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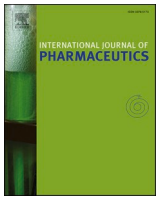

Review

Metal-based nanoparticles in cancer therapy: Exploring photodynamic therapy and its interplay with regulated cell death pathways

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ABSTRACT

Photodynamic therapy (PDT) represents a non-invasive treatment strategy currently utilized in the clinical management of selected cancers and infections. This technique is predicated on the administration of a photosensitizer (PS) and subsequent irradiation with light of specific wavelengths, thereby generating reactive oxygen species (ROS) within targeted cells. The cellular effects of PDT are dependent on both the localization of the PS and the severity of ROS challenge, potentially leading to the stimulation of various cell death modalities. For many years, the concept of regulated cell death (RCD) triggered by photodynamic reactions predominantly encompassed apoptosis, necrosis, and autophagy. However, in recent decades, further explorations have unveiled

Abbreviations: ACD, Accidental Cell Death; AgNPs, Silver Nanoparticles; ALA, 5-aminolevulinic Acid; AlPc, Chloroaluminum Phthalocyanine; AMPK, AMP-activated protein kinase; ANXA1, Annexin A1; APCs, Antigen-presenting Cells; ATF6, Activating Transcription Factor 6; ATG, Autophagy-related Gene; ATP, Adenosine Triphosphate; AuNCs, Gold Nanocages; AuNPs, Gold Nanoparticles; AuNRs, Gold Nanorods; AuNSs, Gold Nanoshells; AuNTs, Gold Nanotriangles; BCL-2, B-cell lymphoma 2; Bip, Binding Immunoglobulin Protein; CALR, Calreticulin; Ce6, Chlorin e6; CTLs, Cytotoxic T cells; CuO, Copper Oxide; CuS, Copper Sulfide; DAMPs, Damage-Associated Molecular Patterns; DCs, Dendritic Cells; DLAT, Dihydrolipoamide S-acetyltransferase; DOX, Doxorubicin; eIF2α, Eukaryotic Translation Initiation Factor 2α; ER, Endoplasmic Reticulum; FADD, Fas Associated Death Domain Protein; FasL, Fas Associated Death Domain Protein Ligand; FDA, Food and Drug Administration; Gd_2O_3, Gadolinium Oxide; GEM, Gemcitabine; GPX4, Glutathione Peroxidase 4; GSH, Glutathione; GRP, Glucose-regulating Protein; H_2O_2, Hydrogen peroxide; HAuNP, Hollow Gold Nanoparticles; HER2, Human Epidermal Growth Factor Receptor 2; HMGB1, High Mobility Group Box 1 Protein; HMME, Hematoporphyrin Monomethyl Ether; HpD, Hematoporphyrin Derivative; HSPs, Heat Shock Proteins; ICD, The immunogenic Cell Death; IFN, interferon; IL-1, Interleukin-1; IL-6, Interleukin-6; IONPs, Iron Oxide NPs; IRE-1, Inositol-requiring Enzyme Type 1; ISR, Integrated Stress Response; JNK1, c-Jun N-terminal Protein Kinase 1; LC3, Microtubule-associated protein 1A/1B-light chain 3; LIP, Labile Iron Pool; MAPK, Mitogen-activated Protein Kinase; MEK, Mitogen-activated Protein Kinase Kinase 2; MHT, magnetic hyperthermia, MKLK: Mixed Lineage Kinase Domain-like; Mn, Manganese; MnO_2, Manganese Dioxide; mPEG, methoxy polyethylene glycol; MOF, Metal Organic Framework; MRI, Magnetic Resonance Imaging; mTOR, Mechanistic Target of Rapamycin Kinase; MTX, Mitoxantrone; NCCD, The Nomenclature Committee on Cell Death; NIR, Near-infrared; NMs, Nanomaterials; NP, Nanoparticle; NPe6, N-aspartyl chlorin e6; NRCD, Non-Regulated Cell Death; Nrf2, Nuclear Factor E2-Related Factor 2; N-TiO_2, Nitrogen-doped Titanium Dioxide; PBLs, Peripheral Lymphocytes; PCD, Programmed Cell Death; PDT, Photodynamic Therapy; PEG, Poly Ethylene Glycol; PERK, Protein Kinase R-like ER Kinase; PGA, Polygalacturonic Acid; PI3K, Phosphatidylinositol-3-kinase; PLGA, Poly Lactic-*co*-glycolic Acid; PRRs, Pattern Recognition Receptors; PS, Photosensitizer; PTT, Photothermal Therapy; RCD, Regulated Cell Death; RIPK1, Receptor-interacting Protein Kinase 1; RIPK3, Receptor-interacting Protein Kinase 3; ROS, Reactive Oxygen Species; Ru(II), Ruthenium; SMAC, Second Mitochondrial Activator Of Caspases; TAAs, Tumor-Associated Antigens; TiO_2, Titanium Dioxide; TME, Tumor Micro Environment; TNFR, Tumor Necrosis Factor Receptor; TNF-α, Tumor Necrosis Factor-α; TRADD, TNFR1-associated Death Domain Protein; TRAIL, TNF-related apoptosis-inducing ligand; ULK1, Unc-51-like Kinase 1; UPR, Unfolded Protein Response; WRC, Walker Rat Carcinoma; ZnO, Zinc Oxide; ZnP, Zinc Pyrophosphate.

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additional cell death modalities, such as necroptosis, ferroptosis, cuproptosis, pyroptosis, parthanatos, and immunogenic cell death (ICD), which helps to achieve tumor cell elimination. Recently, nanoparticles (NPs) have demonstrated substantial advantages over traditional PSs and become important components of PDT, due to their improved physicochemical properties, such as enhanced solubility and superior specificity for targeted cells. This review aims to summarize recent advancements in the applications of different metal-based NPs as PSs or delivery systems for optimized PDT in cancer treatment. Furthermore, it mechanistically highlights the contribution of RCD pathways during PDT with metal NPs and how these forms of cell death can improve specific PDT regimens in cancer therapy.

1. Introduction

Photodynamic therapy (PDT) has been employed as a medical procedure for over a century, primarily to eliminate unwanted biological tissues such as those found in skin cancer (Tampa et al., 2019). The concept of "photodynamic action" was first noted by a medical student who observed the paramecia incubated with a fluorescent dye, acridine orange, perished when exposed to light, while those kept in darkness survived . Subsequent discoveries affirmed the essential role of oxygen in the photosensitization reaction and leveraged the lethal effect of PDT to treat skin tumors (Ochsner, 1997; Weishaupt et al., 1976). Nowadays, PDT stands as a promising therapeutic approach for an extensive array of diseases, notably cancer (Niculescu & Grumezescu, 2021). This modality presents significant potential as an alternative to traditional treatment methods such as radiotherapy and chemotherapy, or in combination with them (Fernandes et al., 2019). The distinct advantages of PDT include its comparatively less invasive nature, reduced systemic toxicity, and broad cellular target range (Li et al., 2018). PDT relies on the activation of a light-sensitized tumor-targeting compound known as a photosensitizer (PS), which is stimulated by suitable light irradiation (Dąbrowski & Arnaut, 2015). PS molecules possess the ability to absorb and relay electrons to oxygen molecules, leading to the generation of cytotoxic reactive oxygen species (ROS) within cells (Agostinis et al., 2011). The production of these ROS results in irreversible damage to the targeted tissue, further prompting a sequence of survival and death signals. In circumstances where cells fail to detoxify and repair the induced damage, intense oxidative stress initiates mechanisms culminating in cell death (Donohoe et al., 2019).

The photodynamic reaction is capable of initiating various cell death modalities (Donohoe et al., 2019; Mishchenko et al., 2022). The identification of cell death pathways in PDT is a complex task as these pathways can overlap and be simultaneously activated. The Nomenclature Committee on Cell Death (NCCD) has suggested two major classes of cell death (Galluzzi et al., 2018). First, non-regulated cell death (NRCD) or accidental cell death (ACD) which represents the rapid and uncontrolled termination of cells facing intense physical, chemical, or mechanical forces, such as, extreme pH or temperature conditions (Donohoe et al., 2019; Galluzzi et al., 2015). The second group, consists of regulated cell death (RCD), which are cell death mechanisms integrated with signaling cascades and molecular-mediated effector mechanisms that may result from intense or prolonged disturbances that exceed the cell's adaptive responses (Cui et al., 2021; Galluzzi et al., 2016; Tang et al., 2019). RCD can also occur under physiological conditions such as during development and tissue turnover, where it may be referred to as Programmed cell death (PCD). Over 20 different types of RCD have been broadly classified, including apoptosis, necroptosis, pyroptosis, entosis, ferroptosis, etc (Galluzzi et al., 2018). The predominant cell death mechanisms that are activated after PDT include apoptosis autophagy, and necrosis/necroptosis. However, these vary according to the localization of PS, the intensity of light dose, and the time between the PS delivery and the light exposure. (Abrahamse et al., 2017; Piette, 2015). At low and non-lethal doses of PDT, signaling pathways, such as AMPK, allow cancer cells to response protecting adaptive autophagy (Blázquez-Castro et al., 2014; Mihaylova & Shaw, 2011). When cells undergo stress, there can be an accumulation of autophagosomes. Under certain conditions, notably when the clearance mechanism is hindered, this buildup can trigger various cellular death pathways, encompassing both apoptosis and necrosis (Shen & Codogno, 2011). Above a certain level of PDT stress intensity, cancer cells cannot cope with the heavy damage, and signaling pathways are activated leading to cell deaths, including apoptosis and necrosis (Maiuri et al., 2007). Recent discoveries have shed light on the involvement of other forms of RCD, including ferroptosis, cuproptosis and paraptosis, in the cancer cells exposed to PDT (Han et al., 2020; Kessel, 2019a; Zhang et al., 2022a; Li et al., 2021; Mishchenko et al., 2022; Wang et al., 2023b, a; Xu et al., 2022). PDT can also induce immunogenic cell death (ICD), promote the release of tumor-associated antigens (TAAs) from dying tumor cell, and increase the proliferation, activation, and infiltration of antigen-presenting cells (APCs) and antigen-specific T cells (Falk-Mahapatra & Gollnick, 2020; Hua et al., 2021). The ICD induced by PDT can differ in the damage-associated molecular patterns (DAMPs)' profile and has also been linked to different cell death modalities such as apoptosis, necroptosis and ferroptosis (Razan et al., 2021; Turubanova et al., 2019). This effect of PDT makes it clinically more favorable for cancer treatment as ICD stimulates anticancer immune responses that are critical for the efficacy of the therapy and long-term anticancer immunity.

Many research efforts have been aimed at refining PDT to promote its standardization as a clinical procedure. Key areas of focus include enhancing specific targeting, increasing the solubility of hydrophobic PSs, augmenting drug load, and addressing the challenge of limited light penetration to tumor tissues (Abrahamse & Hamblin, 2016; Chen et al., 2020; Lucas, 2020). A significant contribution to these enhancements comes from the field of nanotechnology, which has notably aided in overcoming several challenges associated with PSs (Li et al., 2020). Metal and metal-oxide nanoparticles (NPs) have been extensively used in biomedical applications, with diverse nanoscale metallic materials acting either directly as PSs or as delivery agents for PSs in PDT studies related to cancer (George et al., 2022; Sargazi et al., 2022; Shang et al., 2021; Yi et al., 2020).

In this review, we delve into the roles played by metal-based nanoparticles (NPs) in enhancing PDT for cancer treatment. We provide insights into the cellular mechanisms influenced by these NPs, the intricacies of various cell death pathways during PDT, and how the integration of metal-based NPs can possibly optimize these processes for better therapeutic outcomes.

2. Photodynamic therapy (PDT)

2.1. Mechanism of PDT

PDT operates via synergistic interplay of a non-toxic photosensitizing agent, specific wavelength light, and molecular oxygen, resulting in the production of cytotoxic ROS (Niculescu & Grumezescu, 2021). The PS drugs can be administered from different routes such as intravenous, topical, oral, intraperitoneal, intra-arterial, and intratumoral injections, with either method resulting in their selective accumulation within the tumor. Subsequent exposure to light activates the PS, while the presence of molecular oxygen triggers a photochemical reaction (Ma et al., 2021). This activation process begins where the PS is excited from a ground

state (singlet state, 1PS) to a short-lived excited singlet state (1PS*). The excited 1PS* radiates part of this energy in the form of a quantum of fluorescence, and the remaining energy directs the PS into a long-lived, electronically excited state (triplet state, 3PS*) via intersystem crossing (Li et al., 2022). The triplet excited state can transfer the energy into biological molecules. At this point, two key reactions occur: Type I reaction involves proton or electron transfer to surrounding oxygen and water molecules, yielding free radicals like superoxide anion radical ($O_2^{\bullet -}$), hydroxyl radical ($OH^{\bullet}$), and hydrogen peroxide (H_2O_2) •, and type II reaction entails direct energy transfer to surrounding oxygen molecules in cytoplasm, generating singlet oxygen ($^1O_2$) (Fig. 1) (Sai et al., 2021; Tavakkoli Yaraki et al., 2022). PSs serve as fundamental components of PDT, as they are capable of absorbing light of a specific wavelength - ideally within the therapeutic window (600–800 nm) - and of triggering photochemical or photophysical reactions (Kim & Daraf-sheh, 2020; Lan et al., 2019). The first PS introduced for treatment was the "hematoporphyrin derivative" (HpD). Over 1000 natural and synthetic PSs have been identified (Kwiatkowski et al., 2018; Park et al., 2018). Different classes of PSs have been employed in PDT, starting with the first generation of PSs comprised of various forms of HpD, including Photofrin®, the foremost photosensitizer molecule that the US Food and Drug Administration (FDA) approved for cancer treatment in 1995 (Baskaran et al., 2018; Lee et al., 2020).

