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EDITORIAL

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Immunogenic cell death and its emerging inducers: the next generation immunotherapy

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ABSTRACT

Understanding immunogenic cell death (ICD) and its ability to trigger potent antitumor immune responses has revolutionized cancer treatment. Innovative approaches like oncolytic virotherapy, photodynamic therapy (PDT), and nanotechnology have remarkable potential in promoting ICD and enhancing the immune response against cancer. Combining these therapies with immunotherapies improves effectiveness and reduces side effects. ICD can be induced by various agents such as chemotherapeutic drugs, oncolytic viruses, and PDT, activating endoplasmic reticulum stress and generating reactive oxygen species. Nanotechnology plays a crucial role in drug delivery and enhancing ICD induction. These advancements offer a transformative era in cancer treatment, leveraging the immune system's power and promising improved patient outcomes in the fight against cancer.

KEYWORDS

Immunogenic cell death; Immunogenic cell death inducers; Danger-associated molecular patterns; Immunotherapy

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"Harnessing the process of cell death as a means to safeguard our survival is both paradoxical and captivating."

Cell death, an important biological process, may occur due to accidental injuries caused by physical, chemical, or mechanical factors or may be a physiological process that eliminates redundant, irreversibly damaged, and potentially harmful cells. Physiological cell death can occur in two forms: non-programmed, known as necrosis, and programmed, referred to as regulated cell death. The latter has been further classified into various types (Figure 1) based on distinct morphological changes, underlying mechanisms, or involvement of specific biomolecules.

Galluzzi et al. introduced a groundbreaking concept in cell death research called immunogenic cell death (ICD) [1]. This phenomenon can be triggered by various stimuli, including invading pathogens, physical cues like irradiation or high hydrostatic pressure (HHP), necroptosis, and chemotherapeutic drugs [1]. ICD is characterized by the increased expression and release of endogenous danger-associated molecular patterns (DAMPs) during cell death. These DAMPs, such as calreticulin (CRT), adenosine triphosphate (ATP), high mobility group protein B1 (HMGB1), heat shock proteins, and others, play a pivotal role by acting as "eat me" and "find me" signals. These signals attract immature dendritic cells (DCs) and facilitate their maturation. As DCs mature, they process and present the released molecules to naive T cells, leading to the differentiation of cytotoxic cells and initiating a potent antitumor immune response (Figure 1).

The intricate mechanisms involved in ICD have become the focus of intense scientific investigation. By understanding and harnessing ICD, scientists aim to develop innovative therapies that selectively target and eliminate cancer cells, bolster the immune response, and combat various diseases. This paradoxical concept of utilizing death to preserve life showcases the complexity of our biological systems. It represents an exciting frontier in medical research, offering the possibility of novel treatments and improved human health.

ICD immunotherapy has emerged as a captivating strategy in cancer research, garnering attention from researchers worldwide. While traditional inducers such as chemotherapy, radiotherapy, and photodynamic therapy (PDT) have shown a limited ability to induce ICD, recent advancements have introduced novel therapies that elicit a more robust antitumor immune response while minimizing complications and side effects (Figure 1).

The induction of ICD by various agents relies on a fundamental mechanism involving the initiation of endoplasmic reticulum (ER) stress, which is associated with reactive oxygen species (ROS). ER stress occurs when misfolded or unfolded proteins accumulate in the ER lumen, disrupting ER homeostasis and triggering the unfolded protein response (UPR). The UPR is a signaling pathway that monitors and regulates the protein folding capacity of the ER. In response, the UPR can restore ER homeostasis or promote cell death.

Garg et al. proposed a classification of ICD inducers into two types based on whether they indirectly or directly induce ER stress [2]. Type I inducers include chemotherapeutic drugs such as anthracyclines, PP1 phosphatase inhibitors, bleomycin, cyclophosphamide, paclitaxel, Bortezomib, cardiac glycosides, as well as radiotherapy, and PDT. On the

