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Intrinsic cancer vaccination

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ABSTRACT

Immunotherapy is revolutionizing the treatment of cancer, and the current immunotherapeutics have remarkably improved the outcomes for some cancer patients. However, we still need answers for patients with immunologically cold tumors that do not benefit from the current immunotherapy treatments. Here, we suggest a novel strategy that is based on using a very old and sophisticated system for cancer immunotherapy, namely "intrinsic cancer vaccination", which seeks to awaken our own immune system to activate tumor-specific T cells. To do this, we must take advantage of the genetic instability of cancer cells and the expression of cancer cell neoantigens to trigger immunity against cancer cells. It will be necessary to not only enhance the phagocytosis of cancer cells by antigen presenting cells but also induce immunogenic cancer cell death and the subsequent immunogenic clearance, cross-priming and generation of tumor-specific T cells. This strategy will allow us to avoid using known tumor-specific antigens, *ex vivo* manipulation or adoptive cell therapy; rather, we will efficiently present cancer cell neoantigens to our immune system and propagate the cancer-immunity cycle. This strategy simply follows the natural cycle of cancer-immunity from its very first step, and therefore could be combined with any other treatment modality to yield enhanced efficacy.

Contents

1. Introduction

The need to develop novel strategies for cancer therapy is tremendous. In the late 1800s, Dr. William Coley investigated anti-tumor effects mediated by microbe-derived toxins, establishing initial concept

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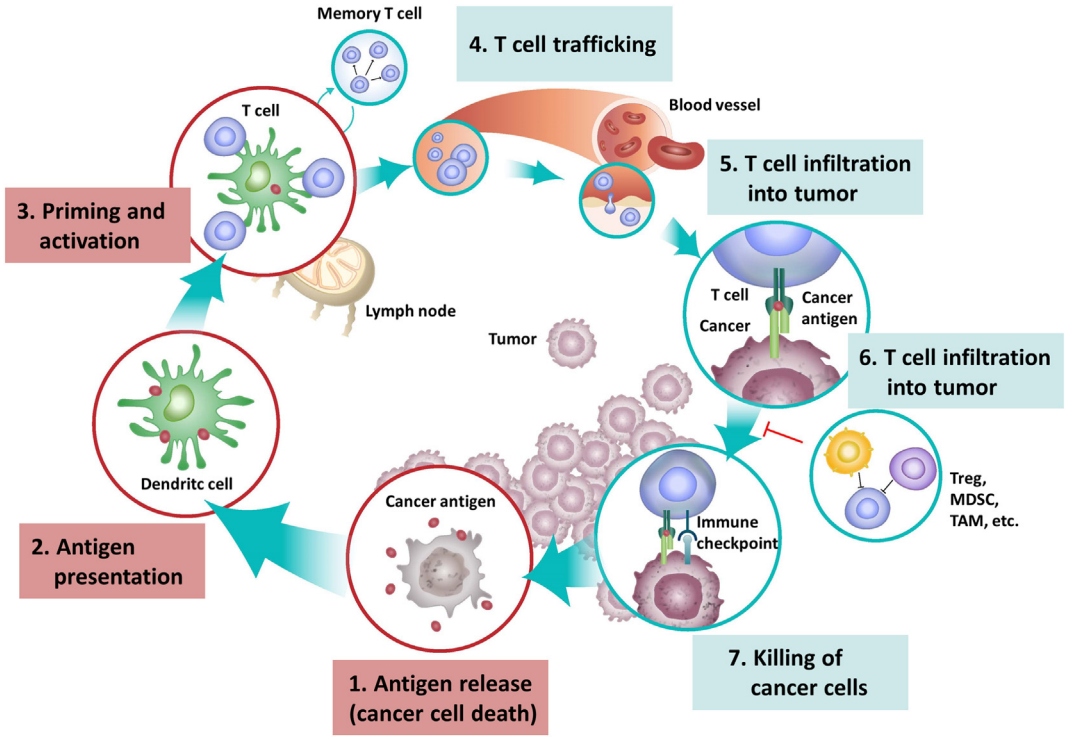

Fig. 1. Cancer-immunity cycle. This cycle is a self-sustaining multistep process that involves: (1) the release of cancer cell antigens; (2) cancer antigen presentation; (3) priming and activation; (4) the trafficking of T cells to the tumor; (5) the infiltration of T cells into tumors; (6) the recognition of cancer cells by T cells; and (7) the killing of cancer target cells. Each step is described in the manuscript along with various cancer immunotherapy strategies. Figure modified from Chen and Mellman **[9]** with permission from Elsevier.

of exploiting the immune system to combat cancer. Since then, the field of cancer immunotherapy has evolved intensively, accompanying our understanding of the complexity of the immune system. In contrast with therapies that act on the tumor itself, immunotherapeutic agents target the patients' immune system to control tumor progression, and such immune responses can be sustained even after the treatment has finished [1,2]. Research in the field of cancer immunotherapy has flourished in recent years, yielding both crucial breakthroughs and information on important immunosuppressive pathways that can limit the success of cancer immunotherapy.

Tumor cells often overexpress immune checkpoint molecules, which limit the immune system's search function and tamp down the immune response. To overcome this problem, researchers have developed a number of different antibody proteins that block these checkpoint molecules and enable the immune system to destroy tumors. Such cancer immunotherapy can add extra years to patients' lives. However, checkpoint blockade therapies work only when anti-tumor T cells are present but anergic of exhausted; these cells are reactivated *in situ* through the molecular inhibitors. Moreover, not all tumors appear to respond to the current immunomodulatory maneuvers [3–5]. For instance, only a fraction of patients with melanoma respond to single-agent immune checkpoint blockade using anti-PD-1/PD-L1 therapeutic antibodies. In some cases there is no response even when the checkpoint molecules are blocked, because there are too few active T cells in the vicinity of the tumor or the tumor doesn't display enough of the T cell targets (neoantigens) on its surface [6–8]. In another immunotherapeutic strategy, T cells are amplified *ex vivo*, activated, genetically engineered to be highly combative (Chimeric antigen receptor T cells, also known as CAR-T), and then reinfused into the patient to target to the tumor. While CAR-T cell therapy has shown great success for the treatment of hematologic tumors, response rates of patients with solid tumors are less favorable; it is also antigen-specific and requires foreknowledge of the relevant cancer antigens to which the patient would be sensitive. Since emerging cancer immunotherapies using immune checkpoint blockades work predominantly at steps 6 and 7 of the cancer-immunity cycle (Fig. 1), effective cancer immunotherapies require successful passage through the early stages of the cycle to improve T cell priming and activation (steps 1–3). Thus, rational strategies need to be designed to overcome the activation energy threshold of the immunosuppressive tumor microenvironment (TME) that turn cold tumors hot and allow our primed immune systems to recognize the tumors as foreign or aberrant.