These PSs, however, had two primary drawbacks: 1) their low chemical purity reduced activation wavelengths below 640 nm, and 2) their long half-life made patients' skin light-sensitive for up to 6 weeks (Zhang et al., 2018). The second generation of PSs comprised synthetic aromatic compounds such as benzo porphyrins, chlorins, bacterio-chlorins, and phthalocyanines, which exhibited rapid elimination from the body, fewer side effects, and enhanced tissue penetration (650–800 nm) compared to their predecessors. Nevertheless, these compounds suffered from poor biodistribution, rapid clearance from the circulatory system and aggregation in physiological conditions (Hak et al., 2023; Kou et al., 2017; Nowak-Stepniowska et al., 2013). The third-generation PSs are photoactivatable drugs designed to target cells with increased specificity (Mfouo-Tynga et al., 2021). Different strategies such as encapsulation of PSs in biodegradable/biocompatible NPs or their conjugation with a monoclonal antibody directed towards a specific cancer cell antigen (e.g., tumor surface markers such as such as growth factor receptors, transferrin receptors or hormones) can enhance affinity and efficacy of PSs for targeting cancer cells without detectable dark toxicity effects (Mokwena et al., 2018; Wang et al., 2021). Despite numerous advantages of PDT in cancer treatment, the development of new PS delivery systems is required to enhance PDT's bioavailability and its potential in clinical applications (Mfouo-Tynga et al., 2021; Tavakkoli Yaraki et al., 2022; Zhao et al., 2021).

2.2. PDT for cancer treatment

Delving deeper into the intricacies of PDT, the choice and delivery method of photosensitizers play a pivotal role in treatment efficacy. The therapeutic impact is influenced by the ability of PSs to target tumor cells selectively and their subsequent cellular interactions. Metal-based nanoparticles have emerged as a promising approach in this context, enhancing photosensitizer delivery and augmenting PDT outcomes (Agostinis et al., 2011; Sun et al., 2018). The unique appeal of PDT in cancer therapy lies in its three-pronged anti-tumor mechanisms: 1) the direct cytotoxic effects on tumor cells by generating ROS production, 2) damage to the tumor vasculature, and 3) stimulation of the immune system by enhancing cancer cell antigen presentation to T cells and phagocytic uptake of dying cancer cells by dendritic (Agostinis et al., 2011; Donohoe et al., 2019; Jin et al., 2021). The direct cytotoxic effect of PDT depends on the cellular localization of the PS, where the resultant ROS may inflict damage on mitochondrial, lysosomal, or endoplasmic reticulum (ER) compartments (Tan et al., 2022). The ROS-induced damage could be either permanent or repairable, hinging on its severity. Indeed, mild oxidative stress triggers adaptative response aimed at maintaining homeostasis and repairing the damage (Broek-gaarden et al., 2015). These pro-survival mechanisms, such as integrated stress response (ISR), unfolded protein response (UPR) and antioxidant stress responses such as nuclear factor E2-related factor 2 (Nrf2) pathway, focus on halting protein synthesis and eliminating oxidized biomolecules (Broekgaarden et al., 2015; Ferino et al., 2020; Pakos-Zebrucka et al., 2016). However, in PDT scenarios, if photo-oxidative

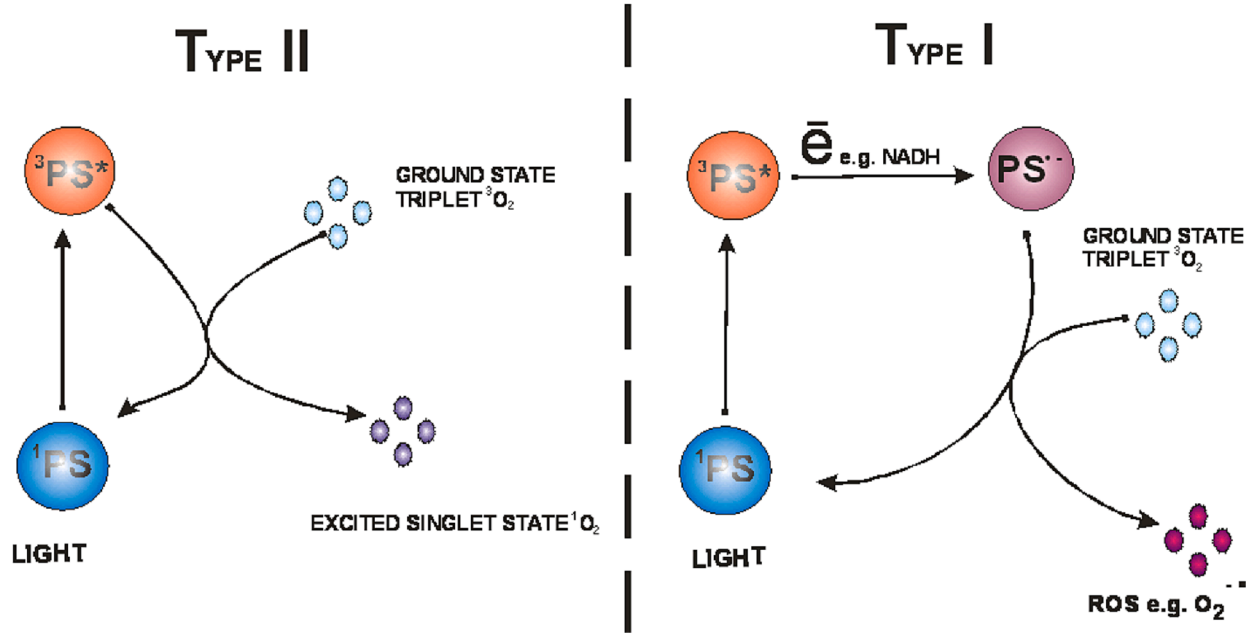

Fig. 1. Type I and II photodynamic reactions. An excited triplet state can either react directly with a reductant, e.g., an organic molecule in a cellular microenvironment, acquiring a hydrogen atom or electron to form a radical and produce a superoxide anion radical ($O_2^{\bullet -}$), type I reaction or, more likely, transfer its energy to molecular oxygen ($^3O_2$) and form singlet oxygen ($^1O_2$), type II reaction. (Reprinted from: Mroz P, Yaroslavsky A, Kharkwal GB, Hamblin MR. Cell Death Pathways in Photodynamic Therapy of Cancer. *Cancers*. 2011; 3(2):2516–2539. https://doi.org/10.3390/cancers3022516).

stress exceeds a certain threshold in intensity or duration, the cells fail to restore homeostasis, thereby cell death mechanisms (Kessel, 2012; Moserova & Kralova, 2012).

In addition, the efficacy of in vivo PDT is further enhanced by the activation of coagulation processes in tumor microvasculature (occlusion of tumor vessels) and the systemic anti-cancer immune response (Fig. 2) (Juarranz et al., 2020; Tan et al., 2022). Tumor cells that evade the direct cytotoxic effects of PDT can potentially be eradicated by vascular occlusion, leading to persistent tumor tissue hypoxia and nutrient deprivation (Mashayekhi et al., 2019). Furthermore, PDT stimulates direct interaction between immune cells and cancer cells by spurring the immune response primarily by PDT-released DAMPs that stimulate the innate immunity, thereby triggering the adaptive immunity. This systemic anti-tumor immunity plays a crucial role in the long-term management of the disease or in the control of distant metastasis (Juarranz et al., 2020; Tan et al., 2022). Currently most PDT-related research are revolving around optimizing ICD and antitumor immune responses in PDT /immunotherapy combination strategies (Hua et al., 2021; Huis Huis In't Veld et al. 2023).

Despite the desirable multi-pronged PDT mechanisms in cancer treatment, this article will focus on the direct tumor cell killing effect of PDT and the cell death pathways that can be triggered by photodamage. Also, in the last section of this article, we mention ICD and briefly explain how PDT triggers an antitumor immune response.

2.3. Metal-based NPs in PDT

Nanomaterials (NMs), contain particles with external dimensions ranging from 1 to 100 nm that show enhanced performance over their bulk counterparts (Jeevanandam et al., 2018). Both natural and synthetic NMs have provided significant advancements in various industrial and biomedical applications over the recent years (Barhoum et al., 2022; Sajid, 2022). These nanoscale entities are utilized in various biomedical fields, including disease diagnosis, as therapeutic delivery systems, biosensors, probes, and as materials for tissue engineering (Feng et al., 2020; George et al., 2022; Zeng et al., 2022). NPs can be classified into two major categories: 1) organic materials encompassing phthalocyanine, liposomes, and chitosan, and 2) inorganic materials including metal or semiconductor materials (Yezhelyev et al., 2009). Among the inorganic NPs, metallic NPs have gained widespread recognition for their various biomedical applications. They have demonstrated an extreme sensitivity in diagnostic assays, radiotherapy enhancement, and gene and drug delivery (Burlec et al., 2023). Multiple studies indicate that metallic NPs are beneficial in PDT, thanks to their high stability, adjustable size, optical properties, and ease of surface functionalization. These traits make them ideal as PSs, delivery vehicles for PSs, and upconversion tools in PDT (Montaseri et al., 2021; Shang et al., 2021).

2.3.1. Characteristics and commonalities of metal-based NPs

As mentioned above, metallic NPs are considered to be congenial PSs because of the various features the offer, specifically optical properties,

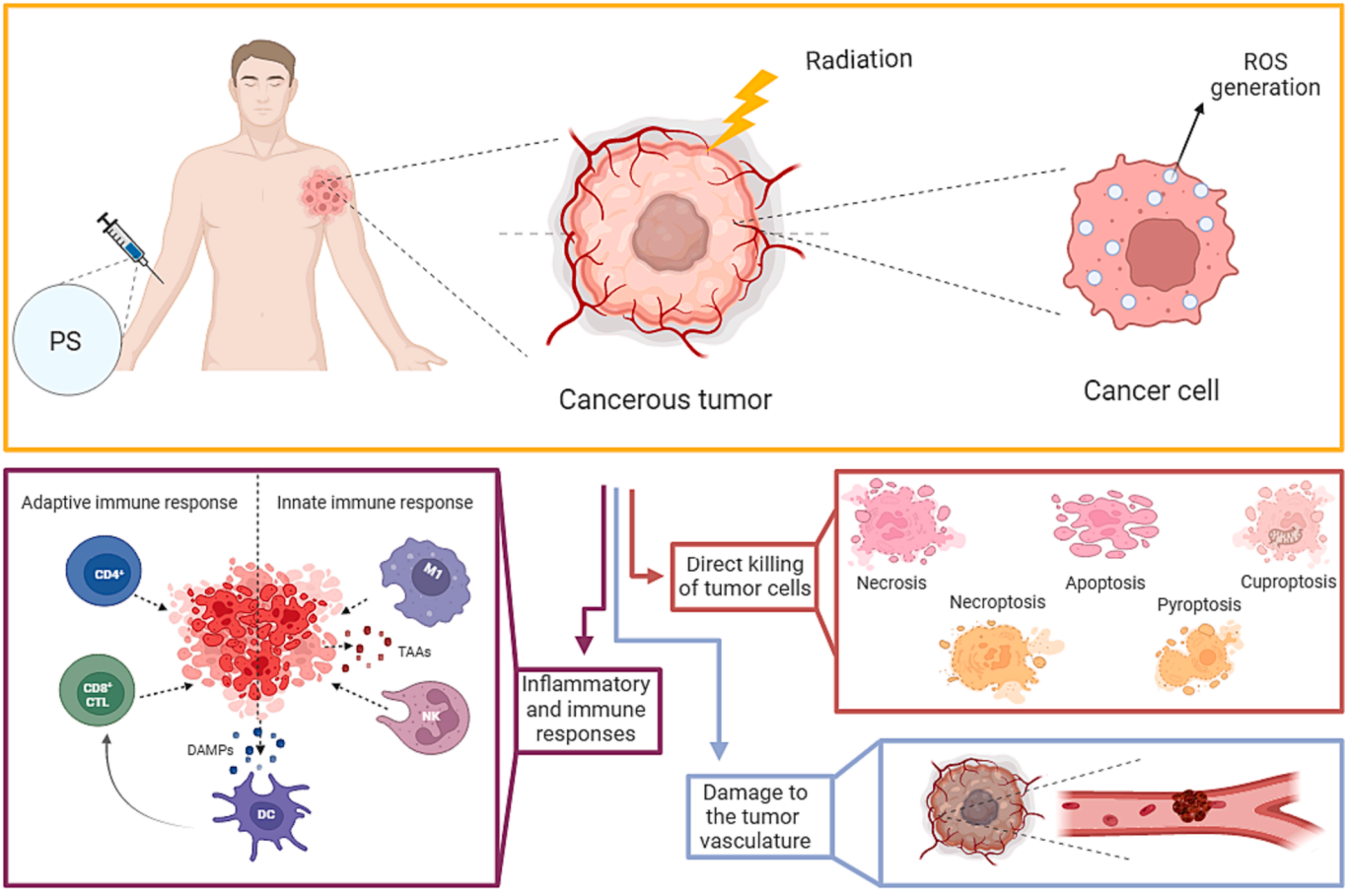

Fig. 2. In vivo procedure and mechanisms of PDT. PDT starts typically by intravenous or intratumor injection of a PS drug. PS accumulates in tumor tissues by passive (size or surface chemistry of PS) or active (using high-affinity ligands) targeting. Light source with a specific wavelength is then locally administrated to the tumor tissues. Cytotoxic effects of PDT ideally result in tumor destruction by generating ROS in tumor cells. Three mechanisms of PDT are involved through in vivo tumor treatment: (1) direct killing of tumor cells, (2) inflammation and immune responses, and (3) coagulation and damage to the tumor vasculature. (DAMPs: Damage Associated Molecular Patterns, CTL: Cytotoxic T cell, DC: Dendritic Cells, M1: type-1 Polarized Macrophages, NK: Natural Killer Cells, PDT: Photodynamic Therapy, PS: Photosensitizer, ROS: Reactive Oxygen Species, TAAs: Tumor Associated Antigens). Created with BioRender.com.

long circulation time and accumulation rate in tumors, and easy surface functionalization (Atiyeh et al., 2023). Moreover, metallic NPs can be functionalized to become near infrared (NIR) activatable agents, which gives them the upper hand over organic PSs in PDT for deep tissue penetration irradiation (Sarbadhikary et al., 2021).