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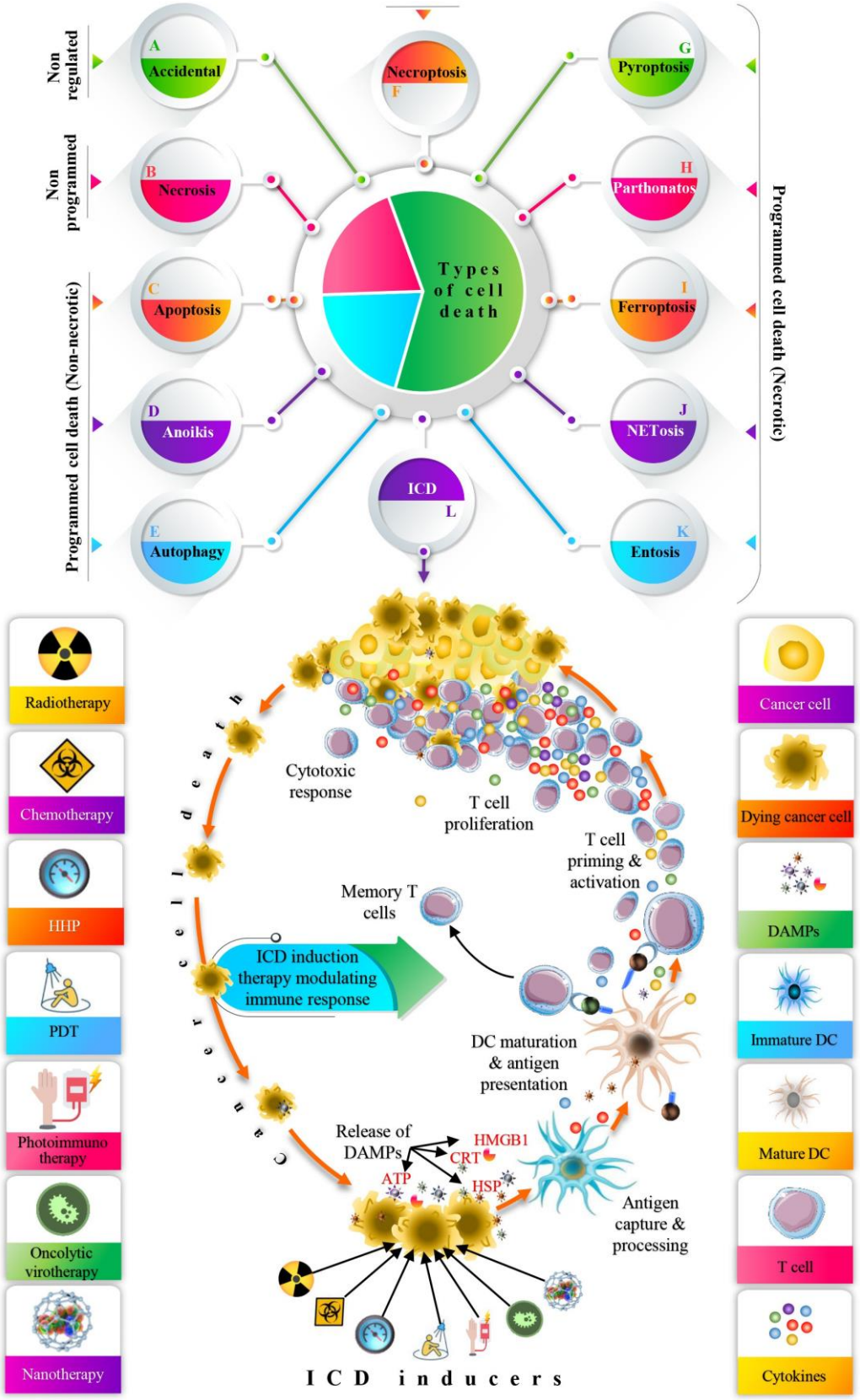

Figure 1. Types of cell death processes and the induction mechanism of ICD by various immunotherapeutic modalities resulting in the generation of the antitumor immune response.

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other hand, type II inducers primarily consist of oncolytic viruses like adenovirus, Newcastle disease virus, coxsackievirus, etc. These classifications provide valuable insights into the diverse range of agents that can induce ICD, shedding light on their mechanisms of action and potential applications in cancer treatment [3].

PDT is a highly effective two-step process that utilizes photosensitizing drugs, which activate when exposed to light and produce ROS. This targeted therapy has gained significant popularity due to its ability to selectively attack tumor cells while causing minimal damage to healthy cells. Recent advancements in PDT have led to the discovery of fourth-generation peptide or nanoparticle-based photosensitizers, which offer improved selectivity, efficacy, and precise targeting of tumor cells.

Similarly, oncolytic virotherapy is an innovative approach that generates a potent antitumor immune response when a naturally occurring or genetically engineered virus selectively replicates within and kills the tumor cells. Combined with other therapies, oncolytic virotherapy by inducing ICD can further enhance the antitumor immune response, potentially leading to a breakthrough in anticancer therapy.