For an anti-cancer immune response to lead to effective killing of cancer cells, the immunogenic cell death (ICD) pathway must initiate a series of stepwise events in which the ICD pathway in the tumor releases neoantigens created by oncolysis, which are engulfed by dendritic cells (DCs) for antigen processing (step-1, Fig. 1) [9]. In order for this step to yield an anti-cancer T cell response, it should be assisted by immunogenic signals released by dying tumor cells. Notably, ICD is accompanied by the spatiotemporally defined release of damage-associated molecular patterns (DAMPs) and/or danger signals that raise the potential immunogenicity of dying cells. Next, DCs engulf and process the tumor-derived antigens, then travel to the lymph node to undergo maturation. DCs use MHC class I and MHC class II molecules to present the captured antigens to T cells (step-2), leading to the priming, activation, and clonal expansion of cytotoxic T cell responses against cancer antigens (step-3) that have triggered incomplete central tolerance. The nature of the immune response is determined at this stage, with the final outcome resting on the critical ratio of T effector cells versus regulatory T (Treg) cells. Finally, the activated effector T cells migrate to and infiltrate into (step-4, 5) the tumor core, specifically bind to cancers via an interaction between T cell receptor (TCR) and the MHC class I-bound cognate antigen (step-6), and conclusively kill tumor cells via the release of cytolytic effectors (e.g., perforin and granzyme A/B) (step-7) [9,10].

Therapeutic cancer vaccines, which represent a viable option for active immunotherapy, seek to facilitate efficient T cell priming. However, therapeutic vaccination has thus far failed to induce a robust immune response against tumors in clinical trials. Tumor-induced immunosuppressive mechanisms in the TME have been reported to be a major cause of the limited success of the current therapeutic cancer vaccines.

In this review, we discuss the novel strategy of "intrinsic cancer vaccination", which seeks to control the entire cancer-immunity cycle of cancer neoantigen release, cross-priming and T cell proliferation, cancer cell elimination and converting immunosuppressive TME to an immunogenic microenvironment. In addition, we cover the use of nanoparticle-based platform to improve delivery of immunotherapeutic drugs to specific target tissues and/or to maximize their efficacy. This strategy focuses on allowing our immune system to recognize and eliminate cancer cells, and hence should greatly increase the patient population that will benefit from the cutting-edge science of cancer immunotherapy.

2. Intrinsic cancer vaccination

In an attempt to awaken our own immunity against cancers, here we discuss the novel approach of using intrinsic cancer vaccination, which takes advantage of the genetic instability of cancer cells. An anti-cancer intrinsic vaccine is designed to activate immune cells those are professional phagocytes which can consequently enhance efficient recognition toward cancer cells as non-self. This strategy allows tumor antigens to stimulate the host immune system, resulting in total tumor eradication via amplification of anti-tumor T cells and the induction of a lasting anti-tumor immune response.

Intrinsic cancer vaccination causes the vaccine to develop within the patient by efficiently providing various cancer cell neoantigens and DAMPs to the immune system, thereby reducing the resource distribution required for *ex vivo* processing. This universal and effective approach can exploit the complete antigenic repertoire of a tumor rather than being limited to a single tumor-specific antigen by generating polyclonal T cell immunity against cancer. This strategy is expected to enhance the immune surveillance of primary cancer, metastatic cancer, and even recurrent cancer.

In order to elicit an augmented anti-tumor immune response, an intrinsic vaccine should ideally be able to induce ICD to facilitate the immunogenic release of tumor neoantigens; and enhance antigen uptake by (activated) antigen presenting cells (APCs) to induce anti-tumor T cell responses that will trigger systemic anti-tumor immunity. The triggering of danger signals in immunogenic dying cancer cells and the enhancement of phagocytosis in an immunosuppressive TME requires proficient interconnection of the innate and adaptive immune responses. This strategy also includes means to recruit DCs (especially $CD103^+$ DCs) into the tumor site and to enhance cross-priming between mature DCs and T cells (Fig. 2). In this section, we describe the

