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REVIEW

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Immunogenic cell death: A new strategy to enhancing cancer immunotherapy

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ABSTRACT

Immunogenic cell death (ICD) is a distinct type of stress-induced regulated cell death that can lead to adaptive immune responses and the establishment of immunological memory. ICD exhibits both similarities and differences when compared to apoptosis and other non-apoptotic forms of regulated cell death (RCD). The interplay between ICD-mediated immunosurveillance against cancer and the ability of cancer cells to evade ICD influences the host-tumor immunological interaction. Consequently, the restoration of ICD and the development of effective strategies to induce ICD have emerged as crucial considerations in the treatment of cancer within the context of immunotherapy. To enhance comprehension of ICD in the setting of cancer, this paper examines the interconnected responsive pathways associated with ICD, the corresponding biomarkers indicative of ICD, and the mechanisms through which tumors subvert ICD. Additionally, this review explores strategies for reinstating ICD and the therapeutic potential of harnessing ICD in cancer immunotherapy.

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Introduction

The demise of cells through various crucial cell death pathways facilitates physiological homeostasis in both normal and stress-challenged conditions.[1] The loss of control over single or mixed types of cell death in response to different stresses contributes to the turnover process in the context of the tumor microenvironment.[2,3] Regulate cell death (RCD) can be classified as either immunogenic RCD or non-immunogenic RCD, depending on its capacity to elicit an adaptive immune response. Immunogenic RCD, including necroptosis, ferroptosis, pyroptosis, and cuproptosis, has been identified as playing pivotal roles in modulating the immunosuppressive tumor microenvironment (TME) and influencing the clinical outcomes of cancer therapeutic strategies via tuning tumor immunity.[4–6]

To elucidate the fundamental determinants governing the capacity of dying cells to elicit an adaptive immune response and foster the development of enduring immunological memory, the mechanisms endowing dying cells with antigenicity and adjuvanticity have been examined.[7,8] Furthermore, surrogate biomarkers, including soluble DAMPs and cytokines associated with ICD, have played a pivotal role in delineating the principal molecular participants and identifying potential ICD inducers through extensive screening endeavors.[9] Nevertheless, the evaluation of ICD necessitates empirical validation from a variety of in vitro and in vivo assays to certify the ability of malignant cells undergoing ICD to recruit antigen processing cells (APCs) and initiate adaptive anti-cancer immunity.[10]

In contrast, the microenvironment surrounding developing tumors can hinder the initiation or execution of ICD through various mechanisms.[11–13] To address this deficiency, several strategies have been suggested to counteract the compromising effect of cancer on the ability of RCD to stimulate adaptive immunity. In this review, we have examined the immunosuppressive factors within the tumor microenvironment (TME) that impede ICD and proposed corresponding strategies to enhance its efficacy. Furthermore, we have highlighted the significance of ICD-based immunotherapy, as well as nanoparticle-based ICD, as prominent therapeutic approaches for activating the immune system against cancer, which in turn determines the long-term success of anticancer therapies.[14–16]

Immunogenic RCD and ICD

Cells, including tumor cells, can undergo various forms of death in response to different stresses, facilitating the elimination of unwanted cells by the body. According to the Nomenclature Committee on Cell Death (NCCD), cell death can be categorized into accidental cell death (ACD) and RCD based on functional characteristics.[17] ACD is an uncontrolled process of cell death that occurs in response to an unexpected attack or injury. Conversely, RCD denotes a genetically encoded molecular-controlled form of autonomous and orderly cellular demise.[18] According to the ability to drive antigen-specific adaptive immune response culminating in

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immunological memory or not, RCD can be further categorized as ICD or non-immunogenic cell death.

Apoptosis

Apoptosis, an early recognized form of RCD, was traditionally believed to be immunologically silent or even tolerogenic. During apoptosis, cells exhibit cytoplasmic membrane blebbing, nucleus condensation, fragmentation of cellular organelles and DNA, and the formation of apoptotic bodies that encapsulate the ruptured nucleus and cell debris.[19] However, late apoptotic cells are ultimately engulfed by phagocytic cells of the innate immune system, without releasing pro-inflammatory cellular contents into the extracellular environment. However, in the presence of prolonged and severe endoplasmic reticulum stress (ERS), including factors such as oxidative stress, ischemia, hypoxia, disruption of calcium homeostasis, and viral infection, the immunogenicity of apoptosis can be attained.[20,21] In such circumstances, apoptosis and ICD exhibit a mutually reinforcing association. Consequently, a significant area of interest in cancer therapy revolves around the induction of cancer cell-specific apoptosis within the tumor microenvironment (TME), while also ensuring its immunogenicity.[22,23]

Immunogenic RCD

In addition to apoptosis, a series of non-apoptotic RCD mechanisms have been gradually discovered in recent years. These include necroptosis, ferroptosis, pyroptosis, cuproptosis, PANoptosis, entosis, PARthanatos, alkaliptosis, oxeiptosis, lysosome-dependent cell death.[24,25] Some of these mechanisms have also been found to have immunogenic potential and are connected to tumor immunity, promoting the enrichment of either anti-tumor effector immune cells or regulatory immune cells, ultimately leading to either tumor regression or progression, as shown in Figure 1. However, the ability of immunogenic RCD to induce adaptive immunity relies on two main factors: antigenicity and adjuvanticity, both of which are not inherently intrinsic to dying cells.