Furthermore, nanotechnology has revolutionized the delivery of chemotherapy or anticancer drugs. Encapsulating these drugs within nanoparticle carriers improves their efficacy and allows for better control over dosage and side effects. Additionally, when administered as combined chemoimmunotherapy, nanoparticle-encapsulated drugs can potentiate the induction of ICD. For example, monoclonal antibody-based CD47 antagonists, which block the "don't eat me" signal emitted by cancer cells, can produce severe side effects when injected alone. However, when combined with a tumor microenvironment (TME) - activatable prodrug vesicle-a nano platform consisting of an oxaliplatin prodrug and a PEGylated photosensitizer this nano-enabled combination results in better tumor suppression due to enhanced propagation of ICD-induced antitumor immunity and reduced side effects [4]. Another form of nano immunotherapy described is TME-responsive manganese dioxide-coated gold nanocages, which have demonstrated the ability to alleviate hypoxia within the TME. When exposed to near-infrared (NIR) irradiation, these nanocages generate oxygen and produce ROS that kills tumor cells and triggers a robust immune response by releasing DAMPs. As a result, they exhibit high efficacy against primary tumors and aggressive forms of breast cancer, such as triple-negative metastatic breast cancer. These innovative nanocages overcome the challenges posed by hypoxia within the TME and provide a highly effective therapeutic approach for combating aggressive forms of breast cancer [5].

Another promising approach is using HHP treatment, which has shown potential in effectively destroying cancer cells by inducing apoptosis and triggering the release of DAMPs. HHP can be harnessed for developing autologous tumor vaccines by subjecting tumor cells to high pressure, rendering them non-viable while retaining immunogenic properties. This approach enables the preparation of personalized vaccines derived from a patient's tumor cells, stimulating a targeted immune response against the specific cancer cells in their body [6]. Nano vaccines have demonstrated remarkable potential, especially in significantly enhancing the abscopal effect when combined with radiotherapy. In a notable study, Min et al. showed that the engineered antigen-capturing nanoparticles specifically designed to bind and transport tumor-specific proteins released after radiotherapy efficiently delivered the released proteins to adjacent draining lymph nodes and effectively facilitated the antigen capture by the DCs [7]. This groundbreaking approach has shown promising results in a melanoma model, offering exciting prospects for leveraging nano vaccines to elicit a robust and targeted immune response against tumors, thereby amplifying the therapeutic impact of radiotherapy [7]. Additionally, nano vaccines have been successfully combined with immune checkpoint inhibitors, immunostimulatory cytokines, and other therapeutic agents, successfully eradicating tumors in specific murine models. These promising findings highlight the potential of nano vaccines in synergistic combination therapies for cancer treatment.

Furthermore, a novel bioelectric modality, nano pulse stimulation therapy, has emerged as a safer and non-invasive treatment option for malignant tumors. This innovative approach involves delivering ultrashort electrical pulses in the nanosecond range. Nano pulse stimulation therapy has shown great potential in selectively targeting and eliminating cancer cells while minimizing damage to healthy surrounding tissues. When these ultrashort electrical pulses enter tumor cells at high speed, they permeabilize cellular organelles and trigger the rearrangement of calcium ions. This disruption leads to calcium release from the ER, causing ER stress, which further amplifies the release of ROS. This cascade of events contributes to the induction of ICD and enhances the overall efficacy of cancer treatment. Its non-invasive nature makes it an attractive option for patients seeking safer and more tolerable treatment alternatives for their malignancies [8].

In addition, various other emerging strategies have shown promise in tumor eradication. These include oxygen-boosted PDT, NIR photoimmunotherapy, HHP, and electro-chemotherapy with an inducible T cell co-stimulator. Additionally, using electromagnetic sources such as magnetic fields, ultrasound, and X-rays in conjunction with nanomaterials represents a non-invasive method for inducing ICD. These innovative techniques hold great potential in harnessing the power of nanomaterials to trigger ICD and facilitate tumor eradication, either through direct cytotoxic effects or by leveraging the immune system's response.

Understanding the process of ICD and its subsequent impact on provoking robust antitumor immune responses has ushered in a transformative era in cancer treatment. While conventional therapies like chemotherapy and radiotherapy excel at eliminating tumor cells, the advent of groundbreaking approaches such as oncolytic virotherapy, PDT, and nanotechnology, including nano biomaterials, have demonstrated the remarkable ability to incite robust antitumor immune responses by promoting ICD. When integrated into combined immunotherapies, these approaches exhibit enhanced efficacy in eradicating cancer cells while minimizing adverse effects. By harnessing the immune system's inherent capabilities to combat cancer, these emerging modalities hold immense promise in revolutionizing future medicine and

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spearheading the next generation of immunotherapy. Their potential to reshape the landscape of cancer treatment is unparalleled, fuelling optimism for improved patient outcomes and a brighter future in the fight against cancer.

Authors contributions

Authors shared in conceiving, drafting, and literature review for the editorial and approved the final version. Both authors contributed to the article and approved the submitted version.

Disclosure statement

No potential conflict of interest was reported by the author.

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