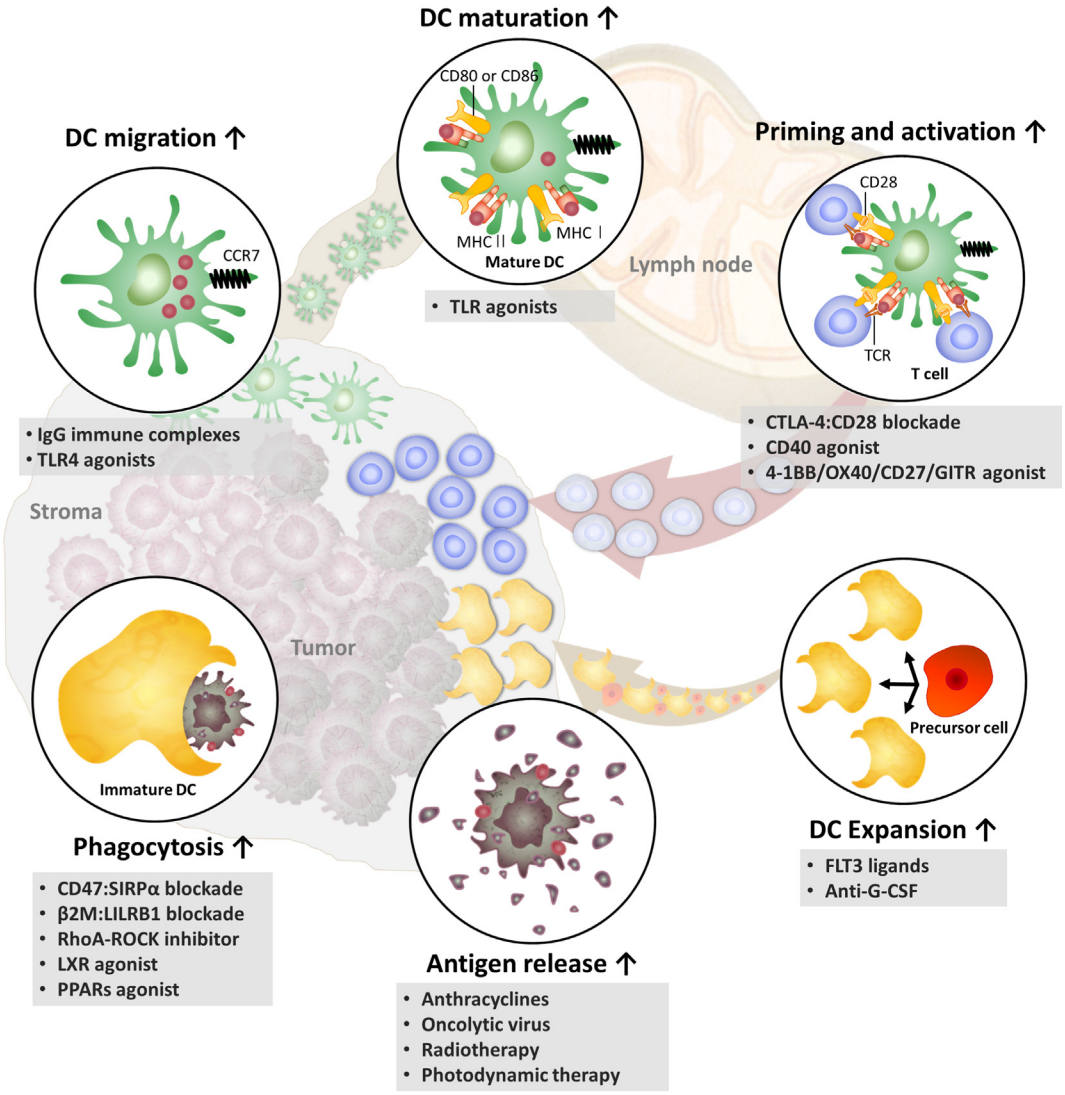

Fig. 2. The strategy of intrinsic cancer vaccination. In order to obtain a strong immunity against cancer, APCs should selectively recognize cancer cells as non-self and effectively digest them to activate anti-tumor T cell immunity. This strategy includes: 1) DC expansion; 2) enhancement of non-self signals; 3) enhancement of phagocytosis; 4) DC migration; 5) DC maturation; and 6) enhancement of priming and T cell activation. The enhanced phagocytosis of cancer cells undergoing ICD could improve APC functions, leading to tumor-specific T cell immunity.

several ways to 1) induce ICD of cancer cells and 2) recruit DCs into tumor site. The importance of 3) enhancement of phagocytic function of DCs and 4) their maturation and migration to the lymph node are also explained. In addition, our discussion will also focus on the 5) cross-priming between DCs and T cells to generate tumor-specific T cells. Finally, we will cover 6) suitable combined examples for effectively inducing intrinsic tumor immunity.

2.1. Inducing ICD to release neoantigens and DAMPs

Some dying cells elicit extensive immune responses; this phenomenon is called ICD [11–13]. When dying cells undergo ICD, they stimulate local inflammatory responses and trigger the maturation of DCs. Moreover, cancer cells undergoing ICD emit neoantigens and spatiotemporally defined pattern of DAMPs that are capable of acting as danger signals: 1) an "eat me" signal arising from translocation of calreticulin (CRT) from endoplasmic reticulum (ER) to the cell membrane [14]; 2) a "find me" signal including active secretion of ATP [15,16]; and 3) extracellular secretion of nuclear high-mobility group box 1 protein (HMGB1), signal to promote antigen processing and presentation to T cells [17,18] (Table 1). However, as none of these molecules can predict the immunogenicity of cancer cell death with absolute certainty, ICD must be assessed by in vivo experiments using appropriate tumor-mouse models; The gold-standard approach to test the ability of ICD inducers depends on vaccination experiments involving immunocompetent murine models and syngeneic cancer cells.

We also note that, non-ICD or tolerogenic cell death can also release neoantigen. However, epigenetic profiling of human tumors has revealed that only 1% of mutation (neoantigen) causes spontaneous immune responses [19]. Therefore, activation of immune cells by inducing increased DAMPs (immune activating factors) as well as neoantigen burden by ICD is required to elicit anti-tumor immunity.

ICD induction requires reactive oxygen species (ROS)-driven ER stress or (at a minimum) nearly simultaneous activation of ER stress and ROS production [11,12]. The activation of both ER stress and ROS production is critical for trafficking and emission of DAMPs, which may function as danger signals. Recent work has demonstrated that many different cancer cell lines undergo ICD *in vitro*, and their *in vivo* relevance has been verified in a variety of mouse models (Table 2). Abundant pre-clinical immunological data [14,16,18,20] and even retrospective clinical data [21,22] confirm the occurrence of ICD-based anti-tumor immunity (Table 3).

ICD-induced anti-tumor immune responses require that pathogen-associated molecular patterns (PAMPs) or DAMPs released from immunogenic dying cells interact with varied receptors on the surface of innate immune cells, including pattern-recognition receptors (PRRs), phagocytosis-related receptors, and purinergic receptors [16,18,20,23–25]. Recently, much attention has been focused on toll-like receptors (TLRs), a family of PRRs that detect a plethora of PAMPs [26–28]. Upon activation of innate immune cells, such as DCs, the surface expression of co-stimulatory molecules increases; this enhances the antigen presentation capacity, which allows adaptive immunity to be induced via the activation of cytotoxic T cells (CTLs). Although recent studies have focused on improving the maturation and function of DCs, the literature currently lacks an in-depth investigation of the various cancer-immunity-related DC subsets and their maturation.

Several oncolytic viruses are known to induce ICD in preclinical models, and this has been associated with increased cross-priming of tumor-associated antigens. For example, CD40 ligand-expressing adenovirus [29], measles virus [30], and coxsackievirus B318 [31] have been shown to induce ICD phenotypes, including increased surface expression of CRT and higher levels of extracellular ATP and HMGB1 (Table 2). In addition to host-derived DAMPs, oncolytic virotherapy can induce the local expression and release of virus-derived PAMPs; this can enhance the recruitment of immune cells to the TME, leading to efficient cross-priming of tumor-associated antigens (TAAs) [32,33].

Recently, it has been reported the spiky gold nanoparticles coated by polydopamine as a new photothermal agent for inducing ICD of cancer cells. This nanoparticle combined with a sub-therapeutic dose of doxorubicin was shown to trigger robust anti-tumor immune response against metastatic tumors [34].

ICD is characterized by the early cell surface exposure of chaperone proteins, CRT, HSPs, and HMGB1 (a late cell apoptosis marker), all of which affect the maturation of DCs and their uptake and presentation of tumor antigens [35,36]. As such, inducing immunogenic tumor cell death may enhance the effectiveness of DC-based anti-tumor therapies.

2.2. DC recruitment and expansion

Myeloid cells consist of a heterogeneous population of bone marrow-derived cells that play crucial roles in the growth and metastasis of malignant tumors. Myeloid cells are significant infiltrated in the tumors, and actively recruited to the TME. Both *in situ* expansion of DCs and recruitment of them from bone marrow to the tumor site are required to initiate T cell-dependent anti-cancer immunity [37,38]. The density and quality of DCs present in the TME determines the magnitude and class of the T-cell response. Following regional recruitment and expansion of DCs within tumors, the myeloid APCs (which include multiple subsets of DCs) act as professional phagocytes that can acquire tumor antigens to stimulate an anti-tumor immune reaction.