Immunogenic RCD plays a collaborative role in modulating the tumor microenvironment (TME).[5,26,27] The four potentially novel mechanisms of immunogenic cell death, namely necroptosis, ferroptosis, pyroptosis, and cuproptosis, have been confirmed to exhibit reciprocal interaction between tumor cell death and the activation of antitumor immunity.[3,28] Necroptosis, for instance, has been extensively studied concerning various stimuli, including the activation of death receptors (e.g., Fas and TNFRA), toll-like receptors (e.g., toll-like receptors 3 and 4), as well as RNA- and DNA-sensors (e.g., Z DNA-binding protein 1 [ZBP1], retinoic acid receptor responder 3 [RIG1], transmembrane protein 173 [TMEM173, also known as STING]).[29] Mechanically, RIPK3-stimulated MLKL is necessary for membrane rupture formation in necroptosis;[30] Pyroptosis is primarily induced by the cleavage of gasdermin D (GSDMD) by CASP1 and CASP11 in response to pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), or cytosolic lipopolysaccharide (LPS);[31] Ferroptosis is typically initiated by the excessive accumulation of intracellular reactive oxygen species (ROS) following lipid peroxidation-induced destruction of cellular membranes in an iron-dependent manner.[32] Enhanced susceptibility to ferroptosis is correlated with reduced expression of GPX4, which can be induced directly through the binding of compounds such as RSL3, or indirectly through the inhibition of the cystine/glutamate antiporter(system xc-);[33] Cuproptosis is a recently discovered RCD that is linked to the immunogenicity of the tumor microenvironment. The underlying mechanism involves the transportation of excess Cu(II) from cells to mitochondria through ionophores. Within the mitochondria, the enzyme ferredoxin 1 (FDX1) reduces Cu(II) to Cu(I). The increased amount of Cu(I) directly binds to lipoylated components (like DLAT) of the tricarboxylic acid (TCA) cycle, leading to lipoylated proteins aggregation and destabilization of Fe – S cluster proteins, eventually, cell death.[34]

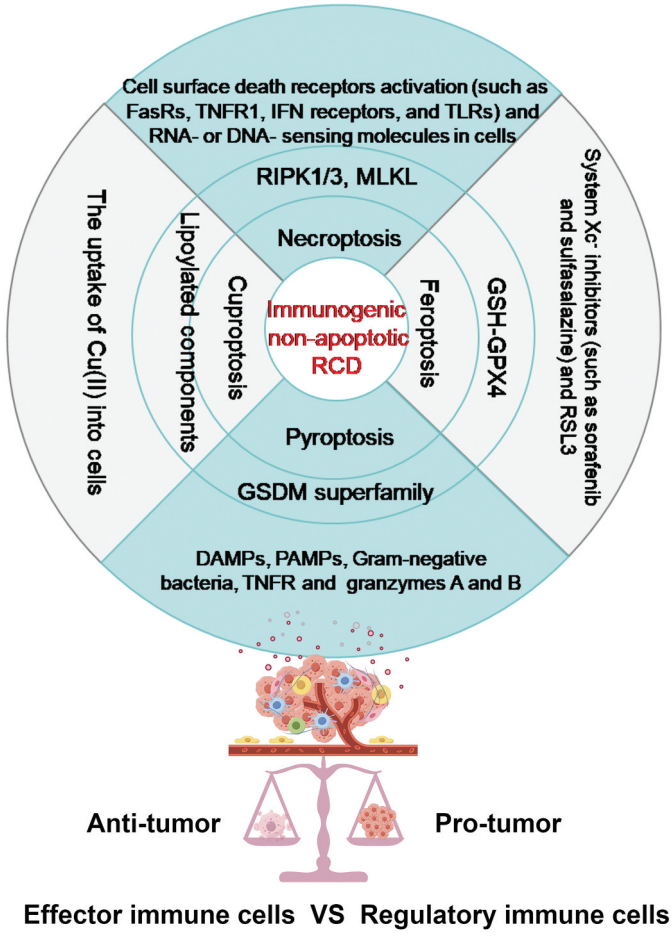

Figure 1. The core mechanism underlying four distinct forms of immunogenic non-apoptotic RCD. Within the context of various extracellular stresses and intracellular signaling pathways, cancer cells have the potential to undergo a specific type of cell death that is regulated by a specific set of genes and signaling molecules. These four types of RCD, namely necroptosis, pyroptosis, ferroptosis, and cuproptosis, represent typical immunological processes within the microenvironment(tme). These processes play a crucial role in balancing the TME by promoting the enrichment of either anti-tumor effector immune cells or regulatory immune cells, ultimately leading to either tumor regression or progression.

Detection of ICD

To distinguish the immunogenicity of certain variants of RCD from ICD, standardized experimental assays have been developed and guidelines for interpreting ICD have been established.[10,35] Various cellular stressors have been linked to ICD in immunocompetent syngeneic hosts, some of which are commonly used in the therapy of cancer patients.[36,37] Mechanistically, a crucial characteristic of molecules that induce ICD is their ability to render dying cells antigenicity and adjuvanticity through stress-responsive pathways, such as endoplasmic reticulum (ER) stress, and transcriptional/translational stress. The common inducers of ICD and the associated cellular stress related to antigenicity or adjuvanticity have been discussed, as shown in Figure 2.