Metal-based NPs in PDT can be utilized in various formulations. The first category of metallic NMs are pure metal NPs including, but not limited to silver, copper, gold, iron, magnesium, titanium, platinum, and zinc. Metal/transition-metal oxide NPs (e.g., MnO_2, TiO_2, ZnO, MoO_3, CeO_2), metal sulfide NPs (e.g., Ag_2S, CuS, FeS NPs), metal-based nano formulations doped with other metals (e.g., Au-TiO_2 or Pt-ZnO) and/or non-metals such as nitrogen and graphene oxide, and metal organic frameworks (MOFs), are other classes of metal-based NM with (George et al., 2022; Khlyustova et al., 2020; Mahboob et al., 2021; Sun et al., 2018). These nanoscale materials have shown photodynamic efficacy in numerous in vitro and in vivo studies, often being employed to transport conventional photosensitizers such as phthalocyanines, porphyrins, and other dyes (Ziental et al., 2020). Additionally, there exist metallic NPs that exhibit maximum absorption and scattering of near-infrared radiation (NIR). These are advantageous as they can be utilized as PSs in the PDT for cancer treatment (Debele et al., 2015).

Plasmonic metal NPs including gold, silver and platinum particles, have unique optical properties such as scattering (Rayleigh scattering and Raman scattering), absorption, extinction, and adjustable spectral range, and can interact with electromagnetic radiation in the visible and NIR regions (Ou et al., 2021). The optical properties of plasmonic NPs make them superior to other metallic NPs in various biomedical applications (Wang et al., 2020). Plasmonic metallic NPs show enhanced PDT efficiency based on a physical phenomenon called metal-enhanced singlet oxygen generation. and can be used for biosensing, bioimaging, and drug delivery purposes along with PDT (George et al., 2022; Tavakkoli Yaraki et al., 2022).It is worth mentioning that in many studies metallic NPs are conjugated with functional groups in order to fulfil a desired biomedical applications, enhance the NP stability, achieve specific cell targeting, and ameliorate their therapeutics performance (Song et al., 2016). To name a few, NP functionalization with antibodies, peptides, RNA, and DNA oligonucleotides, works as a targeting strategy, and surface coating with polyethylene glycol (PEG) polymer can prevent recognition by the immune system and therefore, improve the blood circulation period of the NM (Vankayala & Hwang, 2018; Wei et al., 2023).

2.3.2. *Metallic NPs facilitating effects of PDT*

Metallic NPs perform several potential roles in PDT: They can serve as PSs themselves, be employed as PS delivery systems, or as energy transducers (Agostinis et al., 2011; Debele et al., 2015). NPs, particularly those with unique optical absorption properties, have the capacity to generate ROS and thus can operate as independent PSs by themselves (Lucky et al., 2015). With a high surface-to-volume ratio and the possibility of high drug loading, certain metallic NPs can be utilized as PS delivery vehicles in PDT. In these systems, PSs are either encapsulated in or conjugated to NP platforms through covalent or noncovalent interactions (Debele et al., 2015; Luo et al., 2014).

The photostability and resistance to enzymatic degradation of these NPs are more prominent than those of organic PSs. Thus, in some instances, they may be able to substitute organic PSs in PDT therapy (Krajczewski et al., 2019). Also, traditional PSs combined with plasmonic metallic NPs such as gold and silver, exhibit excellent optical and surface plasmon resonance properties. This leads to a significant increase in singlet oxygen production and prolonged excitation properties that can be obtained from visible and near-infrared lights (George et al., 2022).

Gold NPs (AuNPs) constitute the most prevalent type of metallic NP leveraged in PDT as a drug delivery system. These particles offer notable advantages due to their high surface-to-volume ratio, diverse optical properties, chemical stability, and biocompatibility. They are typically utilized in conjunction with a light treatment of wavelength between 700 and 800 nm and can be surface-modified with a variety of agents including peptides, antibodies, aptamers, and biocompatible polymers such as PEG (Debele et al., 2015; Shang et al., 2021). Moreover, AuNPs can be employed for the delivery of oligonucleotide therapeutics, further expanding their applications in medicine (García-Garrido et al., 2021). Among these modifications, the hydrophilic PEG represents the most frequently used covalent conjugate in metallic delivery systems, effectively increasing blood circulation duration and thereby enhancing therapeutic outcomes (Barry & Sadler, 2013). An added advantage of using AuNPs in PDT is their capability to elevate the temperature, further harming tumor cells through a treatment technique called hyperthermia therapy. Moreover, AuNPs can also enhance the excitation efficacy of PSs through localized surface plasmon resonances (Debele et al., 2015). PS drugs can be affixed to AuNPs by either covalent or non-covalent conjugation (Calixto et al., 2016). For example, Wieder et al. demonstrated a method for conjugating AuNPs with hydrophobic phthalocyanines, thereby increasing singlet oxygen generation and cell mortality post-PDT in HeLa cells (Wieder et al., 2006). It is important to note that the use of AuNPs in PDT is not confined to spherical shape or gold nanospheres; other forms of gold nanomaterials, such as gold nanorods (AuNRs), gold nanotriangles (AuNTs), nanostars and gold nanoshells (AuNSs), have also been utilized as delivery agents in PDT (Cheng et al., 2008; García Calavia et al., 2018; Vinita et al., 2023; Youssef et al., 2019; Zhao et al., 2012).

Beyond AuNPs, various metallic NPs of different combinations have also been implemented as PS carriers. For example, Shi et al. adopted PEGylated iron oxide NPs (IONPs) in conjunction with fullerene to deliver the PS hematoporphyrin-monomethyl-ether (HMME) to targeted cells (Shi et al., 2013). This method notably amplified PS uptake, enhancing the photodynamic cancer cell killing effect both in vitro in B16-F10 cells and in an in vivo murine tumor model. Additionally, water-soluble iron-based coordination trimers have been demonstrated to increase the generation of ROS in cancer cells, showing their potential as a potent adjunct in photodynamic therapy (Cordani et al., 2021). Moreover, Duan et al. targeted 4 T1 breast cancer tumors with zinc pyrophosphate (ZnP) core–shell NPs loaded with the photosensitizer pyrolipid (ZnP@pyro) (Duan et al., 2016). They further tailored the structure by incorporating PD-L1 antibody for checkpoint-blocking immunotherapy, successfully eliminating cancer cells through both apoptosis and necrosis under 670 nm irradiation. It is worth mentioning that certain metallic nanomaterials are inherently capable of ROS generation owing to their unique optical absorption properties. Such materials can serve as standalone PSs. Some metal oxide NPs, such as nano-sized titanium dioxide (TiO_2) and zinc oxide (ZnO) exhibit slower degradation rates and longer lifecycle compared to traditional PS, further enhancing their potential utility (Lucky et al., 2015; Sargazi et al., 2022).

TiO_2 NPs, ultra-fine nanocrystalline particles measuring approximatively100 nm, have gained significant attention as potential photosensitizing agents for PDT. Their wide-ranging application in advanced cancer treatment strategies is attributed to their low toxicity, excellent oxidation capability, biocompatibility, and unique photocatalytic activity (Carbone et al., 2006; Fabian et al., 2008; Li et al., 2013). Rapid binding to cancer cells in acidic microenvironment further establishes their efficacy (Sargazi et al., 2022). However, exciting the electrons of TiO2 NPs and generating ROS requires a wavelength shorter than 387 nm, equating to 3.2 eV as the band gap energy of anatase TiO2 (Lagopati et al., 2010). This limitation restricts NPs absorption to the ultraviolet (UV) and not the NIR light region (Sargazi et al., 2022). To enhance photochemical properties, researchers are exploiting modifications of TiO_2 by integrating it with inorganic dopants and carbon-based nanomaterials. The investigations have demonstrated that such an approach provides a superior alternative to both neat TiO_2 and conventional PSs in PDT (Li et al., 2013; Ziental et al., 2020). For instance, Moosavi and colleagues employed nitrogen-doped titanium dioxide (N-TiO2) NPs

with visible light to amplify ROS generation and increase photokilling of leukemia cells (Moosavi et al., 2016). Additionally, TiO2 NPs have been reported as effective carriers of PSs for theranostic purposes, employing PSs like zinc (II) phthalocyanine derivate (MCZnPc) and Chlorin e6 (Ce6) to examinate antitumor activity against human cervical adenocarcinoma cells (HeLa) and glioblastoma cells (U87), respectively (Youssef et al., 2018; Yurt et al., 2018).

ZnO NPs, comparable to TiO_2 in photocatalytic activity, are low-cost metal oxide with a wide band gap (3.37 eV) capable of producing ROS and inducing oxidative damage to the cell upon UV radiation (Yi et al., 2020). Recognized as safe by the Food and Drug Administration (FDA) owing to its negligible dark toxicity in vitro and in vivo (Hu et al., 2013), ZnO NPs are notably more toxic to cancer cells than normal human cells. This is primarily due to the abundance of anionic phospholipids on the surface of cancer cells and the acidic microenvironment, which dissolves Zn^{2+} ions, thereby heightening the oxidative stress levels of cancer cells (Sadjadpour et al., 2016). Given their high surface- to-volume ratio, ZnO serve as ideal carriers for PSs or anticancer drugs. Various organic PSs, such as 5-aminolevulinic acid (ALA) and Photofrin®, have been loaded onto ZnO NPs, demonstrating a synergistic effect in PDT (Fakhar-e-Alam et al., 2012; Fakhar-e-Alam et al., 2011; Kishwar et al., 2014). To facilitate PDT in deep tissues and organs, lanthanides Europium and Gadolinium are incorporated into ZnO nanoparticles, synthesizing a self-illuminating composite nanostructure excitable by highly penetrating X-ray and capable of producing ROS (Ghaemi et al., 2016; Rimoldi et al., 2016).

2.3.3. Metallic NPs in PDT combination therapy

Nanotechnology-based PDT has been applied in combination therapy methods to overcome weaknesses of chemotherapy, radiotherapy (RT), photothermal therapy (PTT), sonodynamic therapy, chemodynamic theapy, gas therapy, immunotherapy, anti-angiogenesis therapy, and tumor targeted therapy (Songca, 2023; Wei et al., 2023).

Photothermal therapy (PTT) in cancer refers to employment of optical radiation, usually in the NIR wavelength range (700–2000 nm), and its conversion to heat by PTT agents, aimed to raise tissue temperature and subsequently kill tumor cells via protein denaturation and cell membrane destruction (Han & Choi, 2021). Harnessing additive or synergistic PTT/PDT effects has been considered to be a coherent strategy to promote the efficacy of both therapeutic approaches. Some metal-based nanostructures such as gold copper sulfide NPs and gold NMs, are capable of photothermal energy conversion as well as generation of ROS, which together make them potential candidates in combination of PTT and PDT (Bharathiraja et al., 2017; Li et al., 2017; Wu et al., 2020). Furthermore, functionalized with PS molecules such as aluminum phthalocyanine tetrasulfonate and Ce6, gold and CuS nanostructures are studied in synergistic PTT/PDT treatment (Goel et al., 2018; Jang et al., 2011; Lin et al., 2013; Wu et al., 2020).

In combination therapy with chemotherapy, functionalized metal nanostructures offer promising solutions to the shortcomings and side effects of chemotherapeutic drugs. They are capable of encapsulating, or binding to drugs, responding to light irradiation, and thus exhibiting lower drug toxicity, superior targeting efficiency, and a prolonged half-life (Shang et al., 2021). We present several in vitro studies illustrating the joint applications of PDT and chemotherapy. For instance, Imanparast et al. explored the utility of functionalized hollow gold nanoparticles (HAuNP) to encapsulate mitoxantrone (MTX), a chemotherapy drug. Upon lighting by a Light Emission diode (LED), the hollow gold nanoparticles demonstrated an enhanced efficacy of PDT in the human breast adenocarcinoma cell line MCF7 (Imanparast et al., 2018). Natural chemotherapeutic drugs such as curcumin can also be delivered be metal based nanocarriers in PDT/chemotherapy. In a study, Aghajanzadeh et al. synthetized two curcumin delivery systems, MnFe2O4 (Mn) and Cr2Fe6O12 (Cr)-based nanocarriers and PSs in combination therapy (Aghajanzadeh et al., 2020). These in vivo and in vitro experiments demonstrated that nontoxic manganese-iron oxide (MnFe2O4) nano structures have pH-dependent drug release and better cytotoxic effects upon light irradiation, making this nanocarrier a competent system for PDT.