Specific subsets of DCs possess specialized antigen-processing machinery, such as $CD103^+$ DCs in mice (equivalent to $CD141^+$ DCs in humans). $CD103^+$ DCs, which depend on the transcription factors, IRF8, Zbtb46, and Batf3, have developed the capacity to limit acidification of their phagosomes to prevent proteolytic degradation of antigenic peptides. They are able to efficiently cross-present phagocytosed antigens to $CD8^+$ T cells, and thus excel at activating $CD8^+$ T cells even in an immune suppressive TME. Clinically, a quantitative increase of intratumoral $CD103^+$ DCs is expected to play a crucial role in activating anti-tumor immunity by re-stimulating CTLs, thereby enhancing the efficacy of immune checkpoint blockade and adoptive T cell therapies.

FLT3 ligands (FMS-like tyrosine kinase 3 ligands) act as growth factors, play key roles in the survival and proliferation of DCs, support the differentiation of hematopoietic progenitor cells to DC lineages, and can promote the quantitative increase of DC precursors and immature $CD103^+$ DCs in the myeloid compartment of the tumor site [39–41]. Conversely, tumor-released granulocyte colony-stimulating factors (G-CSF) downregulate interferon regulatory factor-8 (IRF8) to reduce $CD103^+$ DC development and increase immune suppressive myeloid cells. A reduction of $CD103^+$ DCs impairs tumor-specific $CD8^+$ T cell function and is correlated with poor patient outcomes [42,43]. FLT3 ligand therapy has been developed for use in patients to bolster $CD103^+$ DC numbers and function, and a recent report suggested that neutralization of G-CSF synergizes with FLT3 ligands *in vivo* to elicit effective anti-tumor immune response [42,44]. Table 3 shows several drugs for inducing DC expansion that are currently being tested in clinical trials.

2.3. Enhancement of phagocytosis

Innate immune cells, such as macrophages, DCs, and B cells, can rapidly remove pathogenic bacteria and cell debris via PRRs that allow them to distinguish self from non-self materials. PAMPs can determine the character of a pathogen; they are recruited to phagosomes, and thus are ideal candidates as linkers of phagocytosis to inflammation. There are several classes of PRRs, such as the TLRs, nucleotide oligodimerization domain-like receptors, retinoic acid-inducible gene-1-like receptors, and several C-type lectin receptors. As DCs are professional APCs of the immune system, they express broad repertoire of PRRs. Upon being activated by antigen uptake, DCs begin migrating to the lymph node, where they will educate T cells. During this migration, they undergo maturation [45–47]; their antigen uptake ability declines,

Table 1
DAMP signals

DAMPs	Receptor	Properties	Cell death type	Emission pathway	Site	Ref
ATP	P2RX7	Acts as a "find me" signal (Immunostimulatory activity) Macrophage recruitment IL-2β secretion by DC	Accidental necrosis Immunogenic apoptosis	Autophagy and PANX1- dependent mechanism Released passively Pre-apoptotic or early apoptotic active secretion	Cytosol	[16,205]
BCL-2	TLR2	Reduces reperfusion injury of skeletal or cardiac muscle when injected extracellularly	Secondary necrosis	Released passively	Mitochondria	[206]
CRT	CD91	ER chaperone Acts as an "eat me" signal	Secondary necrosis Immunogenic apoptosis	Exposure to ER stress through Golgi secretory pathway Released passively Pre-apoptotic or early or mid-apoptotic surface exposure	ER	[14,207,208]
Cyclophilin A	CD 147	Highly pro-inflammatory Induces recruitment of inflammatory cells	Necrosis	Secreted actively	Cytosol	[209]
HSPs	CD91, TLR2, TLR 4	Molecular chaperones Have immunostimulatory activity Induce NK cell activation and DC maturation	Necrosis Immunogenic apoptosis	Released upon PMP detection or secreted via active, exosome dependent routes Released passively Surface exposure	Cytosol	[210,211]
HMGB1	CD24,TLR2, TLR 4, RAGE and TIM3	Multifunctional nuclear factor Has immunostimulatory activity	Accidental necrosis Immunogenic apoptosis Cell death with autophagy	Released upon NMP and PMP detection Released passively Early or mid apoptotic active secretion	Nucleus	[212,213]
F-actin	DNGR1	Helps DCs recognize necrotic cells	Accidental necrosis Secondary necrosis	Released passively Exposed upon plasma membrane permeabilization	Cytosol	[214]
Histones	TLR9	Induce initiation of TLR9- and MyD88-mediated inflammatory responses	Accidental necrosis	Released passively Surface exposure Secreted actively	Nucleus	[215,216]
HMGN1	TLR4	Induces DC maturation, recruitment of APCs	Secondary necrosis	Uncertain	Nucleus	[217,218]
IL-1α	IL-1R	Induces strong pro-inflammatory activity	Accidental necrosis	Released passively	Nucleus	[219]
IL-33	ST2	Induces secretion of pro-inflammatory and TH2 cytokines Repressor of nuclear transcription Anti-inflammatory factor	Accidental necrosis	Released passively Released upon permeabilization of nuclear membrane and plasma membranes	Nucleus	[220,221]
IL-6	IL-6R and GP130	Induces strong pro-inflammatory activity	Necroptosis	Released passively	Mitochondria?	[222,223]
Mitochondrial DNA	TLR9, NLRP3	Induce activation of macrophages and neutrophils Induce activation of NLRP3 inflammasome	Accidental necrosis	Released passively Released upon mitochondrial damage and plasma membrane permeabilization	Mitochondria	[224,225]
Mitochondrial transcription factor A	TLR9 and RAGE	Mitochondrial danger signal Induces activation of DCs	Accidental necrosis	Released passively	Mitochondria	[226,227]
Monosodium urate	Unknown	Derived from uric acid Possesses pro-inflammatory properties Causes DC maturation and neutrophil attraction	Accidental necrosis	Released passively	Cytosol	[228,229]
N-formyl peptides	FPR1	Act as a find me signal Chemoattractant for platelets, monocytes and neutrophils	Necrosis	Released passively Released upon mitochondrial damage and plasma membrane permeabilization	Mitochondria	[224,230]
Reactive carbonyls and oxidation-specific epitopes	CD36, SRA, TLR2, TLR4 and CD14	Enhance antigen presentation with TH2 cell polarization	Apoptosis or necrosis induced by ROS-producing agents or cell death associated with ROS production	Released passively Surface exposed		[231,232]
Ribonucleoproteins, mRNA and genomic DNA	TLR3	Induce strong pro-inflammatory activity	Accidental and secondary necrosis	Released passively	Nucleus	[233,234]
S100 proteins (S100A8, S100A9 and S100A12)	RAGE	Have potent immunostimulatory activity Recruit monocytes and neutrophils	Accidental necrosis	Released passively Secreted via conventional secretory pathways or released upon plasma membrane permeabilization	Cytosol	[235,236]

while improvements are seen in their capacity to digest the absorbed antigens and present them to co-stimulatory molecules or major histocompatibility complexes (MHCs) of the various classes [48,49]. T cells can be activated by the interaction of an MHC class I-presented antigen on the DC surface with the TCR of a CTL; this is called "cross-presentation" [50,51].