Antigenicity from ICD

Antigenicity is attributed to the expression and presentation of antigens that do not induce clonal deletion within the framework of central or peripheral tolerance in their basal state.[38] Transcriptional and translational stress seem to be particularly effective in generating potential neoantigens.[39] While there are at least three approaches to confer sources of ICD antigenicity, it is generally believed that the majority of ICD inducers have minimal impact on antigenicity. Firstly, it has been observed that latent endogenous retroviruses and/or retroviral genes can be activated in response to certain ICD stressors, leading to the production of potentially antigenic proteins.[40] Secondly, the antigenic peptide repertoire can be enhanced through enzymatic or non-enzymatic post-translational modifications (PTMs) that modify the structure of proteins. These modifications include but are not limited to, phosphorylation, acetylation, glycosylation, citrullination, nitration/nitrosylation, glycation, oxidation, and ubiquitination.[41] Lastly, the accumulation of mutations and the landscape of tumor neoantigens evolve in response to increased genetic stress, under the pressure of ICD stressors, such as chemotherapeutic or radiotherapeutic interventions.[42,43]

Adjuvanticity from ICD

Multiple mechanisms contribute to the adjuvanticity of ICD, which plays a significant role in the initiation of adaptive immunity. These mechanisms include: (1) ICD-associated pattern recognition receptors (PRRs) activation, encompass numerous Toll-like receptors (TLRs), cyclic GMP-AMP synthase (CGAS), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), Z-DNA binding protein 1 (ZBP1), and heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1);[44] (2)Integrated stress response(ISR) activation, which is a part of the ER stress response, ultimately stimulate the phosphorylation of eukaryotic translation initiation factor 2 subunit alpha(eIF2α) and the upregulation of activating transcription factor 4 (ATF4);[45] (3)activation of autophagy, a cytoprotective mechanism related with ISR. However, the ultimate impact of autophagy on damage-associated molecular patterns (DAMPs) emission by ICD exhibits considerable context dependency. For example, autophagy limits the exposure of

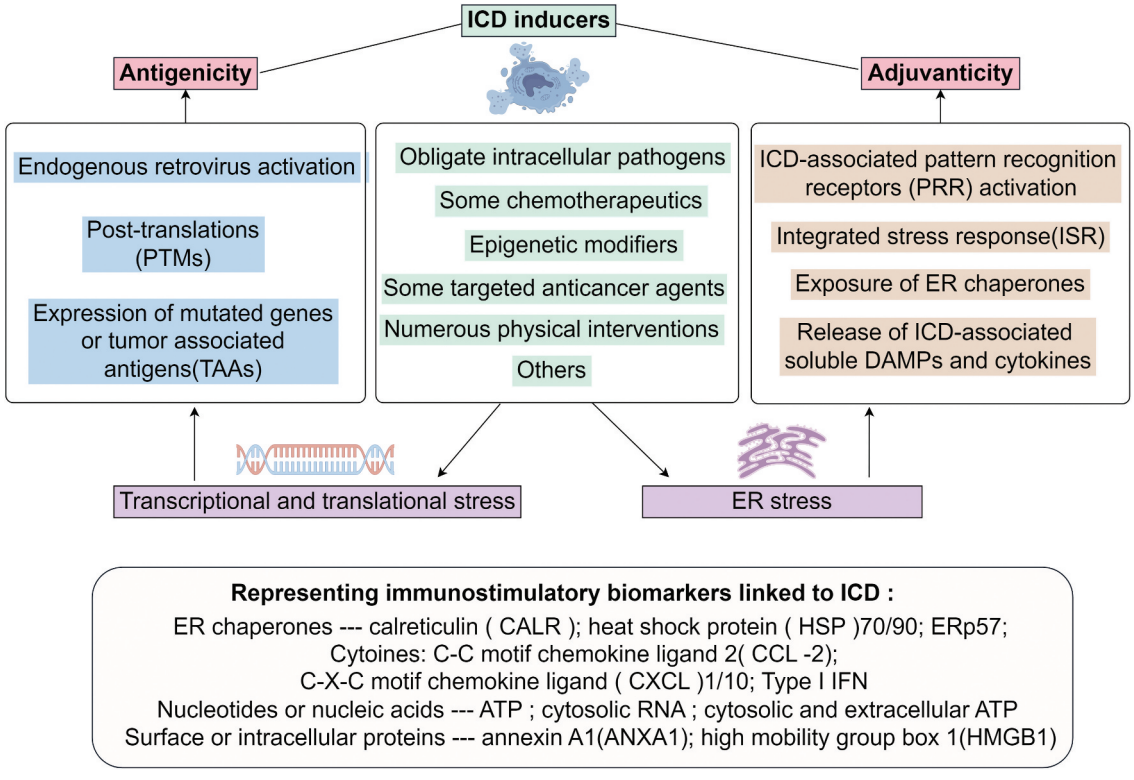

Figure 2. The core mechanisms of ICD involve the induction of transcriptional/translational stress or ER stress in dying cells by ICD inducers. These dying cells are then endowed with antigenicity or adjuvanticity through various approaches. Several immunostimulatory DAMPs and cytokines released during ICD have been identified as biomarkers of this process.

