oxygen, the reactions leading to ROS formation under PDT are usually rapidly attenuated. A recent study reported that the presence of Fe(III) in nanoparticles derived from the initial hem supports the Fenton redox reaction, which provides oxygen as the starting material for $^1O_2$ formation. Furthermore, Fe(III) can react with the antioxidant capabilities of GSH, resulting in its deactivation. Inhibiting cystine uptake via the cystine/glutamate antiporter through p53 activation limits the production of intracellular GSH, ultimately shielding tumor cells from ferroptosis [177, 178]. GPX4 plays a crucial role in the reduction of phospholipid hydroperoxides (PLOOH) to phospholipid alcohols. Furthermore, GSH is essential for the normal physiological operation of GPX4. Intracellular synthesis of GSH is catalyzed by glutamate–cysteine ligase. Therefore, cysteine, which is taken up as cystine by the cystine/glutamate antiporter (xCT) system, has been described as the rate-limiting amino acid in GSH synthesis. Therefore, depriving cells of cysteine by inhibiting the xCT system also indirectly contributes to GPX4 inhibition. Consequently, GPX4 inactivation can lead to PLOOH accumulation, resulting in cell membrane damage and ferroptotic death [177, 178].

PDT-ACTIVATED IMMUNOGENIC CELL DEATH PATHWAYS

We were interested in the relationship between photodynamic exposure and ICD induction. Several studies have convincingly demonstrated the link and identified the pathways. Chen et al. described the mechanism of apoptosis induced by methylene blue-mediated photodynamic therapy (MB-PDT) in B16F1 cells. Western blotting showed the activation of caspase-3-dependent apoptosis 6 h after MB-PDT. Furthermore, immunoblot analysis showed a rapid increase in caspase-9 and cytochrome c release, indicating the activation of the intrinsic pathway. Apoptosis occurs via the intrinsic mitochondrial pathway through cytochrome c release and subsequent caspase-9 activation. Cell death depends on mitochondrial stress [179]. Intrinsic apoptosis is activated by intracellular and extracellular stresses. The cascade is initiated by mitochondrial membrane permeabilization and subsequent release of cytochrome c into the cytosol. The released cytochrome c binds to APAF-1, and procaspase-9 enters a mature state and forms the apoptosome. Caspase-9 cleaves procaspase-3. Thus, apoptosis-inducing factor released into the cytosol rapidly enters the nucleus and promotes nuclear DNA degradation in a caspase-independent manner [180]. In another study using MB-PDT, Lu et al. described apoptosis in HeLa cells. The detection of cytochrome c and poly (ADP-ribose) polymerase suggests the occurrence of intrinsic apoptosis [181].

Xie et al. showed that translocator protein-targeted photodynamic therapy (TSPO-PDT) on MC38 cells induces immunogenic apoptosis as a mode of ICD [182]. Caspase-3 was also involved in intrinsic apoptosis. The authors also analyzed the association between apoptosis and DAMP release, following the “golden standard” for ICD indication [183], and found high levels of CRT and heat shock protein 70 (HSP70). Interestingly, the effects of TSPO-PDT were measured in the context of ER stress. The upregulation of ER stress markers was observed at different time points, indicating the ability of TSPO-PDT to induce ER stress. A high rate of dendritic cell maturation was observed [182].

Panzarini et al. described several cell death pathways after RBAc-PDT [184]. In this study, the cell type was differentiated by quantifying caspase-9, -8, -3, and cleaved caspase-12. The highest levels of caspase-9 were observed

immediately after PDT. This process correlated with the onset of caspase-3 and cytochrome c release, and early appearance of apoptotic cells at the 12-h time point. At 8 h after PDT, caspase-9 levels were lower, whereas caspase-3 levels were still high at 72 h after PDT, indicating further activation of the apoptotic pathway at different time points [182, 184].

The key role of caspases-3 and -9 in the induction of immunogenic apoptosis after PDT is evident. Cytochrome c represents the initiation of the intrinsic pathway of apoptosis, which appears to be associated with ATP release and nuclear membrane disassembly with the release of HMGB1. This mechanism requires further discussion and refinement.