Within the TME, the phagocytic function of innate immune cells can be modulated by upregulation of "don't eat me" signals on the tumor

Table 2
ICD inducers

Type I inducer	DAMPs	Site of DAMP induction	Stage of cell death	Main target of cell death	Ref
Type I inducer					
Oxaliplatin	Ecto-CRT, release of HMGB1, release of ATP	ER, autophagy, pannexin channels, lysosomes	Apoptosis	Nucleus	[112,237]
Anthracyclines (doxorubicin, epirubicin, idarubicin, mitoxantrone)	Ecto-CRT, ERp57, release of HMGB1, release of ATP, ecto-HSP70	ER, autophagy, pannexin channels, lysosomes	Apoptosis	Nucleus	[13,14,35,238]
Cyclophosphamide	Ecto-CRT, release of HMGB1	ER	Apoptosis	Nucleus	[239]
Shikonin	Ecto-CRT, ecto-Hsp70, ecto-GRP78	ER	Apoptosis	Mitochondria	[240]
Bortezomib	Ecto-CRT, ecto-Hsp70, ecto-Hsp90	ER	Apoptosis	Cytosol	[211,241]
7A7 (EGFR-specific-antibody)	Ecto-CRT, ERp57, ecto-Hsp70, ectp-Hsp90	ER	apoptosis	Cell surface	[242]
Cardiac glycosides	Ecto-CRT, release of HMGB1, release of ATP	ER, pannexin channels, lysosomes	Apoptosis	Cell surface	[243]
UVC irradiation	Ecto-CRT, ERp57, release of HMGB1, release of ATP	ER, autophagy, pannexin channels, lysosomes	Apoptosis	Nucleus	[244]
Radiotherapy	Ecto-CRT, ecto-HSP70, release of HMGB1	ER, autophagy, pannexin channels, lysosomes	Apoptosis	Nucleus	[245,246]
Bleomycin	Ecto-CRT, ERp57, release of HMGB1, release of ATP	ER, pannexin channels, lysosomes	Apoptosis	Nucleus	[247]
Clostridium difficile toxin B	Ecto-CRT, ecto-Hsp70, ecto-Hsp90, release of HMGB1, release of ATP	ER	Apoptosis	Cytoskeleton	[248]
High hydrostatic pressure	Ecto-CRT, ecto-Hsp70, ecto-Hsp90, release of HMGB1, release of ATP	ER	Apoptosis	Membrane	[249–251]
Microwave thermal ablation	Ecto-CRT, release of HMGB1, release of ATP	ER	Apoptosis	Hyperthermic ablation of cellular components	[252]
Paclitaxel	Ecto-CRT	ER	Apoptosis	Cytosol	[253,254]
PDT with Photofrin	Ecto-CRT, ecto-Hsp70, ecto-Hsp60, release of HMGB1	ER	Apoptosis	Mitochondria, ER	[255]
RIG-I-like helicases (RLH)	Ecto-CRT, release of Hsp70 release of HMGB1	ER	Apoptosis	Cytosol	[256]
Vorinostat (HDAC inhibitor)	Ecto-CRT, release of HMGB1, release of ATP	ER, pannexin channels, lysosomes	Apoptosis	Nucleus, cytosol	[257]
Wogonin	Ecto-CRT, release of HMGB1, release of ATP	ER, pannexin channels, lysosomes	Apoptosis	Mitochondria	[258]
Type II inducer					
PDT with hypericin	Ecto-CRT, ecto-Hsp70, ectp-Hsp90, release of HMGB1, release of ATP	ER, autophagy	Apoptosis	Mitochondria, ER	[210,259]
Oncolytic virus (coxsackievirus B3, adenovirus)	Ecto-CRT, HMGB1 translocation, release of ATP	ER	Apoptosis	ER	[31,32,260]
PtII N-heterocyclic carbene complex	Ecto-CRT, release of HMGB1, release of ATP	ER	Apoptosis	ER	[261]

cell surface, the "tickling" signals of phagocytic cells, and the expression level of the phagocytic machinery on the surface of immune cells. Tumor cells overexpress CD47 as a "don't eat me" signal on their surface in order to avoid being removed by innate immune cells. The CD47:signal regulatory protein alpha (SIRPα) axis is an important molecular interaction that suppresses the activation of phagocytes (e.g., macrophages and DCs) against tumors [52,53]. As the CD47:SIRPα axis functions as an immune checkpoint, it has emerged as one of the most promising new targets for immuno-oncology. The blockade of CD47, particularly using an anti-CD47 antibody, has proven to induce potent anti-tumor efficacy [52,54,55]. Given that phagocytosis participates in both innate and adaptive immunity in cancer, it is notable that CD47 blockade in immunocompetent mice enhances the cross-priming ability of DCs and the generation of a tumor-specific $CD8^+$ T cell response [54–58]. Therapeutics targeting the CD47:SIRPα have shown success in a wide variety of pre-clinical tumor models and are currently conducted in clinical trials for both hematologic malignancies and solid tumors [59] (Table 3). Recently, Weissman's group identified a second "don't eat me" signal and its complementary receptor: they found that the LILRB1 protein on the surface tumor-associated macrophages binds to a β2-microglobulin of MHC class I on cancer cells, and that this inhibits the ability of macrophages to engulf and kill the cancer cells [60]. Human tumors with the high-level surface expression of MHC class I are more resistant to anti-CD47 treatment than those with lower levels of the complex, and inhibition both the CD47-mediated pathway and the LILRB1 pathway significantly slowed tumor growth in mice. Furthermore, CD46 expressed on apoptotic/necrotic cells [61] and cell-to-cell detachment-related CD31 [62] also reportedly inhibit the phagocytic functions of innate immune cells against tumors.