calreticulin(CALR) by cancer cells undergoing photodynamic therapy (PDT)-driven ICD, but optimizes ATP release in the course of chemotherapy-driven ICD;[7,46] (4) release of immunostimulatory DAMPs and cytokines, most of them have been recognized as the biomarkers of ICD, which enable the recruitment of antigen processing cells (APCs) or their precursors to sites of ICD (eg, ATP), spatially guide the interaction between APCs and dying cells (eg, ANXA1), favor the phagocytosis of dying cells or their corpses (eg, CALR, ERp57, HSP70/90), promote the maturation and cross-presentation of APCs (eg, ATP, HMGB1, type I IFN and TFAM), or facilitate the recruitment of T cells (eg, CCL2, CXCL1 and CXCL10).[8,47]

Interpretation of ICD

It is important to note that not all inducers of ICD operate through the same molecular mechanisms, and the release of damage-associated molecular patterns (DAMPs) associated with ICD is not always sufficient for antigen-presenting cells (APCs) to initiate cytotoxic T lymphocyte (CTL)-dependent immune responses against dying cells.[48,49] Therefore, it is necessary to conduct gold-standard vaccination and therapeutic assays in vivo to confirm genuine ICD inducers. In the vaccination assay, malignant cells that have undergone cell death in vitro due to a potential ICD inducer are utilized as a vaccine, either in their original form or loaded onto immature, syngeneic dendritic cells (DCs). The ability of mice to reject or control tumor growth reflects the level of immunogenicity.[35,50] Specificity is confirmed by re-challenging tumor-free mice with another syngeneic cancer cell line at the conclusion of the experiment, which is anticipated to result in the development of palpable neoplastic lesions in 100% of the mice. In the therapeutic assay, grafted tumors that are either genetically-driven or chemically-induced are established in subcutaneous or orthotopic locations and subsequently treated with a putative inducer of ICD in both immunocompetent and immunodeficient mice. In this experimental configuration, genuine ICD inducers demonstrate optimal antineoplastic effects in immunocompetent mice, but not in immunodeficient mice.[50,51] Importantly, the therapeutic assay is of significant importance in validating the outcomes of vaccination experiments. However, it is insufficient on its own to distinguish between the induction of ICD and immunostimulation unrelated to ICD.

Tumor subversion of ICD and corresponding restoring strategies

Malignant cells have devised various strategies to diminish the antigenicity and adjuvanticity of ICD, including direct inhibition of the essential components of the ICD-associated responsive apparatus. These mechanisms employed by cancerous cells enable them to evade the adaptive immune response triggered by ICD.[52,53] Enhancing our comprehension of this process is expected to facilitate the clinical application of ICD.

Defects compromising the antigenicity and adjuvanticity in cancer

Numerous studies have documented the involvement of tumor subversion in the reduction of antigenicity, including loss of chromosome 6 and 15 (LOH), mutations in the beta-2-microglobulin (β2 M), and alterations in the IFN signaling pathway.[54–56] These alterations significantly impact the synthesis of a functional major histocompatibility complex (MHC) class I exposure. Therefore, it is imperative to restore MHC class I defects in tumor cells to ensure efficient antigenicity of ICD.

Additionally, malignant cells can interfere with the release of ICD-associated damage-associated molecular patterns (DAMPs), such as Calreticulin (CALR), ATP, and annexin A1 (ANXA1), thereby subverting the adjuvanticity of ICD. For example, Certain malignant cells have the ability to manipulate CALR signaling through the internal retention of CALR upon interaction with stanniocalcin 1 (STC1) or by limiting CALR binding sites on the cell surface.[57] Additionally, these malignant cells can evade the release of ATP associated with ICD by upregulating or promoting the upregulation of two ectonucleotidases, CD39 and CD73, which sequentially convert extracellular ATP into adenosine.[58,59] Furthermore, studies have demonstrated that some malignant cells reduce the expression of ANXA1, thereby impacting the ability of cancer cells to expose CALR in response to ICD inducers.[60]

TME factors influencing ICD and corresponding enhancing strategies

In addition to the aforementioned factors originating from malignant cells, the microenvironment surrounding dying cancer cells significantly influences their capacity to induce adaptive immunity at the microenvironmental level, even when there is an adequate presence of antigens and adjuvants. The TME factors influencing ICD and corresponding enhancing strategies have been studied extensively, as shown in Figure 3.

Firstly, The presence, activation, and costimulation of tumor-infiltrating lymphocytes (TILs), such as CD8+ T cells, CD4+ T cells, B cells, and innate lymphoid cells, are essential for a successful immune response against tumors and are correlated with favorable prognoses in various types of tumors.[61,62] However, in tumors characterized as immune-desert or immune-excluded ("cold" tumors), tumor-infiltrating lymphocytes (TILs) are either absent or fail to efficiently penetrate the tumor, thereby impeding the induction of adaptive immunity through ICD. The utilization of adoptive cell therapy (ACT) involving TILs has been extensively studied in various solid tumors, revealing sustained responses by enhancing T-cell infiltration, even in patients resistant to immune checkpoint blockade (ICB).[63,64] Nonetheless, in immune-inflamed tumors ("hot" tumors), the issue of T-cell exhaustion continues to pose a challenge to effective anti-cancer immune responses.[65] Immune checkpoint blockade therapy targeting coinhibitory receptors expressed by infiltrating T cells, including CTLA-4, TIM-3, and PD-L1, has been shown to enhance the effectiveness of ICD.[66,67]