Metallic NPs used in combination PDT method, can play roles beyond drug delivery. For example, in an innovative approach to counteract tumor hypoxia, MnO_2 NPs have been utilized not only as carriers but also as oxygen generators. By decomposing the tumor's endogenous H_2O_2 into oxygen molecules (O_2), they can increase the efficacy of PDT (Han et al., 2020). PDT can be combined with immunotherapy as well. In tumor treatment, phototherapy can trigger innate and adaptive immune responses including creating a local inflammatory reaction, infiltration of various immune effector cell (e.g. neutrophils), secretion of cytokines, and activation of CD8 + T lymphocytes (Hou et al., 2018). In addition, PDT using metal-based nanostructures can induce immunogenic cell death (ICD), which is described later in this review. ICD is accompanied by the release of tumor-specific antigens and certain damage-associated molecular patterns (DAMPs), which in turn, can lead to generation of long-term immunological memory (Alzeibak et al., 2021). It is noteworthy that nanotechnology has improved photodynamic immunotherapy to be targeted to tumor cells or tumor vasculature (ischemia) in order to reduce toxicity as compared to conventional PDT (Liu et al., 2021).

2.3.4. Potential toxicity of metallic NPs

The toxicity of metal-based NPs depends on their physicochemical properties, such as size, shape, chemical composition, surface chemistry, and solubility (Zhang et al., 2022a). Relative to their bulk form, small sized metallic NPs assert increased ROS production and cytotoxicity (Sun et al., 2018). Metal and metal oxide NPs have good dispersibility and stability in water and therefore, can enter and accumulate in the human body. Exposure to metallic NPs is feasible through breathing, skin contact, eating and drinking, and various injection routs such as intravenous, intraperitoneal, intradermal, and intramuscular, effecting respiratory tract (lung), nervous system (brain), circulatory system (transportation to other organs), gastrointestinal tract and lymphatic system (Das et al., 2016). Due to their small sizes, Ag and Cu NPs can move through the circulatory systems, enter various organs and penetrate the blood–brain barrier into the nervous system (Sun et al., 2018). Metallic NPs have also shown reproductive toxicity, as they can embryogenesis and developmental processes by accumulating inside the testis or ovarian cells, and cross the placenta to have direct pathological impact on the offspring (Bai & Tang, 2020). Gold and silver NPs were found to have transplacental crossing ability in animal models, leading to structural and functional abnormalities in the fetuses. (Hougaard et al., 2015; Zhang et al., 2021).

Although cytotoxicity is the principal of PDT, the potential systemic toxicity of metal-based NMs in PDT for cancer treatment can be investigated from various aspects including aggregation, dark toxicity, destructive effects on normal cells, degradation into toxic byproducts, and their long circulation time (Zhang et al., 2022a). In order to reduce the toxicity of metallic NPs, targeted delivery methods and adjustable functionalized properties should be developed by surface modifications and nanocomposite formulation (Shah et al., 2019).

2.4. Cell death pathways associated with PDT

As mentioned above, the type of cell death observed after PDT is dependent on many factors. PS concentration and light dosage, which together constitute the dose of PDT, are of the main determinants (Debele et al., 2015). Generally, PDT utilizing high PS concentrations or strong irradiation dose provokes ACD such as necrosis (Luo et al., 2015; Miki et al., 2014). As an illustration, when murine leukemia P388 cells were exposed to low light doses with chloroaluminum phthalocyanine (AlPc) as the PS, apoptosis was predominantly observed. In contrast, higher light doses resulted in necrosis (Luo & Kessel, 1997). Parallel outcomes were seen in studies involving human bladder carcinoma

HT1197 cells treated with 5-aminolevulinate (ALA)-induced PDT (Wyld et al., 2001). Additionally, similar findings were noted in CNE2 cells, TWO-1 cells (human nasopharyngeal carcinoma cells), and AY-27 cells (chemically-induced rat bladder carcinoma cells) when sensitized using hypericin (Ali & Olivo, 2002; Kamuhabwa et al., 2001).

Different cell types have distinct responses to the same PS and dose of PDT. Wyld et al demonstrated that the same light dose (LD50/90) triggers different cell deaths after ALA sensitized PDT in HT1197 (Human Bladder Carcinoma), WRC (Walker Rat Carcinoma) and MCF-7 (Human Mammary Carcinoma) cell lines (Wyld et al., 2001). Following a low LD50 light dose, HT1197 cell line died predominantly by apoptosis, where WRC cell line responded by necrosis and after 24 h apoptotic cells appeared. Both these cell lines responded to PDT predominantly by necrosis at a higher light dose (LD90). Interestingly, MCF-7 cells only died of necrosis in low and high doses of light, because these cells contain a mutated form of caspase 3, which is an important downstream effector of apoptosis (Larsen & Sørensen, 2017; Wyld et al., 2001).

The intercellular localization of PSs in another influential factor on the mode of cell death following PDT (Oliveira et al., 2011). The necrotic pathway may be initiated when PSs are localized in the plasma membrane (Kessel et al., 2006). PSs that tend to accumulate in the cell membrane in short incubation periods, such as Photofrin and Phthalocyanine zinc (II) can mediate the loss of membrane integrity and ATP depletion upon photoactivation and therefore, trigger necrosis (Fabris et al., 2001; Hsieh et al., 2003). Mitochondria, ER and nucleus localization of PSs normally lead to the apoptotic pathway (Hitomi et al., 2004; Moserova & Kralova, 2012; Oleinick et al., 2002). Mitochondrial membrane damage disrupts the membrane potential, releases cytochrome *C* into the cytoplasm and attributes to apoptosome complex formation. In addition, lysosome localization of PSs, such as N-aspartyl chlorin e6 (NPe6), interrupts the lysosomal membrane, thereby releasing proteases that activate Bid, a pro-apoptotic member of the Bcl-2 family, and triggering the mitochondrial apoptotic pathway (Reiners et al., 2002).

The molecular mechanisms underlying PDT-induced apoptosis and autophagy represent the most thoroughly studied pathways of regulated photokilling (Agostinis et al., 2011; Donohoe et al., 2019; Kushibiki et al., 2013). Other RCDs induced by PDT include mitotic catastrophe, paraptosis, pyroptosis, parthanatos, necroptosis, ferroptosis, and cuproptosis (de Melo Gomes et al., 2023; Kessel & Reiners, 2020; Mascaraque et al., 2019; Mishchenko et al., 2022; Xu et al., 2022; Zeng et al., 2023; Zhu et al., 2019).

In the subsequent sections of this review article, we explore metal-based NPs and the cell death pathways that they trigger as a consequence of PDT in cancer cells.

3. Metallic nanoparticles modulating regulated cell death pathways in PDT

Recently, considerable attention has been given to the various facets of PDT facilitated by nanomedicine, specifically its potential to significantly enhance therapeutic outcomes by manipulating RCD mechanisms. This section explores how **metal, metal-oxide NPs, and metal-based nano formulations** influence different RCD pathways and their consequent impact on PDT in cancer cells (Table1).

3.1. Apoptosis

Apoptosis is an orchestrated cellular self-destruction process devoid of inflammatory response that involves a sequence of molecular events (Kushibiki et al., 2013). A range of physicochemical stressors can initiate this process, including chemicals, DNA damaging agents, nutrients deprivation, hypoxia, free radical-generating compounds such as H2O2, specific growth factors, pro-inflammatory cytokines, as well as physiological processes like development and aging (Greijer & van der Wall, 2004; Haddad, 2002; Kujoth et al., 2005; Ramesh et al., 2009; Simon et al., 2000; Wyllie, 2010). Apoptotic cell death may proceed through the activation of effector caspase molecules or via a caspase-independent route, particularly when the cell is subjected to infection or stress (Ghavami et al., 2009; Negara et al., 2020). The hallmarks of apoptosis include membrane blebbing, cell shrinkage, chromatin condensation, inter-nucleosomal DNA fragmentation (forming DNA "ladders"), and the generation of small vesicles known as apoptotic bodies (Madala, 2015).

In mammalian cells, caspase-dependent apoptosis can be organized into three major pathways (Fig. 3)**:** 1) the intrinsic (mitochondrial), 2) the extrinsic (death receptor), and 3) the endoplasmic reticulum (ER) pathway (Mohammadinejad et al., 2019). The intrinsic pathway is characterized by irreversible permeabilization of the mitochondrial outer membrane, orchestrated by pro-apoptotic proteins such as BAX and BAK from the B-cell lymphoma 2 (BCL-2) superfamilies (Cory & Adams, 2002). This permeabilization is a critical step in apoptosis, leading to the release of mitochondrial proteins like the second mitochondrial activator of caspases (SMAC) and cytochrome *C* into the cytosol (Wang & Youle, 2009). Consequently, an entity known as the apoptosome forms and activates caspase proteins, including caspase 9. Several oxidative stress types, including hypoxia, DNA damage, and growth-factor deprivation, can induce the intrinsic pathway. Anti-apoptotic proteins like BCL-2 can hinder apoptosis by obstructing the oligomerization of BAX and BAK and inhibiting their accumulation at the outer mitochondrial membrane (Leibowitz & Yu, 2010).

The extrinsic pathway, also known as the death receptor pathway, is activated by the binding of tumor necrosis factor receptor (TNFR) family members (Locksley et al., 2001). TNFR is a large family of homotrimer proteins that share a cytoplasmic domain of about 80 amino acids called the "death domain". Death ligands such as FasL (Fas Associated Death Domain Protein Ligand) and TNF-α (Tumor Necrosis Factor alpha), bind to death receptors, such as CD95 (APO-1/Fas) or TNF-related apoptosis-inducing ligand (TRAIL) receptors. Receptors engage with their respective ligands, which leads to the gathering of adaptor proteins like Fas-associated protein with death domain (FADD) and Tumor necrosis factor receptor type 1-associated DEATH domain protein (TRADD). These proteins subsequently attract other downstream elements, prominently Caspase-8, that plays an essential role in driving the extrinsic pathway to cell apoptosis (Elmore, 2007; Fulda & Debatin, 2006). In certain cells like hepatocytes, the caspase cascade requires an interplay with the BCL-2-regulated apoptotic pathway, mediated by the BH3-only protein BID (Aubrey et al., 2018).

Finally, apoptosis induced by ER stress is due to unfolded proteins accumulation and aggregation within the ER (Fribley et al., 2009). In response to ER stress, the cell activates the UPR in order to restore ER function by decreasing input of nascent proteins and increasing output of folded proteins (Schröder & Kaufman, 2005). UPR begins with the dissociation of glucose-regulating proteins (GRPs) from the three ER transmembrane anchors: the protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), and transmembrane protein inositol-requiring enzyme type 1 (IRE-1) (Kopp et al., 2019; Ron & Walter, 2007; Szegezdi et al., 2006). Upon accumulation of unfolded proteins, GRPs, in particular GRP78 (also known as BiP), are detached from the membrane, activating these three UPR sensors. PERK limits protein synthesis by phosphorylating the eukaryotic translation initiation factor 2α (eIF2α), therefore reduces the number of new proteins requiring folding (Scheuner et al., 2001). ATF6 is translocated to the Golgi and cleaved, releasing a NH2 domain fragment which is transported to the nucleus and affects gene expression for UPR regulation (Bell et al., 2016; Read & Schröder, 2021). IRE1 dimerizes and autotransphosphorylates, ending up in UPR genes regulation by both kinase and endoribonuclease activity (RNase) (Hetz et al., 2011).. When UPR can no longer alleviate the stress and restore regular ER function, sustained ER stress triggers apoptosis through the transcriptional and posttranslational regulation of pro-apoptotic proteins of the BCL2 family

Table 1
A summary of different metal-based nanoparticles (NPs), surface functionalization and conjugates, the PDT regimen used (light source and cell line), their organelle targets, and the different cell death pathways they initiate after administrating PDT with a specific light source on cancer cell lines. (Lys: lysosomes; Mit: mitochondria; N/A: not available; NIR: near infrared; NP: nanoparticle; NT: nanotriangle; PS: photosensitizer; UV: ultraviolet).