In addition to blocking the "don't eat me" signal, therapeutic strategies can seek to bypass the "tickling" signal to enhance the activation of phagocytes for improved anti-tumor immunity (Table 4). Among the Rho family GTPases, which contribute to engulfment signaling during the phagocytic process, RhoA seems to negatively affect basal engulfment [63,64]. Within the TME, relatively higher levels of Rho-associated protein kinase (ROCK), which acts as a downstream effector of RhoA protein, have been associated with poor prognosis [65]. Given that inhibition of RhoA-mediated signaling in phagocytes enhances the uptake of apoptotic targets [63,64], ROCK has been targeted by researchers seeking to enhance the phagocytic function of macrophages and DCs. For example, inhibition of ROCK with a single agent in mouse models of melanoma showed anti-tumor efficacy, reduced metastasis, and an enhanced $CD8^+$ T cell-mediated immune response [57,66]. Fasudil (approved for pulmonary hypertension and cerebral vasospasm in Japan and China) has been identified as a selective ROCK inhibitor [67]. Statins, which are currently approved for the treatment of hyperlipidemia, also inhibit the RhoA-ROCK signal by hindering the prenylation of RhoA [68,69]. The repositioning of these drugs for cancer immunotherapy could give us an effective anti-cancer agent without requiring the cost and time needed for *de novo* development. The RhoA-ROCK intracellular signal regulates rearrangement of the actin cytoskeleton of a tumor cell to induce migration, adhesion, and proliferation

Table 3
ICV-inducing drugs that are currently being tested in clinical trials

Target	Drug		Tumor type	Phase	Number
DC Expansion	FLT3 ligand	CDX-301	Non-small-cell lung carcinoma (NSCLC)	Phase 2	NCT02839265
		CDX-301	Low-Grade B-cell Lymphoma	Phase 1&2	NCT01976585
		CDX-301	Melanoma	Phase 2	NCT02302339
		CDX-1140, CDX-301	Melanoma/Non-small Cell Lung Cancer/Breast Cancer	Phase 1	NCT03329950
		Flt3 ligand	Stage IV Melanoma/Stage IV Renal Cell Cancer /Recurrent Renal Cell Cancer/Recurrent Melanoma	Phase 2	NCT00019396
		Ad-hCMV-Flt3 ligand	Malignant Glioma/Glioblastoma Multiforme	Phase 1	NCT01811992
		Recombinant Flt3 ligand	Kidney Cancer/Melanoma (Skin)	Phase 1	NCT00020540
		Recombinant Flt3 ligand	Colorectal Cancer/Metastatic Cancer	Phase 1	NCT00003431
Antigen release	Chemotherapy	Carboplatin and Caelyx or doxorubicin	Recurrent Ovarian Cancer	Phase 1&2	NCT01637532
		FLOX	Colorectal Neoplasms Malignant	Phase 2	NCT03388190
	Radiotherapy	Stereotactic body radiotherapy (SBRT)	Melanoma	Phase 1	NCT02406183
		SIR-Spheres	Hepatocellular Carcinoma	Phase 2	NCT03380130
	Oncolytic virus	Pexa-Vec	Colorectal Cancer/Refractory Cancer	Phase 1&2	NCT03206073
Phagocytosis	CD47:SIRPα blockade	Hu5F9-G4	Acute Myeloid Leukemia/Myelodysplastic Syndrome	Phase 1	NCT02678338
		Hu5F9-G4			NCT03248479
		Hu5F9-G4	Colorectal Neoplasm/Solid tumor	Phase 1&2	NCT02953782
		Hu5F9-G4	Lymphoma	Phase 1&2	NCT02953509
		Hu5F9-G4	Solid Tumor	Phase 1	NCT02216409
		TTI-621	Solid Tumors/Mycosis Fungoides/Melanoma/Merkel-cell Carcinoma/Squamous Cell Carcinoma/Breast Carcinoma/Human Papillomavirus-Related Malignant Neoplasm/Soft Tissue Sarcoma	Phase 1	NCT02890368
		TTI-621	Hematologic malignancy/Solid tumor	Phase 1	NCT02663518
		IBI188	Advanced Malignancies	Phase 1	NCT03717103
		ALX148	Metastatic Cancer/Solid Tumor/Advanced Cancer/Non-Hodgkin Lymphoma	Phase 1	NCT03013218
DC migration & maturation	TLR agonists	Poly-ICLC	Melanoma/Metastatic Melanoma/Mucosal Melanoma	Phase 1&2	NCT02126579
		Poly-ICLC	Low-Grade B-cell Lymphoma	Phase 1&2	NCT01976585
		GLA-SE	Adult Soft Tissue Sarcoma	Phase 1	NCT02180698
		MGN1703	Advanced Cancers/Melanoma	Phase 1	NCT02668770
		GNKG168	Relapsed Acute Lymphoblastic Leukemia/Relapsed Acute Myelogenous Leukemia	Phase 1	NCT01743807
		VTX-2337	Metastatic/Persistent/Recurrent/Progressive Solid Tumors	Phase 1	NCT02650635
		VTX-2337	Locally Advanced/Metastatic/Recurrent/ Squamous Cell Cancer of Head and Neck	Phase 1	NCT01334177
		VTX-2337	Recurrent/Persistent Ovarian Epithelial, Fallopian Tube, or Peritoneal Cavity Cancer	Phase 1	NCT01294293
		Resiquimod	Melanoma	Phase 2	NCT00960752
		SD-101	Follicular Lymphoma	Phase 1&2	NCT02927964
		SD-101	Follicular Lymphoma/B-Cell Non-Hodgkin Lymphoma/Lymphoplasmacytic Lymphoma/Mantle Cell Lymphoma/Marginal Zone Lymphoma/Small Lymphocytic Lymphoma	Phase 1	NCT03410901
		SD-101	Lymphoma	Phase 1&2	NCT02254772
		GSK1795091	Cancer	Phase 1	NCT02798978
		Imiquimod	Breast Cancer/Metastatic Breast Cancer/Recurrent Breast Cancer	Phase 1&2	NCT01421017
		Imiquimod	Breast Cancer	Phase 2	NCT00899574
		Imiquimod	Melanoma (Skin)/Metastatic Cancer	Phase 1	NCT00453050
		CPG-7909	Esophageal Cancer	Phase 1&2	NCT00669292
		CPG-7909	Non-Hodgkin Lymphoma/Mycosis Fungoides	Phase 1&2	NCT00185965
Priming and activation	CD40 agonist	Selicrelumab	Solid Tumor/Neoplasms	Phase 1	NCT02304393
		Selicrelumab			NCT02760797
		ADC-1013			NCT02379741
		ADC-1013	Advanced Solid Tumor	Phase 1	NCT02829099
		Selicrelumab			NCT02665416
		Selicrelumab	Pancreatic Cancer	Phase 1	NCT02588443
		Recombinant CD40-ligand	Kidney Cancer/Melanoma (Skin)	Phase 1	NCT00020540
		SEA-CD40	Carcinoma/NSCLC	Phase 1	NCT02376699
		CD40 ligand	Chronic Lymphocytic Leukemia	Phase 1	NCT00458679
		CD40 ligand	Leukemia	Phase 1	NCT00058799
		CD40L-expressing autologous B-CLL cells	Chronic Lymphocytic B-Leukemia	Phase 1	NCT00058786
		CD40L-expressing autologous K562 cells	Melanoma (Skin)	Phase 2	NCT00101166
		CD40L-expressing autologous K562 cells	Lung cancer/Adenocarcinoma	Phase 1&2	NCT01433172
		CD40L-expressing autologous B-CLL cells	Leukemia/Chronic Lymphocytic B-Leukemia	Phase 1	NCT00078520
		APX005M	NSCLC/Melanoma/Urothelial Carcinoma/MSI-H/Head and Neck Cancer	Phase 1	NCT02482168
		APX005M	NSCLC/Metastatic Melanoma	Phase 1&2	NCT03123783
		APX005M	Melanoma	Phase 1&2	NCT02706353
		APX005M	Esophageal Cancer, GastroEsophageal Cancer	Phase 2	NCT03165994
		CP-870,893	Recurrent Melanoma/Stage IV Melanoma	Phase 1	NCT01103635
	CTLA-4 : CD28 blockade	JTX-2011	Cancer	Phase 1&2	NCT02904226
		AGEN1884	Advanced Solid Cancers	Phase 1	NCT02694822