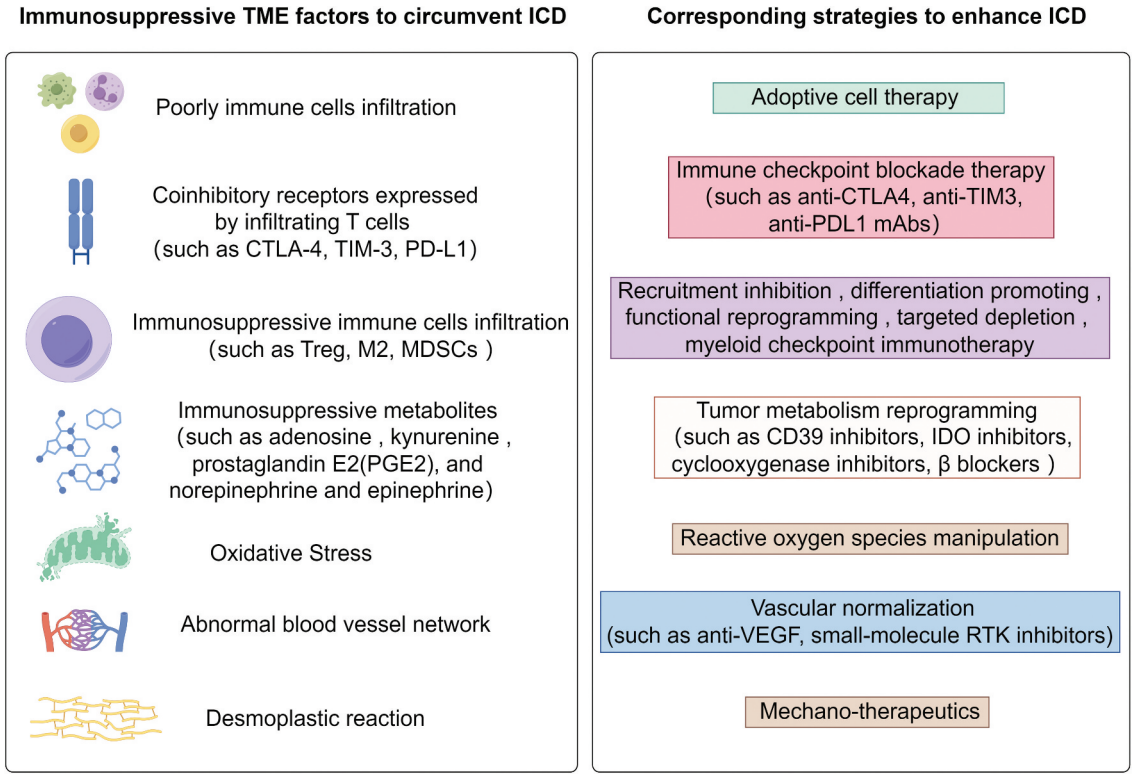

Figure 3. The TME factors influence the capacity of ICD to induce adaptive immunity at the microenvironmental level, along with corresponding strategies aimed at enhancing ICD for improved immunotherapy.

Secondly, immunosuppressive immune cells, such as myeloid-derived suppressor cells (MDSC), M2-like macrophages (M2), and regulatory T cells (Treg), play a crucial role in suppressing antitumor immune responses in cancer immunity.[68,69] However, the efficacy of systemic cell depletion in promoting antitumor immunity is not always guaranteed, as these cells possess a wide range of functions and the tumor microenvironment is highly complex. Consequently, the utilization of various therapeutic approaches, currently being evaluated in clinical settings, encompasses diverse strategies such as targeting recruitment and differentiation, as well as engaging activating or inhibitory receptors (checkpoint receptors) to reprogram the functionality of immunosuppressive immune cells.[70,71] Overall, these approaches are currently not considered independent strategies, but myeloid checkpoint therapy has demonstrated promising outcomes. Notably, the pharmaceutical inhibition of c-Rel, a myeloid checkpoint in MDSCs, has exhibited significant inhibition of cancer growth in mice.[72]

Thirdly, cancer cells possess the ability to suppress immune cells by generating immunosuppressive metabolic byproducts such as adenosine, kynurenine, prostaglandin E2 (PGE2), as well as norepinephrine and epinephrine.[73,74] The synthesis and signaling pathways of these potent immunosuppressive metabolites exhibit inherent redundancy. This redundancy has posed a significant challenge in the development of effective pharmacological interventions against these metabolites. Consequently, the efficacy of inhibitors targeting only one metabolite is limited due to compensatory metabolic pathways. Currently, clinical trials are underway to evaluate the effectiveness of "pan-antagonists" for each subclass of the "metabolic immunosuppressive receptor," including A2A/2BAR, AhR, EP2/EP4, and β-adrenergic receptors. Additionally, broad inhibitors of kynurenine (IDO1/TDO or IDO1/IDO) and PGE2 (COX-1 and COX-2) are being tested.[75,76]

Fourthly, The intricate TME is characterized by a low pH, elevated redox status, and hypoxia, which have been linked to the suppression of immunotherapy.[77] Reactive oxygen species (ROS) have been extensively investigated in the context of cancer and exhibit a dual nature. At lower to moderate concentrations, ROS serve as signal transducers, stimulating cell proliferation, migration, invasion, and angiogenesis. In contrast, elevated levels of reactive oxygen species (ROS) have the potential to induce cellular demise.[78] Under conditions of oxidative stress, tumor-infiltrating regulatory T cells (Treg cells) undergo programmed cell death, known as apoptosis, resulting in a more potent immunosuppressive effect compared to viable Treg cells.[79] Furthermore, ROS can impede the effectiveness of anti-tumor immune responses by activating endoplasmic reticulum (ER) stress-XBP1 signaling in dendritic cells (DCs).[80] These collective findings suggest that heightened ROS levels represent a contributing mechanism underlying the resistance to immunotherapies, including the induction of anti-tumor immunity through ICD.