The role of Metal-based NP	NP	PS	Surface Functionalization/Doping	Light Source	Cell line / animal model	Target Organelle	Cell Death	Ref
Metal-based NPs as PSs	CuS NP	–	Mn	NIR 808 nm	Human ovarian carcinoma A2780 cell line	N/A	**Necroptosis**	(Chen et al., 2019a)
		–	–	NIR 808 nm	Human lung cancer SPC-A-1 cell lineMurine cancer model	Mit	**Apoptosis and Necrosis**	(Li et al., 2017)
		–	Iron oxide multicore structure	NIR	Human prostate adenocarcinoma PC3 cell line	EndosomeLys	**Necrosis**	(Curcio et al., 2019)
	NiO NP	–	–	Red light 660 nm	Human cervical cancer HeLa cell line	Cell membrane	**Apoptosis**	(AlSalhi et al., 2020)
	TiO_2NP	–	Reduced graphene oxide (RGO)	Visible light	Human hepatocellular carcinoma HepG2 cell line	Mit,DNA damage	**Apoptosis**	(Shang et al., 2017)
		–	Nitrogen-doped	Visible light	Human melanoma A375 cell line	Lys	**Necroptosis (Blockade of autophagy flux)**	(Mohammadalipour et al., 2020)
		–	Coated with upconversion NP (UCNP)	NIR	Human cervical cancer HeLa cell line	Mit	**Apoptosis**	(Hou et al., 2015)
	ZnO NP	–	Porphyrin (MTAP)	UV 365 nm	Human ovarian adenocarcinoma OVCAR-3	Mit	**Apoptosis**	(Zhang et al., 2008)
	ZnO nanorod	–	Daunorubicin (anticancer drug)	UV	Human breast cancer MCF-7 cells	DNA damage Cell membrane	**Apoptosis**	(Zhang et al., 2011)
	Au/ZnO hybrid NP	–	Polyethylene glycolPiperlongumine (anticancer drug)	UV	Human breast cancer MCF-7 cells	N/A	**Apoptosis**	(Hong et al., 2019)
	AuNTs	–	Triphenylphosphonium (targeting mitochondria) 5-aminoleuvinic acid targeting breast cancer cells	Halogen lamp	Human breast cancer MCF-7 and MDA-MB-231 cells	Mit, DNA damage	**Apoptosis**	(Vinita et al., 2023)
,	Ag NP	Hypocrellin B (HB)	Poly lactide-co-glycolide	Mercury vapor lamp 590 nm	Human lung adenocarcinoma A549 cell line	Mit	**Apoptosis**	(Natesan et al., 2017)
	Au NP	Zn (II) phthalocyanine	Polyethylene glycol Anti-HER2 monoclonal antibody	Visible red light	Human breast carcinomaK-BR-3 and MDA-MB-231 cell lines	Mit	**Apoptosis**	(Stuchinskaya et al., 2011)
	Iron-based NP	Chlorin E6	Poly lactic-co-glycolic acid (PLGA)	660 nm	Murine breast cancer 4 T1 cell line	Cytoplasm	**Ferroptosis**	(Chen et al., 2021)
	Cu_2O	GOx@[Cu(tz)]	1,2,4-triazole (Htz)Glucose oxidase (GOx)	808 nm	Human breast cancer MCF-7 cells	Mit	**Cuproptosis**	(Xu et al., 2022)
Metal-based NPs as oxygen modulators	MnO2 NP	Chlorin E6	Hyaluronic acid-nitroimidazole (HA-NI)Poly (l-glutamic acid) derivatives (γ-PFGA)Gambogic acid (GA, paraptosis inducer)	638 nm	Murine breast cancer 4 T1 cell line	ER	**Paraptosis**	(Han et al., 2020)

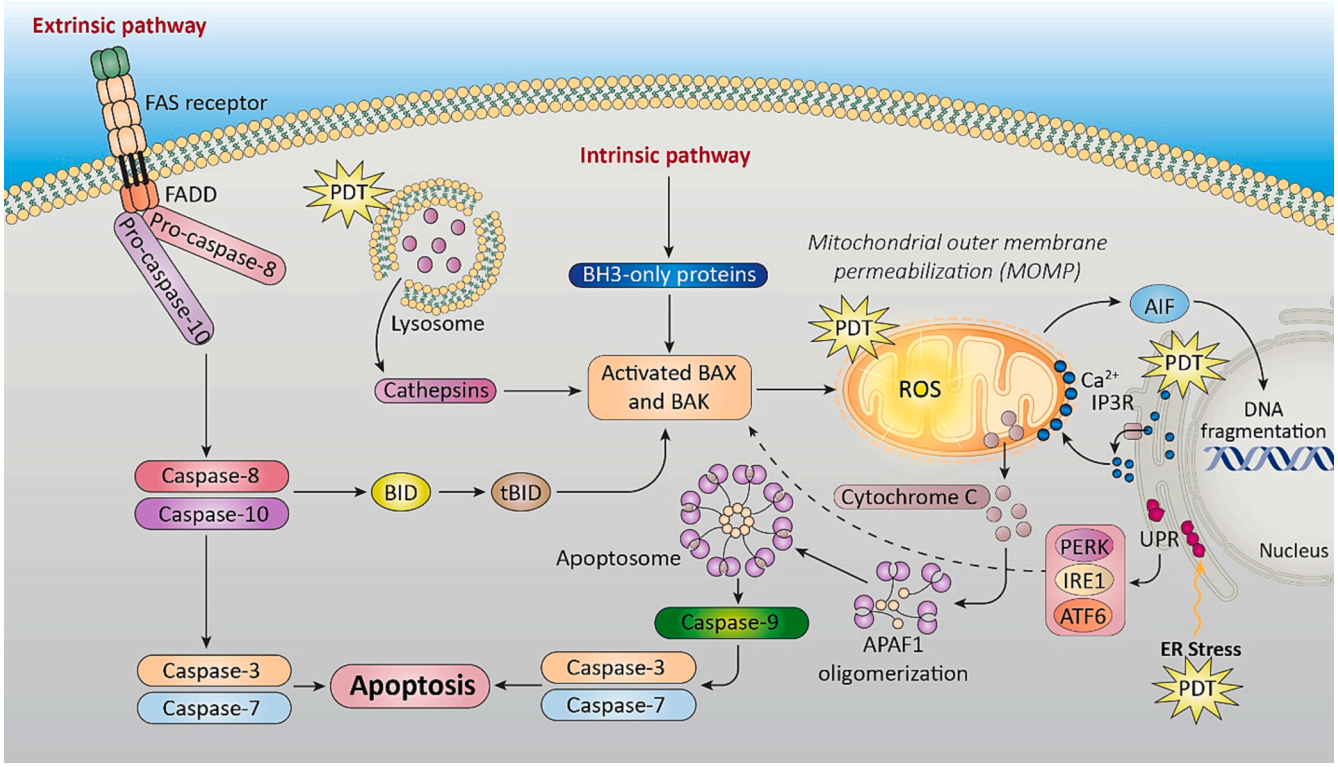

Fig. 3. Apoptotic pathways induced after PDT and the crosstalk between three major apoptotic pathways in mammalian cells. The intrinsic (mitochondrial) pathway may activate after PDT treatment, ROS damage and permeabilization of mitochondrial membrane. This impairment leads to release of mitochondrial cytochrome *C* into the cytosol, formation of the apoptosome, and activation of the caspase cascade. The extrinsic pathway of apoptosis involves binding of death ligands to the extracellular domain of death receptors, such as Fas Receptor/Fas ligand (FasR/FasL) that recruit adaptor protein FAS-associated death domain protein (FADD). The extrinsic and intrinsic pathways of apoptosis are connected through BID, a member of the BCL-2 family. The cleavage of BID to t-BID, facilitates the opening of mitochondrial pores and mitochondrial apoptotic pathway. The endoplasmic reticulum (ER) Ca2 + imbalance can greatly impact the folding capacity and induce ER stress-mediated apoptosis. Upon sustained ER stress, the unfolded protein response (UPR) triggers apoptosis in part through the regulation of proapoptotic BH3-only proteins. The ER stress induced by PDT activates BAX and BAK pro-apoptotic proteins, which permeabilizes of the ER membrane, releasing ER chaperones and Ca^{2+} into the cell cytosol. Release of Ca^{2+} from ER subsequently increases the mitochondrial Ca^{2+} levels, which leads to the induction of cytochrome *c* release. Lastly, lysosomal photodamage induces Cathepsin proteases release into the cytosol, cleavage of the Bid protein is into a pro-apoptotic fragment termed tBID. tBID interacts with mitochondria, inducing an apoptotic response. Created with Adobe Illustrator.

(Pihán et al., 2017). IRE1 and PERK are responsible for activation of several BH3-only proteins, phosphorylation and inhibition of BCL-2, and ATP depletion (Bassik et al., 2004; Puthalakath et al., 2007). The homo-oligomerization and activation of BAX and BAK proteins at the ER membrane, subsequently leads to the permeabilization of the ER membrane, facilitating the release of ER chaperones and Ca2 + into the cell cytosol (Szegezdi et al., 2009). Remarkably, these distinct apoptotic pathways share considerable crosstalk, such that the initiation of one pathway may trigger another (Brunelle & Letai, 2009).

ROS induced by NPs inflicts damage to DNA, proteins, and organelles, including mitochondria. Inherently, metallic nanoparticles can generate oxidative stress and initiate apoptosis, depending upon their size, concentration, and incubation duration. Nanoparticles such as TiO_2, CuO, ZnO, Gd_2O_3, AgNPs, and AuNPs can modulate mitochondrial or ER apoptotic pathways in several tumor cell lines (Mohammadinejad et al., 2019). Furthermore, they might inflict DNA damage and activate TP53, a critical tumor suppressor inhibiting cell cycle at the G1/S phase. This DNA damage, facilitated by TP53, initiates apoptosis (Amaral et al., 2009).

In PDT of cancer, different PSs can effectively alter the expression of BCL-2 family members, depending on the PS's localization within tumor cells. The majority of PSs is associated with mitochondria, lysosomes, and/or intracellular membranes, including the ER (Figs. 3, 5). PS accumulation in the mitochondrial membrane leads to the degradation of anti-apoptotic proteins such as BCL-2 and BCL-xL, thereby initiating apoptosis. Conversely, ER stress stimulates BAX-mediated caspase activation. In both cases, an increased ratio of pro- to anti-apoptotic proteins (BAX/BCL-2 ratio) is evident. Lysosomal photodamage represents a more indirect pathway where proteases are released into the cytosol, and the BID protein is cleaved into a pro-apoptotic fragment termed tBID. This tBID interacts with mitochondria, inducing an apoptotic response (Fig. 3) (Donohoe et al., 2019; Kessel & Oleinick, 2018; Kushibiki et al., 2013; Oleinick et al., 2002). To exemplify the impact of PS localization on determining cell death pathway, consider this case: Primary photo-damage sites for Zn (II) phthalocyanine have been identified as the Golgi apparatus, which instigates cell necrosis as the cell death mode. Stuchinskaya et al. utilized AuNPs to transport Zn (II) phthalocyanine PS into breast carcinoma cell lines (Stuchinskaya et al., 2011). The targeted AuNPs bound anti-HER2 monoclonal antibodies, facilitated the rapid PS delivery to the intracellular environment and the mitochondrial localization, culminating in cell via the apoptotic pathway.

Although apoptosis is deemed the definite molecular mechanism for PDT toxicity induction, its efficacy is limited by the intrinsic or acquired resistance of cancer cells to apoptosis. Consequently, novel therapeutic approaches are necessary to eliminate apoptosis-resistant cancer cells by manipulating other forms of RCD triggered by PDT (Zeng et al., 2022).

3.2. Autophagic cell death

Macroautophagy, commonly referred to as autophagy, is an evolutionarily conserved catabolic activity in all eukaryotic cells that

primarily functions as pro-survival mechanism by breaking down long-lived proteins and damaged organelles to supply cell needs during stressful condition (Glick et al., 2010; Klionsky & Emr, 2000). However, when prolonged or excessive autophagy is occurred, it may culminate in specific form of cell death that called autophagic cell death (Linder & Kögel, 2019). Evidence suggest that autophagy plays a critical role in diverse pathophysiological conditions and diseases, such as cancer, neurodegeneration, autoimmune diseases, aging, heart disease, and infections (Kundu & Thompson, 2008; Mizushima, 2005; Mizushima et al., 2008).

More than 40 autophagy-related genes/proteins (ATGs) facilitate the autophagic process (Klionsky et al., 2003; Ohsumi, 2014). During autophagy, sections of the cytoplasm are encapsulated into a double-membrane vesicle known as an autophagosome. The autophagosome subsequently merges with the lysosome, forming an autolysosome where the enclosed materials are degraded by lysosomal hydrolases (Kroemer & Jäättelä, 2005; Tang et al., 2019; Yang & Klionsky, 2009). This degradation process allows the elimination of damaged material (e.g., unfolded proteins, damaged organelles, microorganisms) and the repurposing of recycled nutrients for cellular processes (Galluzzi et al., 2018). Autophagy is orchestrated by a multitude of molecular signaling cascades. Notably, the mechanistic target of rapamycin kinase (mTOR) acts as a chief inhibitor of autophagy, while kinases such as 5' AMP-activated protein kinase and class III phosphatidylinositol-3-kinase (PI3K) promote the autophagic process (Long et al., 2022).