Table 3 (*continued*)

Target	Drug	Tumor type	Phase	Number
	IBI310			NCT03545971
	MEDI5752			NCT03530397
	Ipilimumab			NCT01750983
	Ipilimumab			NCT03203876
	Ipilimumab			NCT03707808
	Tremelimumab			NCT02261220
	Tremelimumab			NCT02705482
	Anti-CTLA-4/PD-1 expressing MUC1-CAR-T	Advanced Solid Tumor	Phase 1&2	NCT03179007
	Anti-CTLA-4/PD-1 expressing EGFR-CAR-T			NCT03182816
	Anti-CTLA-4/PD-1 expressing mesoCAR-T			NCT03182803
	Ipilimumab			NCT03459222
	Tremelimumab	Advanced Solid Tumor	Phase 3	NCT03084471
	Ipilimumab	Metastatic Solid Tumors/Treatment-Refractory Cancers	Phase 1	NCT03388632
	Ipilimumab	Metastatic Tumor/Advanced Tumor	Phase 1	NCT02977156
	BCD-145	Melanoma	Phase 1	NCT03472027
	CP-675,206			NCT00431275
	CP-675,206			NCT00585000
	CP-675,206			NCT00090896
	Ipilimumab			NCT03068624
	Ipilimumab			NCT01400451
	Ipilimumab			NCT02307149
	Ipilimumab			NCT00803374
	Ipilimumab			NCT03293784
	CP-675,206	Melanoma	Phase 2	NCT00610857
	Ipilimumab			NCT02027935
	Ipilimumab			NCT00050102
	Ipilimumab			NCT00028431
	Ipilimumab			NCT03354962
	Ipilimumab			NCT02743819
	Ipilimumab			NCT01449279
	Ipilimumab			NCT03313323
	Ipilimumab			NCT01323517
	Ipilimumab			NCT02970981
	Ipilimumab	Melanoma	Phase 1&2	NCT02385669
	CP-675,206	Melanoma	Phase 3	NCT00257205
	ADU-1604	Metastatic Melanoma	Phase 1	NCT03674502
	Vaccination with anti-CTLA4 mAb RNA-transfected mature autologous DC			NCT01216436
	Ipilimumab			NCT02608437
	Ipilimumab			NCT01838200
	Ipilimumab			NCT02117362
	Ipilimumab			NCT03597282
	Ipilimumab	Metastatic Melanoma	Phase 2	NCT01216696
	Ipilimumab	Metastatic Melanoma	Phase 3	NCT00094653
	Ipilimumab			NCT03445533
	Ipilimumab	Metastatic Melanoma	Phase 4	NCT01856023
	Tremelimumab	Recurrent Melanoma/Stage IV Melanoma	Phase 1	NCT01103635
	Ipilimumab	Malignant Melanoma	Phase 1	NCT01557114
	Ipilimumab	BRAF V600E Mutation Present/Metastatic Melanoma	Phase 1	NCT01940809
	CP-675,206	Malignant Melanoma	Phase 2	NCT00254579
	Ipilimumab			NCT03153085
	Ipilimumab			NCT01302496
	Ipilimumab			NCT02203604
	Ipilimumab			NCT01708941
	Ipilimumab			NCT01970527
	Ipilimumab	High Risk Stage III Melanoma	Phase 3	NCT00636168
	Ipilimumab	Metastatic Melanoma/Mucosal Melanoma/Uveal Melanoma	Phase 2	NCT02158520
	Ipilimumab	Intraocular Melanoma/Melanoma (Skin)	Phase 1	NCT00025181
	Ipilimumab	Intraocular Melanoma/Melanoma (Skin)	Phase 1&2	NCT00058279
	Ipilimumab	Cutaneous Melanoma	Phase 2	NCT03396952
	Ipilimumab			NCT03033576
	Ipilimumab	Recurrent Melanoma/Cutaneous Melanoma	Phase 3	NCT01274338
	Ipilimumab	NSCLC	Phase 1	NCT03527251
	Ipilimumab			NCT03509584
	Tremelimumab			NCT03275597
	REGN4659			NCT03580694
	Ipilimumab	NSCLC	Phase 2	NCT02221739
	Ipilimumab			NCT01331525
	Ipilimumab			NCT02046733
	Ipilimumab	NSCLC	Phase 3	NCT03409614
	Ipilimumab			NCT03515629
	Tremelimumab			NCT02352948
	Tremelimumab			NCT02542293
	Tremelimumab	NSCLC	Phase 1&2	NCT02000947

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Table 3 (*continued*)