Fifthly, The tumor vasculature consists mainly of hypoxia-induced vessels that are distorted, malformed, and leaky, resulting in inefficiency. This abnormal vasculature has implications for the trafficking and accumulation of CD4+ and CD8 + cells within the tumor.[81] Researchers have investigated vascular normalization therapy, including the use of anti-VEGF and small-molecule RTK inhibitors, to induce the development of high endothelial cells in the vasculature (HEVs).[82,83]

This may facilitate lymphocyte trafficking into the tumor and potentially enhance the effects of immunotherapy by promoting the formation of tertiary lymphoid structures.

Sixly, The desmoplastic reaction to a tumor refers to the proliferation of fibrous connective tissue surrounding tumor cells, which is closely linked to the infiltration of immune cells within the tumor. Several studies have shown that an immature desmoplastic reaction and the presence of myxoid stroma are associated with lower densities of tumor intraepithelial memory cytotoxic T cells and stromal M1-like macrophages.[84,85] Additionally, the presence of a dense extracellular matrix (ECM) and fibrous stroma is also associated with the recruitment of immunosuppressive cells, such as Tregs, which hinder the effectiveness of antitumor immunity.[86] The manipulation of mechanotransduction pathways in myofibroblasts has demonstrated the potential to mitigate organ fibrosis and reduce tumor burden in experimental models. The implementation of mechano-therapeutics, such as inducing a quiescent phenotype in myofibroblasts, promoting myofibroblast apoptosis, or inhibiting pro-fibrotic gene expression programs and TGF-β1 activation, could serve as innovative therapeutic interventions to enhance the efficacy of immunotherapy.[87,88]

ICD-based immunotherapy

In light of an enhanced comprehension of ICD within the context of cancer, ICD-based immunotherapy has emerged as a compelling option for integrating cancer immunotherapy combination regimens in clinical settings. These regimens encompass chemo-immunotherapy, radio-immunotherapy, photo-immunotherapy, and cancer vaccines. The process of ICD-based immunotherapeutic approaches in activating anti-tumor immunity is shown schematically in Figure 4.

ICD-based chemo-immunotherapy

Several traditional chemotherapeutic drugs, including anthracyclines, taxanes, cyclophosphamide, bortezomib, crizotinib, and oxaliplatin, have been identified as genuine inducers of ICD. These drugs can trigger the immunogenic demise of tumor cells, leading to a CD8+T cell-mediated response against tumor antigens expressed by the dying cells.[37,89] The combination of immune checkpoint inhibitors (ICIs) with ICD-inducing drugs has shown promising results in the treatment of various tumors, particularly in challenging-to-treat cancers, with minimal risks of overlapping toxicities among the individual drugs, although the optimal dose, timing, and sequence of chemo-immunotherapy combinations needed to be further explored.[90,91]

ICD-based radio-immunotherapy

Irradiated tumor cells experience ICD, which can stimulate a potent anti-tumor immune response. The integration of radiotherapy (RT) and immunotherapy is increasingly being