DISCUSSION

Cells have various pathways that undergo rapid ICD during photodynamic exposure. ROS emergence activates cascades interconnected with ER and GA, resulting in transcriptional changes that lead to the release of DAMPs and cell death. In 2012, this unique property was applied in the development of a technology to treat mouse glioblastoma with immunogenic dying cells [123]. PDT-related ICD is more effective if it is subjected to focused straight ROS-provided ER stress but not secondary or side ER stress effects. Moreover, targeting the ER allows the immediate triggering of molecular cascades leading to the transcription and emission of DAMPS.

Endoplasmic reticulum is not the sole initiator of ICD in organoids. By combining two photosensitizers according to [185], a pathway that harms both the lysosomes and mitochondria can be triggered. By activating a lysosome-driven pathway, photofrin enables the benzoporphyrin derivative to accumulate in the mitochondria, ultimately resulting in tumor reduction and better therapeutic outcomes. Both lysosome- and mitochondria-dependent pathways can induce ICD.

Whether there is a standard approach for inducing ICD with PDT for treating murine and human tumor cells remains unclear. Many studies have focused on activating death pathways that encourage an immune response in tumor cells, and positive findings suggest that ICD triggered by photoimmunotherapy is an area of significant investigation. Notably, certain tumors, such as mammary carcinoma 4T1, melanoma B16F10, and colon adenocarcinoma CT26, exhibit increased immunogenic potential for immunogenic PDT [73–79]. ICD-PDT is used for the treatment of highly challenging and life-threatening tumors, such as glioma, which are usually resistant to traditional therapies [30, 80].

Further research should concentrate on discovering novel ICD inducers that have clinical potential. In addition, the integration of PDT as a powerful activator of this process should be explored. Previous studies have shown that PDT can induce a mixed form of cell death, combining apoptosis and ferroptosis. Furthermore, ROS affect the expression of PDL1 in tumor cells, increasing therapeutic effectiveness [186, 187]. PDL1 is a protein that belongs to the group of T-cell suppressor receptors. Its function involves inhibiting apoptotic T-cell immunological responses by binding to PDL1 on the surface of tumor cells [188].

In conclusion, research in the last three decades has increasingly proved that PDT is a powerful strategy for ICD induction. However, identifying the molecular mechanisms of the relationship between PDT and ICD may help identify effective inducers and modulate the immunogenicity of the therapy.

CONCLUDING REMARKS

In conclusion, the research of the last three decades have increasingly proved the idea that PDT is a powerful strategy for immunogenic cell death induction. However, uncovering the molecular mechanisms of the relationship between PDT and immunogenic cell death may help to uncover effective inducers and modulate the immunogenicity of the therapy.