The initiation of autophagy begins with the formation of an autophagosome from a small, crescent-shaped structure called a phagophore. This process involves the phosphorylation of the ULK1 (ATG1) complex and FIP200. The formation of an autophagosome proceeds through the nucleation and elongation of the phagophore membrane, involving the activation of the PI3K complex composed of proteins such as ATG14, Beclin1, and UVRAG (also known as p63). Following the completion of phagophore, an autophagosome is formed. The expansion of the autophagosome membrane relies on the incorporation of ATG5-ATG12 complexes and ATG16 facilitated by ATG7 and ATG10. ATG4B, along with ATG7, conjugates LC3-I and lipid phosphatidylethanolamine to form LC3-II. LC3B-II binds to both the internal and external surfaces of autophagosomes, playing a key role in the fusions of membranes and the selection of cargo for lysosomal degradation. Notably, LC3 lipidation and the detection of LC3-II serve as common markers for the autophagy recognition. Ultimately, autophagosomes fuse with lysosomes, leading to the degradation of their contents, a

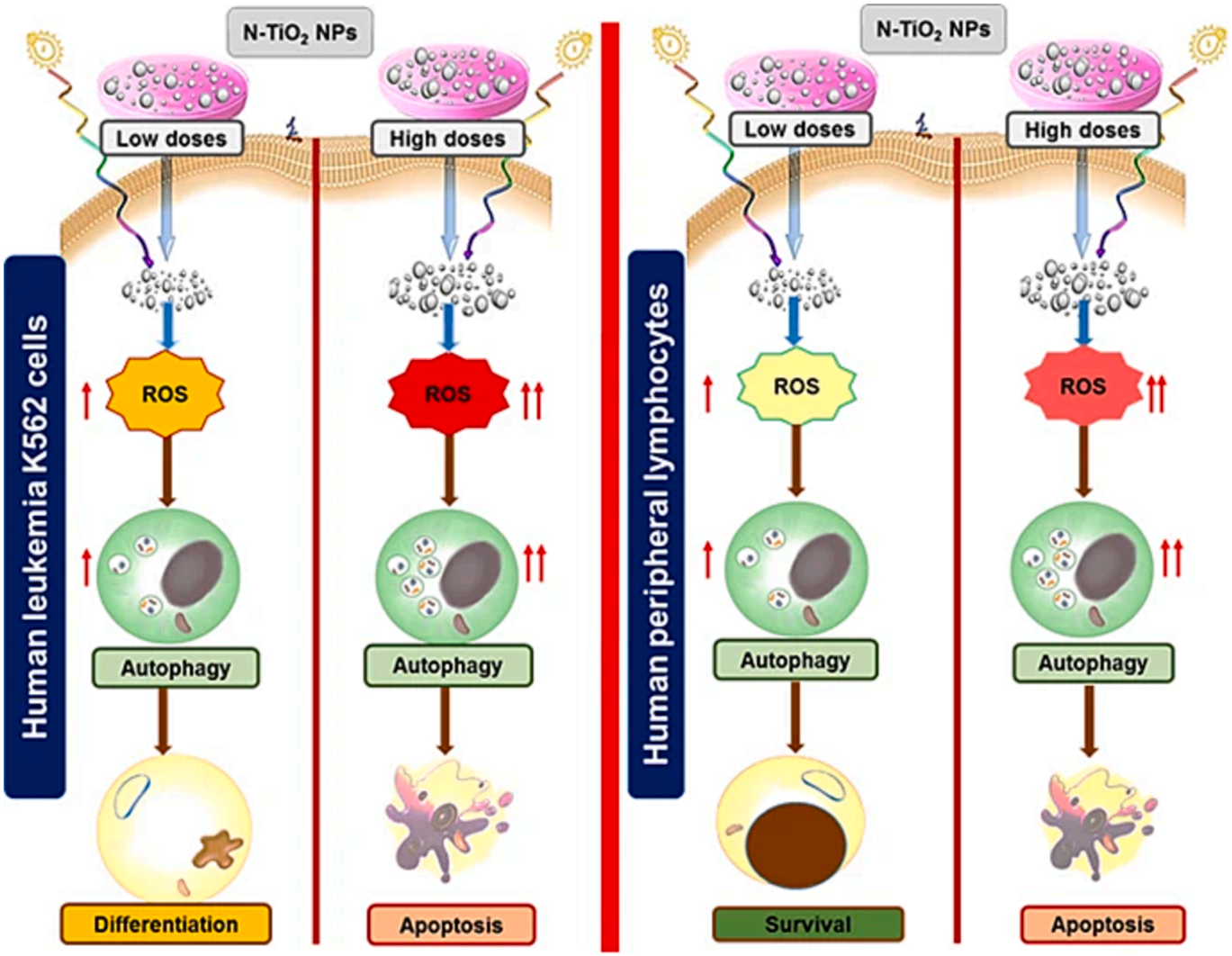

Fig. 4. Cellular outcomes induced by N-TiO2-based PDT in human peripheral lymphocytes (PBLs) and leukemia K562 cells. High doses of PDT (100 μg/ml N-TiO_2, 12 J/cm2) induced autophagy-associated apoptosis in PBLs and K562 cells, while low PDT doses did not lead to any cytotoxic effects in both cells. Indeed, low concentrations of 10 μg/ml N-TiO_2) induced a moderate level of ROS and autophagy levels, which resulted in enhancing viability in PBL cells and provoking differentiation in K562 cells. ROS: reactive oxygen species. (Reprinted from: Moosavi, M., Sharifi, M., Ghafary, S. et al. Photodynamic N-TiO2 Nanoparticle Treatment Induces Controlled ROS-mediated Autophagy and Terminal Differentiation of Leukemia Cells. Sci Rep 6, 34,413 (2016). https://doi.org/10.1038/srep34413).

process known as autophagosome maturation. Through autophagy, the contents are degraded, and the macromolecular precursors are recycled or repurposed to fuel metabolic pathways (He & Klionsky, 2009; Long et al., 2022; Wong et al., 2011).

In PDT, autophagy can either promote survival or induce death mechanism, depending on factors such as the type of PSs, the type of ROS, the presence of apoptotic machinery, and the extent of photo-damage (Chilakamarthi & Giribabu, 2017). The link between ROS and autophagy induction is the cysteine protease Atg4, which cleaves Atg8/LC3 from the autophagosome outer-membrane before, or soon after, autophagosome-lysosome fusion (He & Klionsky, 2009; Scherz-Shouval & Elazar, 2007). Depending on the stress level, autophagy may contribute to other cell death programs, including apoptosis or necroptosis (Denton & Kumar, 2019; Martins et al., 2021). We previously described that autophagy can initiate different cell fate responses upon photo-activation of N-TiO_2 NPs in peripheral blood lymphocytes (PBLs) and leukemia K562 cells, depending on NP concentrations (Fig. 4) (Moosavi et al., 2016). Low doses of photodynamic N-TiO_2 NPs induce moderate ROS challenge and autophagy, leading to the induction of pro-survival or differentiation responses in PBL and K562 cells, respectively (Fig. 4). However, high doses of PDT with N-TiO_2 NPs induced higher levels of ROS and autophagy, which resulted in the induction of autophagy-associated apoptosis in both cells.

Observations have indicated that low PDT doses escalate ROS and autophagy levels in both leukemia K562 and normal peripheral cells, while sparing human normal cells from cytotoxic effects. Conversely, high concentrations of N-TiO_2 NP induced autophagy-related apoptotic cell death. This unique NP-based PDT system confirmed that autophagy is a prerequisite for apoptosis induced by photo-activated N-TiO_2. The critical liaison between autophagy and apoptosis is BCL2, an anti-apoptotic protein, which impedes the function of BECN1 in autophagy. Persistent stress initiates the autophagy cascade via the activation of AMPK, leading, in the long-term, to BCL2 phosphorylation and subsequent inactivation and hence apoptosis induction (Chen et al., 2019b; Mohammadinejad et al., 2019).

Current PDT research suggest that autophagy primarily operates as a death mechanism in apoptosis-deficient cells (Chilakamarthi & Giribabu, 2017; Donohoe et al., 2019; Martins et al., 2021). Indicators of autophagic cell death, including LC3 lipidation and strong vacuolization, have been documented in cells pretreated with PI3K inhibitors and

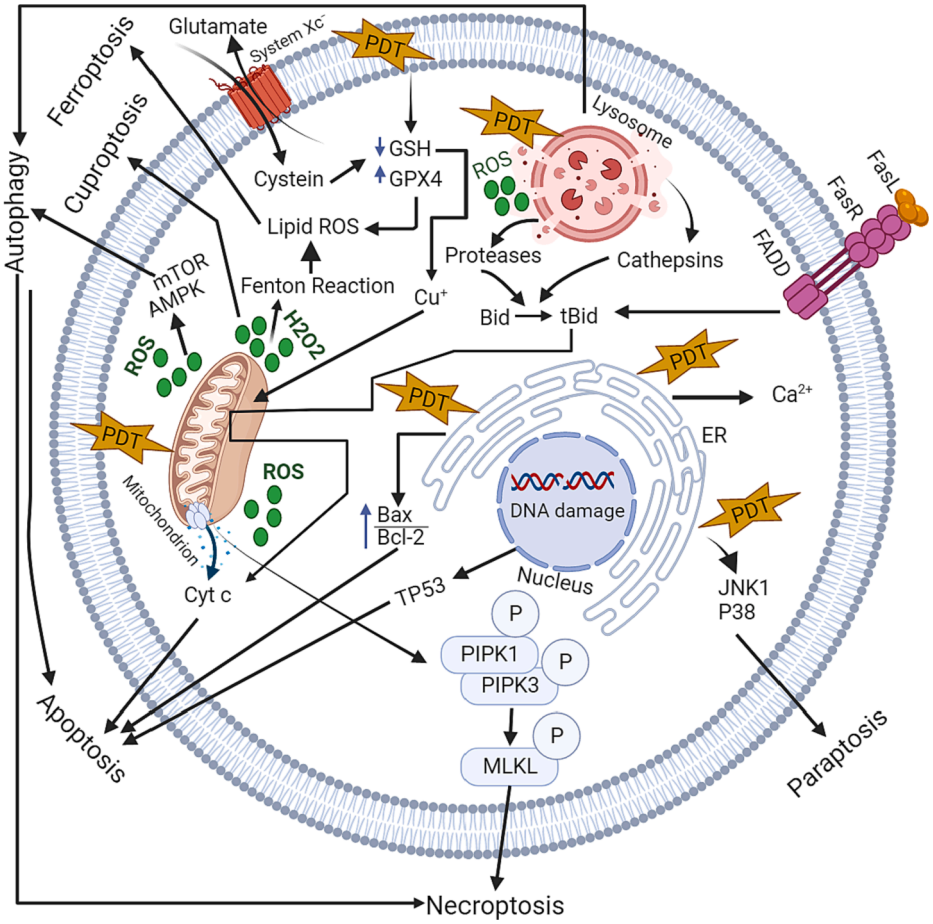

Fig. 5. RCD pathways triggered by PDT. ROS are produced after photochemical reaction and depending on the localization of PS, inflict damage to DNA, plasma membrane, and mitochondrial, lysosomal, or ER loci. Different organelles are associated with several RCD pathways including apoptosis, necroptosis, paraptosis, and Ferroptosis. Apoptosis can be induced by ROS damage to DNA and TP53, ER stress and increase in BAX/BCL-2 ratio, PS accumulation in the mitochondrial membrane and the degradation of Bcl-2, or lysosomal photodamage. Autophagic cell death can be caused by PSs present in the mitochondria, ER and lysosomes, via oxidative stress-dependent AMPK-mTOR pathway. Autophagy may contribute to other cell death programs, including apoptosis or necroptosis. Ligands that initiate the extrinsic apoptosis pathway, initiate necroptosis when CASP8 activation is blocked. Phosphorylation of protein kinases 1 (RIPK1) and 3 (RIPK3) and subsequent mixed lineage kinase domain-like (MKLK) protein leads to membrane permeabilization and necroptosis. Ferroptosis is a type of RCD associated with glutathione (GSH) depletion or inhibition of glutathione peroxidase 4 (GPX4), which ends up accumulating lipid-based ROS causing catastrophic membrane rupture. Heightened ROS levels, such as H2O2, is also favorable to Fenton reaction and ferroptotic cell death. ER photodamage and PSs primarily targeted at the ER may follow with MAPK-dependent pathway leading to paraptosis. PDT mediated cuproptosis is involved with accumulation of Cu^+, aggregation of mitochondrial enzymes, increase in H_2O_2 levels, and a Fenton-like reaction. (Cyt C: Cytochrome *C*, ER: Endoplasmic Reticulum, GPX4: Glutathione Peroxidase 4, GSH: Glutathione, PDT: Photodynamic Therapy, ROS: Reactive Oxygen Species) Created with BioRender.com.

when BAX is knocked out. Hence, autophagic cell death is achieved when apoptosis is blocked by caspase inhibitors or in cells devoid of BAX and BAK (Buytaert et al., 2006a,b; Chen et al., 2008; Kessel et al., 2006).

Impaired autophagy can foster carcinogenesis in cells by failing to remove oxidatively damaged organelles or proteins. Specifically, the mTOR complex bolsters anabolic biosynthesis for cancer cell growth and inhibits autophagy, whereas AMPK signaling triggers the degradation of macromolecules, encompassing lysosomal autophagic catabolism (Cordani & Somoza, 2019). Paradoxically, excessive stimulation of autophagy under sustained stress conditions ceases to be protective and instead triggers autophagic cell death, thereby killing tumor cells. This dual role of autophagy in tumors has prompted the development of two conflicting anticancer strategies: inhibition versus promotion. The choice of strategy should be tailored to the specific circumstances, especially tumor histotype and staging (Long et al., 2022; Mathew et al., 2009; White & DiPaola, 2009).

3.3. Necroptosis

Necrosis is a non-regulated form of cell death, typically perceived as a random, swift, and passive event that neither requires protein synthesis nor energy expenditure. Various inducers, including trauma, toxins, ischemia, infectious agents, and neurodegenerative disorders, can trigger necrotic cell death (Syntichaki & Tavernarakis, 2002). Morphological characteristics of necrosis include cell rounding, cytoplasmic enlargement (oncosis), dilatation of organelles, and no chromatin condensation (Festjens et al., 2006). In addition, elevated cytoplasmic Ca^{2+} and cellular membrane rupture are observed, resulting in the release of cellular content, and causing potent inflammation. In PDT, necrotic cell death typically occurs at high light doses or elevated PS concentration. Alternatively, if PSs accumulate within the plasma membrane due to a short incubation period with PS or PS's affinity for the cell membrane, necrosis can ensue through membrane integrity loss and ATP depletion (Donohoe et al., 2019).