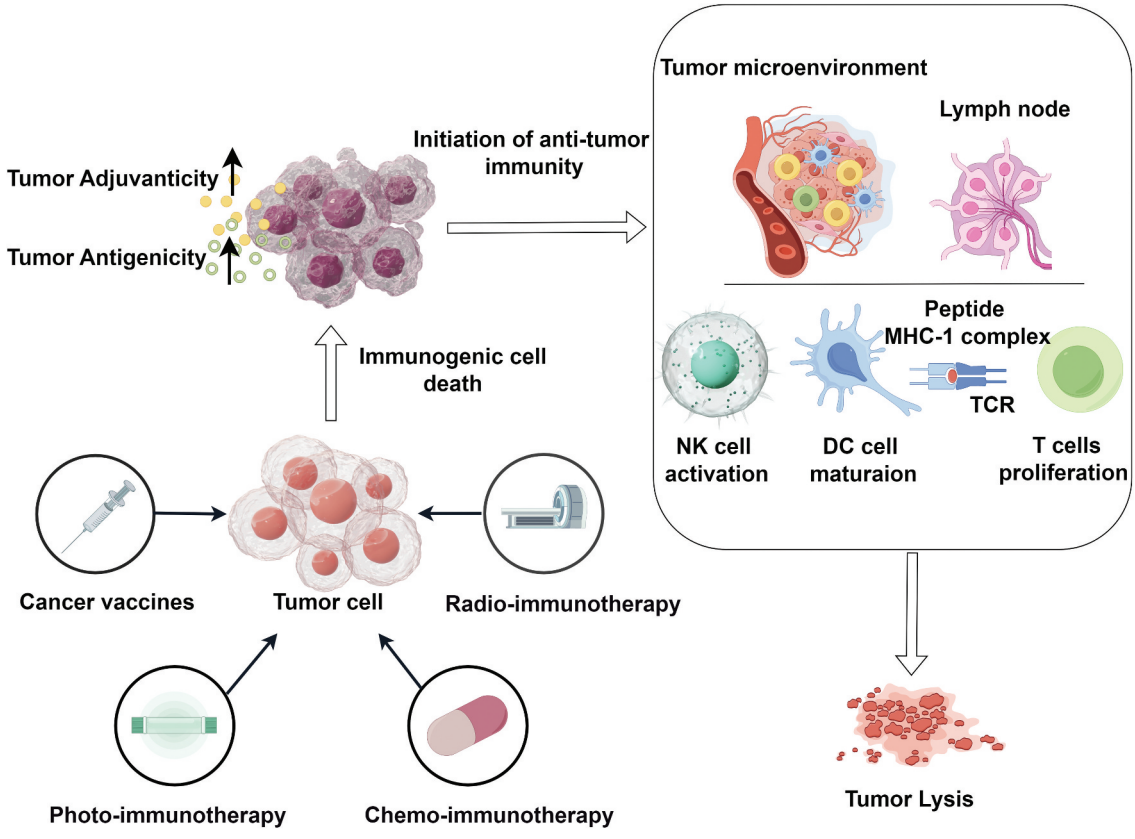

Figure 4. The process of icd-based immunotherapeutic approaches in activating anti-tumor immunity. Chemotherapy, radiotherapy, phototherapy, and cancer vaccine can induce the ICD of cancer by upregulating the antigenicity and adjuvanticity of cancer, then initiate the anti-tumor immunity, including NK cell activation, DC cell maturation, and T cell proliferation.

utilized in routine clinical practice, despite limited high-quality evidence to inform clinical management.[92] In addition to conventional photon RT (utilizing X-ray or gamma-ray beams), particle RT, such as proton RT, carbon-ion radiotherapy (CIRT), and boron neutron capture therapy (BNCT), also exerts a significant impact on tumor cells and various immune cells within the tumor microenvironment, resulting in the release of ICD biomarkers.[93,94] However, the combination of particle RT with immunotherapy is still limited in clinical, because of costs and technique restrictions.

ICD-based photo-immunotherapy

Phototherapies employing suitable photoagents and light doses have been observed to elicit ICD within specific tumors, thereby generating tumor-associated antigens (TAAs) and damaged-associated molecular patterns (DAMPs) as potential sources.[95] This phenomenon has the potential to instigate an inflammatory response. Notably, near-infrared (NIR) light has emerged as the predominant choice for phototherapy, owing to its ability to deeply penetrate biological tissues. This is often achieved through the administration of in situ or naturally occurring absorbance agents.[96] Photosensitizers possess the ability to convert absorbed light energy into heat for photothermal effects, as observed in photothermal therapy (PTT), or into reactive oxygen species (ROS) for photochemical effects, as observed in photodynamic therapy (PDT).[97] Notably, certain photosensitizers, including porphyrins, indocyanine green, methylene blue, and Rose Bengal, have been successfully employed in clinical settings for PDT. These photosensitizers exhibit robust optical absorption at therapeutic wavelengths, high photochemical conversion efficiency, and favorable biocompatibility. A combination of phototherapy and immunotherapy, particularly using immunostimulants, immune-targeting agents, and checkpoint inhibitors, can significantly induce antitumor immune responses.[98,99]

ICD-based cancer vaccine

The cancer vaccine has shown promise as an immunotherapy, but it continues to encounter obstacles, particularly in the identification of immunogenic neoepitopes on diverse cancer cells.[39] The initiation of tumor-specific neoantigens through the process of ICD presents an opportunity for the development of endogenous cancer vaccines.[100] A novel approach to in situ cancer vaccination involves utilizing the patient's tumor antigens, which are produced by ICD inducers. The dendritic cells (DCs) recruited by ICD may also serve as a potential DC vaccine.[101,102] Various strategies have been expanded upon to investigate the potential of neoantigen-based cancer vaccines, but a deeper investigation of their mechanisms and immune-related adverse events (irAE) need more attentions.[103]

Progress, obstacle, and future perspective in ICD-based nanoimmunotherapy in cancer

The efficacy and safety of traditional ICD inducers alone or combinational immunotherapy are constrained by various challenges.[104] Firstly, the efficacy is hindered by inadequate targeting for solid tumors and an unfavorable tumor microenvironment for immunotherapeutics. Secondly, off-target adverse effects increase the likelihood of systemic toxicities and rates of immune-related adverse events (irAEs). To address these challenges, nanotechnology has emerged as an enhanced delivery technology for cancer immunotherapy utilizing ICD.[14,105] The utilization of nanotechnology has the potential to enhance the concentration of immunotherapeutics within tumors, facilitating more precise targeting of desired tumor and immune cells, while also mitigating off-target adverse effects. Additionally, nanotechnology offers a distinctive approach to elicit enduring antitumor immune responses through sustained ICD mediation and concurrently remodeling the tolerogenic tumor immune microenvironment.[106,107]

ICD-based nanoimmunotherapy in cancer

Recent investigations have assessed the efficacy of novel inorganic and polymeric nanoparticles, including AuNPs, Metal-organic frameworks (MOFs), and micelles, as inducers of ICD.[108] Nanotechnology presents a viable approach for inducing ICD and facilitating the targeted administration of ICD inducers, thereby enhancing the efficacy of conventional therapeutic strategies like chemotherapy, phototherapy, and radiotherapy.