ADDITIONAL INFORMATION

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ДОПОЛНИТЕЛЬНЫЕ МАТЕРИАЛЫ

Приложение 1

Table 1. ICD-inducing photosensitizers

Таблица 1. Фотосенсибилизаторы, индуцирующие иммуногенную клеточную смерть

Photosensitizer (PS)	PS generation and type of additional structure	Tumor cell line	Intracellular localization of PS and possible cell death modality	ICD markers and signs of adaptive immunity activation	References
Indocyanine green (ICG)	1st	HT-29, T84, human colorectal adenocarcinoma; human colon cancer	ER, GA, lysosomes	Overproduced ROS	[60, 61]
	3rd, ICG@Fe/FeO–PPP NCs	KB, epidermal carcinoma	—	Overproduced ROS	[62]
	3rd, Pt-ICG/PES and Mg-ICG/PES	4T1, murine mammary carcinoma	—	CRT, HMGB-1, ATP; BMDCs maturation (CD11c+CD80+CD86+) 26.02±0.98% for Pt-ICG/PES and 24.47±0.54% for Mg-ICG/PES of total DCs population	[63]
	3rd, Dox/ICG BSA NPs, T/Dox-ICG NPs	B16F10, murine melanoma SGC7901/VCR, gastric cancer	—	CRT, HSP 70, HSP 90 exposition	[64, 65]
Oxaliplatin	3rd, OXP/ICG/PEP OI_NP	ID8, ovarian cancer	—	CRT, HMGB-1, ATP, ROS; Cytotoxic response of T lymphocytes to tumor cells	[66]
Benzophenazine photosensitizer OR141	3rd	SCC7, murine squamous cell carcinoma; A43, human squamous cell carcinoma	ER	HMGB1, ATP, Annexin V, Annexin A1; MHC-I on cancer cell surface; BMDCs maturation (MHC-II+, CD80+, CD86+) more than 50% of whole BMDCs population	[67, 68]
PIO-based PSs	3rd, PIO + anti-PD-L1	HeLa, human cervical cancer	Predominantly ER	GRP78 emission; CRT, HMGB1; F4/80 macrophages, CD4+, CD8+ T cells in tumor; INF-α, IFN-γ, and IL-6 in serum	[67, 69]
(3-bromopropyl) trimethylammonium bromide	3rd, Cu SAZs nanozyme (PDA NPs)	CT26, murine colon adenocarcinoma	—	Overproduced ROS	[70]
Semiconducting polymer (SP) nanoparticles	3rd, SPSS NPs	CT26, murine colon adenocarcinoma	Lysosomes	Overproduced ROS; CRT HMGB1, HSP70, ATP; ecto-CRT, IFN-γ, TNF-α, granzyme B in tumor; CD8+ T cells in tumor and blood	[71]
Boron difluoride dipyrromethene (BODIPY)-vadimezan conjugate (BDPVDA)	3rd, PVB NPs	4T1, breast cancer (mimics human)	ER	Overproduced ROS	[72]
Heptamethine cyanine small molecules containing with 8 eight carbon atoms of N-alkyl side chains	2nd	4T1, breast cancer (mimics human)	—	CRT, HMGB-1; DC (CD11c+CD86+ and CD11c+CD80+) maturation; TNF-α, IL-6, IL-12p70 in blood	[73]
Ferrocene-containing Ir(III) photosensitizer (IrFc1)	2nd	4T1, breast cancer (mimics human)	Lysosomes	Overproduced ROS; CRT, HMGB-1, ATP; ferroptosis (GPX4), changing mitochondrial morphology; CD8+ and CD4+ T cells, DC in tumor; IL-12p70, IL-6, TNF-α, IL-10 in blood	[74]
Redaporfin (5,10,15,20-tetrakis (2,6-difluoro-3-N-methylsulfamoylphenyl) bacteriochlorin)	3rd	CT26, murine colon adenocarcinoma	ER and GA	IL-2, IL-4, IL-6, IFN-γ, TNF- α, IL-17A и IL-10 in serum; granulocytes, neutrophils, CD4+ and CD8+ T cells in blood; T cells infiltration in tumor	[75, 76]
Aluminum-phthalocyanine chloride	2nd, AlPcNE (aluminum-phthalocyanine nanoemulsion)	B16F10, murine melanoma	—	CRT, HMGB1, ATP	[35, 77]