However, there is a regulated form of necrosis, termed necroptosis, that involves the complex interplay of numerous signaling pathways and the engagement of cell surface death receptors, notably when caspases are inhibited (Mohammadinejad et al., 2019). This RCD manifests in various pathological events, including ischemic brain injury, myocardial infarction, excitotoxicity, and chemotherapy-induced cell death (Berghe et al., 2010). The observation of necroptosis first occurred in 1996 with pig kidney cells infected by the cowpox virus, in which CASP1 and CASP8 were inhibited (Ray & Pickup, 1996). Necroptosis is morphologically comparable to necrosis,and does not exhibit signs of apoptotic cell death. During necroptosis, cellular swelling, moderate chromatin condensation, and rapid plasma membrane permeabilization transpire, leading to cellular content leakage into the extracellular environment (Van der Meeren et al., 2020). Current understanding suggests that necroptosis can be triggered by multiple stimuli, including the activation of tumor necrosis factor receptor 1 (TNFR1), DR4/5 and FAS receptor, pattern-recognition receptors such as Toll-like receptor 3 (TLR3), TLR4, Z-DNA binding protein 1 (ZBP1) and adhesion receptors (Tang et al., 2019).

Intriguingly, certain ligands known to initiate the extrinsic apoptosis pathway, such as TRAIL and Fas ligand (also referred to as FasL or CD95L), can induce necroptosis when CASP8 activation is blocked by caspase inhibitors (such as Z-VAD-FMK) or by the depletion of FADD (Tang et al., 2019). Necroptosis is notably triggered when the TNFR1 receptor interacts with TNFα in the presence of caspase inhibitors. In this scenario, caspase molecules remain inactive, while FADD and receptor-interacting protein kinases 1 (RIPK1) and 3 (RIPK3) undergo phosphorylation and subsequent activation. The RIPK1-RIPK3 complex, termed as necrosome, phosphorylates the mixed lineage kinase domain-like (MKLK) protein. The subsequent oligomerization and translocation of MLKL to the plasma membrane mediates membrane permeabilization and ultimately, cell death (Berghe et al., 2014).

Research has suggested that necroptosis could serve as a cell death mechanism activated by PDT. The specific type of tumor and the PS concentration are critical variables that influence the likelihood of necroptosis activation by PDT. For instance, when a minimal concentration of talaporfin sodium (mono-L-aspartyl chlorine e6, NPe6) is applied, necroptosis is triggered in PDT of human glioblastoma T98G cells. However, a high PS concentration induces necrosis (Miki et al., 2015). This principle also holds true in PDT employing metallic PSs. Lower doses of N-TiO2 nanoparticles elicit a nontoxic autophagy flux response in human melanoma A375 cells. Still, the increase of ROS generation during photoactivation interrupts autophagy, resulting in a cell death switch to RIPK1-mediated necroptosis (Mohammadalipour et al., 2020).

One novel approach proposed integrates nano PSs and combination therapies, with PDT effectively inducing necroptosis of cancer cells. Chen et al. utilized CuS nanomaterials known for their efficacious PTT in cancer treatment, in conjunction with manganese (Mn), which is a great contrast agent for magnetic resonance imaging (MRI), to create CuS–MnS2 nano-flowers (Chen et al., 2019a). This combination reacted to NIR laser with multifunctional capabilities: MRI and photothermal/photodynamic cancer therapy. The researchers suggested that when A2780 ovarian cancer cells were subjected to MRI-guided PPT/PDT (808 nm NIR laser), effective photothermal conversion coupled with simultaneous ROS generation led to an anticancer mechanism likely mediated by necroptosis. Further supporting the potential of nanotechnology in the necroptotic response, iron-based magnetic nanoparticles functionalized with the cytotoxic drug gemcitabine -a cytotoxic drug known to induce necroptosis- have been utilized for efficient drug delivery and magnetic hyperthermia in treating pancreatic cancer (Lafuente-Gómez et al., 2021).

3.4. Ferroptosis

Ferroptosis, defined by iron-dependent oxidative phospholipid membrane modifications, is characterized by unique morphological, biochemical, and genetic traits (Dixon et al., 2012). Biochemically, ferroptosis is initiated by glutathione (GSH) depletion or inhibition of glutathione peroxidase 4 (GPX4), a lipid repair enzyme. Subsequently, the accumulation of lipid-based ROS, particularly lipid hydroperoxides leads to cell death. A known ferroptosis-inducing compound, erastin, was shown to trigger cell death in the absence of classical apoptotic and necroptotic markers, such as caspases, BAX, BAK, and RIPK1 (Yang & Stockwell, 2016). In the ferroptosis process, an increase in the cellular labile iron pool (LIP) prompts a sustained production of O_2 through the Fenton reaction between H_2O_2 and Fe^{2+}, eventually causing catastrophic membrane rupture (Ashraf & So, 2020).

Ferroptosis displays distinct morphological features, including condensed mitochondria, heightened membrane density, diminished or vanished mitochondrial cristae, and breaches in the outer mitochondrial membrane. However, no alterations in nucleus size, chromatin condensation, or margination are noted (Dixon et al., 2012).

The ferroptosis process is controlled by an intricate interplay between lipid, iron, and cysteine metabolism, with a host of genes involved in iron homeostasis and lipid peroxidation metabolism, including GPX4, TFR1, SLC7A11, NRF2, NCOA4, P53, HSPB1, ACSL4, FSP1 (Stockwell et al., 2020). GSH synthesis relies on cellular cysteine availability, which is imported into cells as oxidized form in exchange for glutamate via the cystine/glutamate antiporter (system X_c^-). Disrupting the system X_c^- or depletion of GPX4 levels escalates the production of toxic lipid peroxides and triggers cell death. Thus, lipid peroxide levels are considered indicators of ferroptosis (Zou et al., 2019). Fe2+, accumulation of lipid peroxides, and impaired lipid peroxidation by the inhibition of GPX4, are the major signs of ferroptotic cell death (Dixon & Stockwell, 2019).

In cancer therapy, the release of DAMPs from ferroptotic cancer cells may serve as immune stimulants, which makes ferroptosis an alternative cell death pathway for tumors resistant to apoptosis or necroptosis

(Efimova et al., 2020). The tumor microenvironment, characterized by acidity and heightened ROS levels, such as H2O2, is favorable to Fe2 + -mediated Fenton reactions, thereby facilitating ferroptosis. Consequently, recent advancements in cancer treatment involve the design of Fe-containing nanomaterials (Li et al., 2021).

Studies have demonstrated the role of ferroptosis induction by PDT in tumor cells (Dos Santos et al., 2020a,b; Shishido et al., 2021). PDT-treated cells require the production of large amounts of lipid ROS for ferroptosis induction. Moreover, ferroptosis generates substantial oxygen through the Fenton reaction, reducing hypoxia in the TME and augmenting the PDT effect (Chen et al., 2021). The induction of ferroptosis in cancer cells during PDT is closely tied to the design of PSs. Third-generation PSs such as nano complexes/nanocontainers that incorporates PSs with pharmacological agents, are conjugated with liposomes, sugar molecules, monoclonal antibodies, and peptides and are intrinsically linked to the ferroptosis induction by PDT (Mishchenko et al., 2021). Nanoparticles have the potential to carry PS solely, or in combination with drugs that induce ferroptosis (Li et al., 2021).

Extensive research has been conducted using iron-incorporated nanomaterials in PDT to trigger ferroptosis in cancer cells (H. Wang et al., 2023). For instance, Li et al. developed a polymeric nano complex (PAF) to enhance ferroptosis in cancer PDT within B16 melanoma cells (Li et al., 2021). This NP is derived from a natural polysaccharide, polygalacturonic acid (PGA), and is functionalized with methoxy polyethylene glycol (mPEG). It acts as a vehicle for 5,10,15,20-tetrakis (4-aminophenyl) porphyrin (TAPP) and Fe^{3+} ions. This in vitro study concluded that the singlet oxygen ($^1O_2$) produced during PDT effectively depletes intracellular GSH, thus augmenting the iron-mediated ferroptosis effect.

In a separate study, Chen et al. designed a nanosystem for 4 T1 murine breast cancer cells by loading Ce6 and iron-based NPs (Fe_3O_4 NPs) into FDA-approved poly lactic-*co*-glycolic acid (PLGA), thereby facilitating a combined PDT-ferroptosis strategy (Chen et al., 2021). The Fe3O4-PLGA-Ce6 nanosystem, when exposed to the acidic TME, disintegrates, releasing ferrous/ferric ions and Ce6. The liberated ferrous/ferric ions react with intracellular hydrogen peroxide surplus to generate hydroxyl radicals (OH) and prompt tumor cell ferroptosis. Concurrently, the freed Ce6 amplifies ROS production under laser irradiation, prompting PDT, which further fuels ferroptosis in 4 T1 cells. The exclusive magnetic proprieties of monodisperse Fe_3O_4 in this system enhance MRI capabilities, providing a powerful tool for tracking tumor growth and evaluating the success of antitumor treatment.

PDT combined with other anticancer therapies is a promising strategy for ferroptosis-based synergistic therapy (H. Wang et al., 2023). As reported by Cheng et al., a PTT/PDT/ferroptosis trimodal cancer treatment was carried out using metal nanoclusters, co-loaded with Fe3+, both in vivo and in vitro (Cheng et al., 2021). In this study the oil-soluble Au1Ag24 nanocages as the PS, were modified with ferric ions to constitute the core, and were assembled in vesicles of PEG block grafted polyketal (PK) copolymer (PbP) to passively target tumor cells. The designed core–shell nanoplatform (Fe^{3+}@Au1Ag24@PbP) had both photodynamic and photothermal imaging abilities under NIR laser irradiation and possessed TME/pH stimulated drug release capability. Furthermore, the loaded Fe^{3+} ions performed as multi-TME responsive agents that improved the ferroptosis effect and removed tumor hypoxia by consuming GSH molecules, and catalyzing the production of O_2. Recent studies suggest the potential for concurrent induction of different cell death modalities (such as ferroptosis paired with apoptosis and/or necroptosis) which could pave the way for innovative cancer immunotherapies targeting resistant and highly malignant tumors (Mishchenko et al., 2022).

3.5. Paraptosis

First described by Sperandio et al. in 2000, paraptosis is a distinct form of programmed cell death, characterized by cytoplasmic vacuolation, and mitochondrial and/or ER swelling. Contrasting with apoptosis, paraptosis does not involve caspases activation, chromatin condensation, or cell fragmentation (Fontana et al., 2020). Unlike autophagy, in paraptosis the formed vacuoles are enclosed by a single membrane, as opposed to a double membrane (Kessel, 2019b).

Paraptosis appears to function as a cell death pathway in cells possessing an impaired apoptotic program, and intriguingly, remains unaltered by autophagy. It is linked with changes in calcium (Ca^{2+}) and redox homeostasis and is often reliant on members of the mitogen-activated protein kinase (MAPK) family, including c-Jun N-terminal protein kinase 1 (JNK1), p38, and mitogen-activated protein kinase 2 (MEK-2) (Fontana et al., 2020).

In research concerning PDT, studies have elucidated both MAPK-dependent and MAPK-independent pathways leading to paraptosis following photodamage of the ER (Kessel et al., 2020). Given that misfolded proteins appear in the ER during paraptosis, it is plausible that PSs utilized in PDT should be primarily targeted at the ER to induce paraptosis, as seen with hypericin and verteporfin (Mishchenko et al., 2022). Research advancements also suggest that lowering the elevated levels of GSH found in tumor cells can aid in fostering paraptosis, thus promoting its potential application as an anti-cancer therapy (Seo et al., 2019).

A noteworthy study by Han et al. (2020) proposed a core–shell nanoplatform encompassing MnO2 NPs, and observed the subsequent activation of paraptosis after light irradiation at 638 nm (Han et al., 2020). MnO_2 served as an oxygen generator to counteract tumor hypoxia, enabling the combination of PDT and chemotherapy. The team used hypoxia-responsive hyaluronic acid-nitroimidazole (HA-NI) and poly (l-glutamic acid) derivatives (γ-PFGA) as cores to deliver both gambogic acid (GA, paraptosis inducer), and the PS Ce6. The resulting compound, GC@MCS NPs, was employed for in vitro and in vivo Chemo-PDT against tumor 4 T1 cells. Enhanced PDT was achieved through the deep penetration of PS, facilitated by the GA-loaded γ-PFGA. The PDT-generated ROS reinforced the GA-induced paraptosis by reducing the high level of GSH. This investigation suggested the activation of paraptosis is characterized by the gradual aggregation and fusion around vacuoles of ER and mitochondrial origin. Importantly, it also highlighted that the alterations in GSH-redox system during PDT can potentially activate alternative cell death pathways, such as ferroptosis (Friedmann Angeli et al., 2019).

3.6. Cuproptosis

Recent advances in research have led to the discovery of a novel form of RCD that relies on copper – cuproptosis – which may potentially revolutionize our understanding of the cell death/survival mechanisms and become the target of advanced therapy methods combat a wide range of diseases (Xie et al., 2023; Xu et al., 2022). Copper ions play a vital role in maintaining a balance between oxidation and antioxidation processes in cells in order to prevent oxidative stress, cellular damage, and cardiovascular diseases. However, an excess of copper can result in DNA and lipid damage, oxidative stress, and cardiotoxicity, all of which can contribute to cardiovascular disease (Yang et al., 2023). With its potential to shed new light on the correlation between related genes and cancer prognosis, cuproptosis has emerged as a promising avenue for cancer treatment (J. Wang et al., 2023).

Cuproptosis is a Cu-dependent mitochondria-associated cell death characterized by an accumulation of lipid peroxides (Cobine & Brady, 2022). Copper ionophores may transport copper ions through the plasma membrane or mitochondrial membrane, reducing cupric ions (Cu2 +) to cuprous ions (Cu +). Cancer cells with active TCA-cycle have increased levels of lipoylated mitochondrial TCA enzymes such as dihydrolipoamide S-acetyltransferase (DLAT). The excess intracellular copper binds to lipoyl moiety and induces the aggregation of DLAT (Tsvetkov et al., 2022). However, FDX1/LIAS is an upstream regulator of protein lipoylation, which facilitates the aggregation of mitochondrial

proteins and results in the loss of Fe-S clusters. These aberrant processes lead to proteotoxic stress, ultimately causing cell death (Xu et al., 2022).