In terms of chemotherapy, certain chemotherapeutic drugs that induce ICD have been incorporated into a nano-drug co-delivery system (NDCDS), which combines cytotoxicity and immunostimulatory properties.[109] For instance, a prodrug of Cisplatin(IV) was conjugated to *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer (P-Cis) and coadministered with digoxin (Dig), which induces potent immunogenic cell death, leading to dendritic cell maturation and activation of CD8+ T cell responses.[110] Poly(lactic-co-glycolic acid) nanoparticles (PLGA NPs) loaded with paclitaxel (PTX) and a Toll-like receptor 4 (TLR-4) agonist (SP-LPS) demonstrated enhanced in vivo antitumor activity and a higher proportion of activated immune cells in the TME than the Taxol-treated group.[111]

In terms of phototherapy, several inorganic nano-agents, including AuNPs, CuS NPs, GO, MoS2 nanosheets, and carbon nanotubes, possess inherent NIR light absorption capabilities.[112,113] These nano-agents have been designed to deliver thermal energy and immunoadjuvants. For instance, Mao et al. conducted a study on near-infrared (NIR)-driven immunostimulants, where they combined upconversion nanoparticles with aggregation-induced emission luminogens (AIEgens).[114] This combination resulted in the generation of high-dose reactive oxygen species (ROS) when exposed to high-power NIR irradiation, leading to enhanced immunogenic cell death and antigen release.

In terms of radiotherapy, the utilization of high-Z-element nanoparticles in radiotherapy has demonstrated the potential to improve the radiotherapeutic indices of localized tumors by minimizing radiation doses and adverse effects on healthy tissues. Additionally, these nanoparticles can stimulate the tumor microenvironment (TME) to elicit systemic antitumor immune responses, thereby augmenting abscopal effects.[115,116] On the one hand, The utilization of inorganic nanoparticles

(NPs) as radiosensitizers has been shown to enhance the absorption of ionizing radiation, including X-rays, photons, and gamma rays. On the other hand, Nanotechnology also offers the potential for nanovectorized ionizing radiation, which could effectively enhance the anti-tumor immune response associated with ICD following internal radiation.[117] This approach can be tailored and designed to achieve predictable outcomes. For instance, Zhang et al. successfully designed a multifunctional nanoparticle (PIC) by employing a scalable and straightforward complexation method involving poly-l-lysine (PLL), CpG oligodeoxynucleotide (CpG), and iron oxide nanoparticles (ION). This nanoparticle formulation resulted in the activation of tumor-specific immunity and improved abscopal effects.[118]

Recently, Several intelligent nanoparticle-based platforms have been developed to induce potent ICD through various mechanisms of action, thereby enhancing antitumor immunity.[119,120] For instance, nanoparticles capable of co-delivering ICD-inducing therapeutic drugs (such as OxP, DOX, and PTX) and photosensitizers (such as indocyanine green (ICG), Ce6, and pheophorbide A) have been designed to achieve a synergistic effect. Concurrently, the modulation of the immunosuppressive tumor immune microenvironment (TIME) through the use of agents such as indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors and anti-PD-L1 antibodies provides additional advantages by mitigating the immunosuppressive state and augmenting the effectiveness of cancer immunotherapy.[121–123]

Obstacles and future perspective of nanoimmunotherapy

In a similar vein, the effectiveness of nanoimmunotherapy is impeded by unfavorable tumor microenvironments characterized by limited tumor penetration due to elevated interstitial fluid pressure (IFP), dense extracellular matrix (ECM), transient tumor retention, and inadequate tumor cell uptake. To address these challenges, extensive endeavors have been undertaken to overcome these biological barriers. Primarily, the physiochemical attributes of nanomedicines play a significant role in tumor penetration, encompassing surface area, hydrodynamic diameter, shape, and surface zeta-potential.[124] Moreover, the utilization of tumor-targeting RGD family peptides has demonstrated the ability to enhance the penetration of nanoparticles (NPs) into tumors. For instance, liposomes modified with nRGD and loaded with DOX exhibited superior tumoricidal effects in comparison to standard PEGylated liposomal DOX.[125] Additionally, the degradation of the extracellular matrix (ECM) has also been achieved as a strategy. For instance, Cheng et al. developed PEG-PLGA NPs with surface-conjugated recombinant human hyaluronidase PH 20 (rHuPH20) to enhance tumor penetration. These NPs exhibited improved tumor penetration and more effective perfusion when compared to the physical mixture of free rHuPH20 and PLGA-PEG NPs, after loading with DOX.[126]

In summary, various nanoparticles, both established and newly discovered, have been assessed as carriers or modalities for inducing ICD, thereby enhancing the effectiveness of cancer immunotherapy while minimizing adverse effects on the entire system.[127,128] Nevertheless, further investigation is required to determine the precise effects of each combined approach.[129] It is worth noting that only a limited number of stimuli have been proven to genuinely induce ICD. Furthermore, the animal models used in current studies may not accurately represent real-world scenarios in human subjects. Consequently, numerous challenges must be thoroughly addressed prior to the widespread implementation of these approaches.

Conclusions

The initiation of adaptive immune responses that specifically target antigens found in tumors can be stimulated through the induction of immunological RCD in cancer cells. These cancer cells acquire antigenicity or adjuvanticity through stress-responsive pathways. However, there exist various mechanisms by which both the cancer cells themselves and the TME can hinder the initiation or execution of ICD. Therefore, the use of ICD sensitizers or enhancers becomes necessary in certain ICD-related immunotherapies to achieve optimal effectiveness. Apart from traditional strategies for ICD induction, the field of ICD-based nanoimmunotherapy is gaining increasing attention due to its unique characteristics.

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Disclosure statement

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