Table 1. Continued

Таблица 1. Продолжение

Photosensitizer (PS)	PS generation and type of additional structure	Tumor cell line	Intracellular localization of PS and possible cell death modality	ICD markers and signs of adaptive immunity activation	References
Aluminum phthalocyanine disulfonate	2nd	Rat glioma (F98 and BT4C)	—	Limited tumor development in experimental groups (histology)	[78, 79]
Zinc(II)phthalocyanine	2nd + anti-PD-L1 therapy	B16F10, murine melanoma	ER, mitochondria and lysosomes	TNF-α, IFN-γ and IL-6; CD8+ T and CD4+ T cells in tumor	[80, 81]
	3rd, DH@ZnPc NPs	TC1, murine cervical cells; HeLa human cervical cells	Early (1 h) — lysosomes, late (24 h) — mitochondria	CRT, HMGB1; pyroptosis (caspase-1, NLRP3, IL-1β, IL18)	[82]
Silicon(IV) phthalocyanine	2nd	CT26, murine colon adenocarcinoma	—	CRT, HMGB-1, ATP, ERp57, vasostatin, HSP90 CXCL1, CXCL2, CXCL3, CXCL10, CXCL12, CXCL13	[83, 84]
Photosens	2nd	GL261, murine glioma; MCA205, murine fibrosarcoma	ER and GA	CRT, HMGB-1, ATP; induced DC maturation; IL-6 in serum	[34, 78]
Porphyrin-cisplatin conjugate	3rd, NP@Pt-1	CT26, murine colon adenocarcinoma	Cytosol	CRT, HMGB-1, ATP; mature DCs (CD11C+, CD80+, CD86+) and CD8+ T cells in tumor	[25]
Aluminum-phthalocyanine	2nd, aluminum-phthalocyanine nanoemulsion	B16F10, murine melanoma	—	CRT, HMGB-1, ATP;	[35, 78]
		CT26, murine colon adenocarcinoma; 4T1, murine mammary adenocarcinoma	—	CRT, HSP70, HSP90, HMGB-1; IL-1β	[78, 85]
M-chlorin e6	2nd	4T1, murine mammary adenocarcinoma	ER	CRT; increased proportion of CD80+ CD86+ macrophages	[86–88]
	3rd, PEG-Chlorin e6 (Ce6)-Fe2+ -Gossypol NPs		—	CRT, HMGB1, ATP; IL-6, IFN-γ, IL-12p70, TNF-α; DC maturation 80%; overproduced ROS	[89]
	3rd, Ce6/MLT@SAB NPs		—	Overproduced ROS CRT, ATP; increased percentage of CD80+ CD86+ cells	[90]
Hematoporphyrin	1st	C6, rat glioma	Mitochondria	DC maturation (42.8 CD80+, 50.82 OX-6+); IL-12, IL-10, TNF-α; co-culturing with spleen cells cytotoxicity 95.50±0.016%, 90.20±0.024%	[54, 91, 92]
	3rd, HMME/R837@Lip	4T1, murine mammary adenocarcinoma; CT26, murine colon adenocarcinoma	—	Prophylactic vaccination: TNF-a, IL-6 и IL-12p70; 15% DC maturation (HMME@Lip), 21% DC maturation (HMME/R837@Lip); CD45+ leukocytes in tumor; Therapeutic vaccination: CD4+ CD8+ T cells in spleen; IFN-γ, TNF-α	[93]
IRdye700DX	2nd, NIR-PIT: Antibody+IR700	3T3-HER2, transfected fibroblasts MC38, murine colorectal carcinoma	Lysosomes, membranes	CRT, HSP70, HSP90, HMGB1, ATP; induced DC maturation (CD80, CD86, CD40, HLA-DR, IL-12)	[94–96]
	2nd	MC38, murine colorectal carcinoma A431, human epidermis carcinoma	—	CD8+,CD4+ T-cells, Treg in tumor	[97–99]
Glycoconjugated chlorin (G-chlorin)	3rd	CT26, murine colon adenocarcinoma	—	CRT, HMGB1; promoting macrophage phagocytosis; protect mice against tumour in prophylactic vaccination model	[100, 101]