Xu et al. (2022) have unequivocally harnessed cuproptosis in a nanomaterial mediated PDT synergistic therapy for bladder cancer (Xu et al., 2022). They successfully developed a GOx@[Cu(tz)] nanoplatform, composed of nonporous coordination polymers as scaffold, glucose oxidase (Gox) as H_2O_2 producer, and Cu(I). In this cancer starvation therapy, the catalytic function of Gox was exploited in order to cut off glucose supply of cancer cells. After the endocytosis of the nanocomposite, Gox is activated by over-expressed GSH in cancer cells. After the glucose and GSH depletion, Cu(I) from disassembled GOx@[Cu(tz)] strongly binds to lipoylated mitochondrial enzymes and result in aggregation of lipoylated DLAT, and subsequently GOx@[Cu(tz)]-mediated cuproptosis. Activation of the hypoxia tolerant PDT efficacy of GOx@[Cu(tz)] is due to the increase in H_2O_2 levels resulting from glucose oxidation, thereby producing a significant amount of toxic hydroxyl radicals (•OH) through the Fenton-like redox reaction of Cu(I)/Cu(II).

In Fig. 5 we resume RCD pathways triggered by PDT.

4. Metallic nanoparticles modulating ICD in PDT

ICD refers to a particular form of tumor cell death that is associated with discharge of danger signals/DAMPs, type I interferon (IFN) response, and the production of pathogen response-like chemokines that together raise the immunogenic potential of dying cancer cells (Garg & Agostinis, 2017). ICD is accompanied by the release of TAAs and DAMPs, and can involve several cell death modalities including apoptosis, necroptosis, autophagy, and ferroptosis (Hua et al., 2021; Lorenzo et al., 2020; Razan et al., 2021). The emitted DAMPs promote the recruitment and maturation of APCs such as dendritic cells (DCs). DCs serve as a bridge between innate and adaptive immunity. They capture TAAs and recognize DAMPs via PRRs. As these DCs journey to the lymph nodes and undergo maturation, they process and present these antigens to T cells. This prompts T cell proliferation and their subsequent differentiation into CD8 + CTLs. Such cells play a pivotal role in counteracting tumors, ensuring lasting immune memory, and reducing metastasis probabilities (Fig. 2) (Falk-Mahapatra & Gollnick, 2020; Wculek et al., 2020).

A specific set of DAMPs are known to be hallmarks of ICD, which include: ER chaperones such as calreticulin (CALR, also called CRT) and heat shock proteins (HSPs), adenosine triphosphate (ATP), high mobility group box 1 protein (HMGB1), type I IFN and annexin A1 (ANXA1) (Kroemer et al., 2013; Krysko et al., 2012). Translocation of DAMPs such as CALR, HSP70 and HSP90 to the cell surface, constitutes “eat me” signal, which is recognized by APC receptors that in turn, mediate the engulfment of the dying cells and the cross-presentation of tumor antigens to T cells. HSPs can also be recognized by Natural killer (NK) cells, affecting direct killing of cancer cells. Other DAMPs released into extracellular fluid, such as ATP, are known to be “find me” signals that attract APCs and activate T cells, leading to stimulation of adaptive immunity. HMGβ1 proteins released from dying cells act as proinflammatory cytokines to interact with DC receptors and to stimulate tumor antigen presentation. Lastly, the released ANXA1 contributes significantly in migration of DC towards dead/dying cancer cells (Donohoe et al., 2019). Induction of ICD by anti-cancer therapy is restricted to certain agents or procedures, since this necessitates the prompting of ROS-based ER stress (Garg & Agostinis, 2017).

PDT, as well as other anticancer treatment modalities, can trigger ICD (Deng et al., 2020; Korbelik et al., 2011). An ideal PDT protocol should directly eliminate the primary tumor while activating the ICD pathway to prevent the occurrence of remote metastases. PDT can activate both innate and adaptive immune responses that contribute to tumor eradication and long-term immunological memory. PDT-generated oxidative stress can upregulate the production of numerous pro-inflammatory cytokines, notably TNF-α, IL-1, and IL-6 in order to restore homeostasis. This also prompts the mobilization of innate immune responders like neutrophils, type-1 Polarized Macrophages, NK cells, and DCs which function to clear away the dying tumor cells. Furthermore, the fostering of adaptive immunity, characterized by an antigen-specific immune response post-PDT, is facilitated by the activity of CD4 + T cells. Induction of ICD by photodynamic agents is feasible through the production of ROS and ER stress, and subsequently the release of DAMPs. Characteristically, PSs with ER as their primary target organelle, can result in higher levels of DAMPs release and therefore, development of stronger ICD immunity (Falk-Mahapatra & Gollnick, 2020; Jung et al., 2021; Razan et al., 2021).

In photodynamic strategy for cancer therapy, there are several clinically approved PSs such as photosens and photoditazine that could effectively activate ICD (Turubanova et al., 2019). Metal-based PSs, as well as organic PSs, can induce immunogenic effects on cells. Ruthenium, iridium, and platinum complexes as PSs can significantly increase in the secretion or migration of ICD hallmarks in photoactivated cells (Lifshits et al., 2020; Monro et al., 2019; Novohradsky et al., 2020; Vigueras et al., 2021).

Nano-sized metallic material as PSs or PS carriers can be modified in various ways, in order to develop effective strategies for cancer immunotherapy. In an in vivo cancer starving therapy, where the nutrients supply is blocked to suppress tumor growth, M. Zhang etl al. synthesized multifunctional nanocages using Mn,Cu-doped carbon dots as PSs and induced cancer immunotherapy with high efficiency (Zhang et al., 2020). Knowing that carbon-based PSs induce immunological response against tumor cells, they combined this PDT/PTT study with checkpoint blockade strategy by adding PD-L1 antibody to the treatment, and successfully restore the function of cytotoxic T cells, The biodegradable NM fabricated was also coated with polymer-Poly(γ-glutamic acid) (γ-PGA) to enhance tumor cell endocytosis, and a glucose-metabolic reaction agent-lucose oxidase (GOx) to enhance cancer starving therapy. After administration of laser irradiation at 730 nm, the specific formulation of NPs displayed both photothermal and photodynamic effects along with immunological response.

As mentioned earlier, X. Duan et al. also conjugated PD-L1 antibody to a metal-based NP, ZnP, and loaded it with the photosensitizing pyrolipid, to provoke the cytotoxic tumor-specific cytotoxic T cell response, and significantly prevented metastasis to the lung (Duan et al., 2016). Their findings indicated that photodynamic treatment can enhance the checkpoint blockade immunotherapies, where not only the primary 4 T1 breast tumor cells are irradicated through induced necrosis and/or apoptosis, but also distant metastatic cells are killed indirectly by a systemic antitumor immune response.

Another example of using metallic NM as delivery vehicles for PSs in immunogenic cell death induced by PDT of cancer, is given in the study carried out by J. You and his colleagues. They used hollow gold nanospheres (HAuNS) in an ER-targeting strategy, which promotes ICD-associated immunotherapy by induction of ER stress and translocation of CRTs after NIR irradiation (Li et al., 2019). This PTT/PDT/immunotherapy nanosystem relied on ER associated ROS generation mediated through ER-targeting FAL peptides to accumulate the photosensitizer, indocyanine green, into ER.

The use of a specific PS (the third-generation PSs in particular), combined with a specific PDT regimen, will lead to the induction of alternative regulated forms of cell death with hallmarks of ICD. The cell death programs that can result in exposure or release of DAMPs, have immunogenic properties and therefore, elicit anti-tumor immunity. Apoptosis is the most widely studied form of ICD in the context of PDT (Falk-Mahapatra & Gollnick, 2020; Mishchenko et al., 2022). Immunogenic apoptosis and the release of DAMPs including CRT, HSPs, HMGB1 and ATP have been reported in PDT treatment of different cell lines when hypericin and Photofrin® are used as PSs (Garg et al., 2012; Jalili et al., 2004; Korbelik et al., 2011). Necroptosis is another ICD modality that activates T-cell antitumor immune responses by emission of DAMPs (Aaes et al., 2016). Also paraptosis is accompanied by the

appearance of the ICD hallmarks such as overexpression of HSPs, release of HMGB1, and enhancement of the tumor immunogenicity when treated with high doses of PDT (David Kessel, 2019).

The anti-tumor efficacy and immunogenic consequences of all cell death modalities on cancer cell lines are yet to be studied.

The induction of ICD by PDT has some limitations, including the reduced efficiency in the hypoxic tumor microenvironment due to limited generation of ROS, Therefore, strategies increasing the oxygen content of tumor tissues is essential to improve the efficiency of PDT treatment (Razan et al., 2021). In an attempt to resolve tumor hypoxia, Liang and colleagues developed a tumor microenvironment responsive core–shell nano structure using hollow gold nanocage (AuNC) with a layer of MnO_2 for immunogenic PDT under NIR irradiation (Liang et al., 2018). MnO2 generates a large amount of oxygen in the acidic microenvironment of tumor tissue rich in H_2O_2 and improves tumor hypoxia to achieve ICD and release of DAMPs from dying apoptotic cells.

In conclusion, the induction of ICD by enhanced PDT to promote antitumor immune response is a promising tumor treatment strategy that can be modulated by nanotechnology to enhance the efficiency of PDT.

5. Conclusions

PDT is known to be distinctively more selective and less invasive compared to other therapeutic strategies in eradication of pathological tissues in cancer. Research is continuously unveiling innovative methods to enhance PDT's effectiveness in clinical practice, specifically by merging with nanotechnology to introduce a measure of controlled release and specific uptake by tumor cells (Yan et al., 2020; Zhang et al., 2022b). The appeal of metallic and metal-oxide NPs extends to their widespread use in biomedical applications. Various nanoscale metallic materials have proven effective as PSs or PS delivery agents in PDT cancer studies (Shang et al., 2021).

Complementing the advancements in PDT, the development and optimization of innovative nanoparticles have been pursued for combination cancer therapies. Notably, maghemite-copper sulfide (γ-Fe2O3@CuS) nanohybrids have emerged as a multifunctional platform, capable of integrating magnetic hyperthermia (MHT), PTT, and PDT, thereby offering a promising tri-therapeutic approach to cancer treatment (Curcio et al., 2019). Moreover, copper sulfide nanocomposites have been explored for their potential in both photothermal and photodynamic therapies (Luo et al., 2022). These materials, individually or as components of hybrid nanoparticles, provide opportunities for synergistic therapies targeting hypoxic tumors (Zhang et al., 2019). The development of inorganic nanomaterials like γ-Fe2O3@CuS, tailored for combination therapies, is at the forefront of innovative cancer treatment strategies, presenting enhanced therapeutic potentials through the convergence of MHT, PTT, and PDT (Khafaji et al., 2019). Among nanotechnology-based approaches, the 'NoCanTher' project is noteworthy, which focuses on nanoparticle-enhanced magnetic hyperthermia for the targeted treatment of pancreatic cancer in murine model. (Kolosnjaj-Tabi et al., 2017). Importantly, the project represents a crucial development in MHT-based approaches, using multifunctional nanocomposites, which combine therapeutic agents with iron oxide nanoparticles to enable targeted treatment and real-time imaging for improved efficacy and monitoring (Cotin et al., 2021; Tansi et al., 2021a). The ongoing exploration of these multi-modal treatment strategies, which integrate PDT, MHT, and other therapeutic methods, heralds significant advancements in cancer treatment protocols and clinical research.

Regulated cell death (RCD) pathways intertwine with signaling cascades and molecular-mediated effector mechanisms and serve as critical components of cell fate (Cui et al., 2021). Apoptosis, necrosis, and autophagy represent the traditional RCDs, but other cell death pathways, including mitotic catastrophe, paraptosis, pyroptosis, parthanatos, necroptosis, ferroptosis, and cuproptosis can also be induced by PDT (Mishchenko et al., 2022). Increasing evidence suggests that cancer cells exposed to PDT may undergo multiple cell death pathways, leading to variable PDT outcomes. Remarkably, even identical PSs can evoke disparate cell death responses when paired with different irradiation protocols or cell lines.

6. Future perspective

Despite the promising utilization of metal NPs inherent cytotoxicity in combination with PDT in anti-cancer strategies, selective deficiencies and unpredictable cellular outcomes remains a challenge (Moosavi et al., 2016). Future studies in PDT should aim to tailor light doses according to the individual tumor characteristics, an approach that might curb the cancer cell resistance to certain death types, primarily apoptosis, and necroptosis. Additionally, comprehensive research is needed to decipher the intercellular tropism of metallic PSs and its influence on cell death mechanisms, particularly those that deviate from the traditional norms.

CRediT authorship contribution statement

Parya Pashootan: Investigation, Writing – original draft, Writing – review & editing. **Fatemeh Saadati:** Investigation, Writing – review & editing. **Hossein Fahimi:** Investigation, Writing – review & editing. **Marveh Rahmati:** Investigation, Writing – review & editing. **Raffaele Strippoli:** Investigation, Writing – review & editing. **Ali Zarrabi:** Investigation, Writing – review & editing. **Marco Cordani:** Conceptualization, Investigation, Writing – review & editing, Supervision. **Mohammad Amin Moosavi:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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