Table 1. Continued

Таблица 1. Продолжение

Photosensitizer (PS)	PS generation and type of additional structure	Tumor cell line	Intracellular localization of PS and possible cell death modality	ICD markers and signs of adaptive immunity activation	References
Photodithazine	2nd	GL261, murine glioma; MCA205, murine fibrosarcoma	ER and GA	CRT, ATP, HMGB1; induced DC maturation; IL-6	[34]
2-[1-Hexyloxyethyl]-2-devinyl pyropheophorbide (HPPH)	3rd, pRNVs/HPPH/IND	B16F10, murine melanoma; MC38, murine colorectal carcinoma	ER	CRT; overproduced ROS; CD8+, CD4+ T-cells in tumor; apoptosis	[102]
Ru PS class	2nd	B16F10, murine melanoma	—	Overproduced ROS; HMGB1, ATP; IL6, CXCL10, TLR3	[103]
DPA-TPE-SCP	3rd, peptide dots	4T1, murine mammary adenocarcinoma	—	Overproduced ROS, CRT HMGB1, HSP70, ATP; DC (CD80+ CD86+, CD11c+) in lymph nodes; CD8+ T cells and Treg (Foxp3+, CD4+, CD3+) in tumor	[104]
Cyanoarylporphyrazines	2nd	MCA205, murine fibrosarcoma	GA and lysosomes (pz I), ER and lysosomes (pz III)	HMGB-1, ATP; induced DC maturation	[105, 106]
		GL261, murine glioma		HMGB-1, ATP; smaller tumor size in experimental groups	[105–108]
Methylene blue	1st	H1299 (P53 null) and A549 (P53 wt), human non-small cell lung carcinoma; NSCLC, tumour organoids	—	CRT, MHCII, ICAM-1; CD8+ cells cytotoxic activity	[109, 110]
Rose Bengal acetate	2nd	HeLa, human cervical cancer	Perinuclear	CRT, HSP70, HSP90, ATP; TNF-a, TGF-b and IL-10; macrophage recruiting;	[111, 112]
4,4',4'',4'''-(porphyrin-5,10,15,20-tetrayl) tetrakis(N-(2-((4-methylphenyl)sulfonamido)ethyl) benzamide)	3rd, PEG-s-s-1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000] (Ds-sP) NPs	4T1, murine mammary adenocarcinoma	ER	Overproduced ROS, CRT, HMGB-1; DC (CD80+CD86+) maturation; TNF-α, IL-12p40; CD8+ T cells in tumor	[113]
2-(5-(4-(bis(phenyl)amino)benzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (TPA-DCR)	3rd, TPA-DCR NPs	4T1, murine mammary adenocarcinoma	—	Overproduced ROS, CRT HMGB1, HSP70, ATP; TNF-α; increase of M1 macrophage proportion; CD8+, CD4+ T-cells in tumor	[114]
5-aminolevulinic acid (5-ALA)	2nd	MC38, murine colorectal carcinoma; HCT116, human colorectal carcinoma; B16F10, murine melanoma	—	CRT, HSP70, HSP90, HMGB1, ATP; induced DC maturation; CD8+ T-cells in spleen; IFN-γ, TNF-α; DCs and CD8+ T-cells in tumor	[115, 116]
Hypericin	2nd	AY27, rat transitional cell carcinoma of the urinary bladder; CT26, murine colon adenocarcinoma	—	HMGB1, ATP, CRT	[117, 118]
		T24, transitional cell carcinoma; CT26, murine colon adenocarcinoma; MEF, murine fibroblasts		HSP70, CRT	[117, 119]
		GL261, murine glioma		CRT, HSP70, HSP90, HMGB1, ATP; CD3+ T-cells, CD4+ T-cells, CD8+ T-cells, TH1 cells, CTLs, Th17, Tregs; stimulated DC maturation	[117, 120]
8-Methoxypsoralen (8-MOP)	2nd	B16, murine melanoma; YUCOT, human melanoma; MC38, murine colorectal carcinoma	—	HMGB1, ATP, IFN I; tumor engulfment by monocytes	[121]

Table 1. Ending

Таблица 1. Окончание

Photosensitizer (PS)	PS generation and type of additional structure	Tumor cell line	Intracellular localization of PS and possible cell death modality	ICD markers and signs of adaptive immunity activation	References
Polyethylene glycol-poly(methyl methy-acrylate-co-2-amino ethyl methacrylate (thiol/amine))-poly 2-(dimethyl-amino)ethyl methacrylate (PEG-P(MMA-co-AEMA (SH/NH2)-PDMA)	2nd	MC38, murine colorectal carcinoma	—	Overproduced ROS; CRT HMGB1; induced DC maturation; IL-6, IL-12, TNF-α	[122]

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