Target	Drug	Tumor type	Phase	Number
	Tremelimumab	Metastatic NSCLC/NSCLC	Phase 1&2	NCT03164772
	Ipilimumab	Advanced NSCLC	Phase 2	NCT03430063
	Ipilimumab	Lung Cancer/SCLC	Phase 1&2	NCT03575793
	Tremelimumab	Prostate Cancer	Phase 1	NCT00702923
	Tremelimumab			NCT00113984
	Ipilimumab			NCT03532217
	Ipilimumab			NCT01510288
	Ipilimumab			NCT03477864
	Ipilimumab	Prostate Cancer	Phase 2	NCT01804465
	Ipilimumab			NCT00050596
	Ipilimumab			NCT03061539
	Ipilimumab			NCT02601014
	Ipilimumab	Prostate Adenocarcinoma/Prostate Carcinoma/Recurrent Prostate Carcinoma	Phase 2	NCT00170157
	Ipilimumab	Recurrent Prostate Carcinoma	Phase 1	NCT00064129
	Tremelimumab	Pancreatic Cancer	Phase 1	NCT02868632
	Ipilimumab			NCT01473940
	Ipilimumab			NCT00836407
	Ipilimumab	Pancreatic Cancer	Phase 2	NCT00112580
	Ipilimumab			NCT01896869
	Tremelimumab	Pancreatic Cancer	Phase 1&2	NCT02311361
	Ipilimumab	Breast Cancer	Phase 1	NCT01502592
	Ipilimumab			NCT02453620
	Tremelimumab	Breast Cancer	Phase 2	NCT03430466
	Ipilimumab			NCT03409198
	Ipilimumab			NCT02892734
	Tremelimumab	Malignant Mesothelioma	Phase 2	NCT01655888
	Tremelimumab			NCT01649024
	Tremelimumab			NCT01843374
	Ipilimumab	Head and Neck Squamous Cell Carcinoma	Phase 1	NCT03690986
	Tremelimumab	Head and Neck Squamous Cell Carcinoma	Phase 2	NCT03624231
	Tremelimumab	Head and Neck Squamous Cell Carcinoma	Phase 3	NCT02551159
	Ipilimumab	Gliosarcoma	Phase 1	NCT02311920
	Ipilimumab			NCT03422094
	Ipilimumab	Glioblastoma	Phase 1	NCT03233152
	Ipilimumab	Renal Cell Carcinoma	Phase 2	NCT03297593
	Tremelimumab			NCT03598816
	Tremelimumab	Metastatic Colorectal Cancer	Phase 1&2	NCT03202758
	Tremelimumab	Colorectal Neoplasm	Phase 2	NCT00313794
	Ipilimumab	Gastrointestinal Stromal Tumor	Phase 1	NCT01643278
	Ipilimumab	Gastrointestinal Stromal Tumor	Phase 2	NCT02880020
	Tremelimumab	Ovarian Cancer/Fallopian Tube Cancer/Peritoneal Neoplasms	Phase 1&2	NCT02571725
	Ipilimumab	Ovarian Cancer/Fallopian Tube Cancer/Peritoneal Neoplasms	Phase 2	NCT02498600
	Tremelimumab	Biliary Tract Neoplasm/Liver Cancer/Hepatocellular Carcinoma/Biliary Cancer	Phase 1	NCT01853618
	Tremelimumab	Biliary Tract Neoplasm/Liver Cancer/Hepatocellular Carcinoma	Phase 2	NCT02821754
	Tremelimumab	Hepatocellular Carcinoma	Phase 2	NCT01008358
	Tremelimumab	Ovarian Cancer	Phase 1&2	NCT03249142
	Tremelimumab	Infiltrating Bladder Urothelial Carcinoma Sarcomatoid Variant/Infiltrating Bladder Urothelial Carcinoma, Micropapillary Variant	Phase 1	NCT02812420
	Tremelimumab	Bladder Urothelial Carcinoma	Phase 2	NCT03601455
	Tremelimumab	Muscle-invasive Bladder Cancer	Phase 2	NCT03234153
	Tremelimumab	Endometrial Cancer	Phase 2	NCT03015129
	Tremelimumab	Germ Cell Tumor	Phase 2	NCT03081923
	Tremelimumab	Head and Neck Cancer	Phase 1&2	NCT03019003
	Tremelimumab	Locally Advanced Head and Neck Cancer	Phase 2	NCT03426657
	Tremelimumab	Malignant Glioma	Phase 2	NCT02794883
	Tremelimumab	Lymphoma	Phase 1	NCT00047164
	Tremelimumab	Multiple Myeloma	Phase 1	NCT02716805
	Tremelimumab	Diffuse Large B-Cell Lymphoma	Phase 1	NCT02549651
	Tremelimumab	Colorectal Neoplasm/Melanoma/Prostatic Neoplasm	Phase 2	NCT00378482
	Tremelimumab	Head and Neck Squamous Cell Carcinoma/Lung Cancer/esophageal Cancer	Phase 1&2	NCT03212469
	Tremelimumab	Colorectal Cancer/Liver Metastases	Phase 1	NCT02754856
	Tremelimumab	Advanced Solid Tumors/Breast Cancer/Head and Neck Cancer/Cervix Cancer/Prostate Cancer	Phase 1&2	NCT03518606
	Tremelimumab	Soft Tissue Sarcoma	Phase 1&2	NCT03116529
	Ipilimumab	Inoperable esophageal Cancer	Phase 2	NCT03437200
	Ipilimumab	Anal Canal Squamous Cell Carcinoma	Phase 2	NCT02314169
	Ipilimumab	Acinar Cell Carcinoma/Adenoid Cystic Carcinoma/Adrenal Cortex Carcinoma	Phase 2	NCT02834013
	Ipilimumab	Merkel Cell Carcinoma	Phase 2	NCT01913691
	Ipilimumab	Salivary Gland Carcinoma	Phase 2	NCT03146650
	Ipilimumab	Acute Myeloid Leukemia/Myelodysplastic Syndrome	Phase 1	NCT02846376
	Ipilimumab	Relapsed or Refractory Myelodysplastic Syndrome/Acute Myeloid	Phase 1	NCT02890329

Table 3 (*continued*)

Target	Drug		Tumor type	Phase	Number
			Leukemia		
		Ipilimumab	Refractory B-Cell Non-Hodgkin Lymphoma	Phase 1	NCT01729806
		Ipilimumab	B Acute Lymphoblastic Leukemia/CD19-Positive Neoplastic Cells Present	Phase 1	NCT02879695
		Ipilimumab	Extranodal Marginal Zone B-cell Lymphoma of Mucosa-associated Lymphoid Tissue Nodal Marginal Zone B-cell Lymphoma/Recurrent Grade 1 Follicular Lymphoma	Phase 1&2	NCT02254772
		Ipilimumab	Adult Grade III Lymphomatoid Granulomatosis/B-cell Chronic Lymphocytic Leukemia/Cutaneous B-cell Non-Hodgkin Lymphoma	Phase 1&2	NCT00089076
		Ipilimumab	Sarcoma/Wilm's Tumor/Lymphoma/Neuroblastoma	Phase 1	NCT01445379
		Ipilimumab	Melanoma/Brain Metastases	Phase 2	NCT02115139
		Ipilimumab	Soft Tissue Sarcoma/Bone Sarcoma/Chondrosarcoma	Phase 2	NCT02982486
		Ipilimumab	Melanoma/Renal Cell Carcinoma/NSCLC	Phase 1&2	NCT02983045
		Ipilimumab	Advanced Cancer/Melanoma/NSCLC	Phase 1&2	NCT02658890
		Ipilimumab	Uveal Melanoma/Liver Metastases	Phase 1	NCT03408587
		Ipilimumab	Malignant Neoplasms of Digestive Organs/Hepatocellular Carcinoma	Phase 2	NCT03222076
		Ipilimumab	Synovial Sarcoma	Phase 2	NCT00140855
		Ipilimumab	Mesothelioma	Phase 2	NCT02716272
		Ipilimumab	Metastatic Leiomyosarcoma	Phase 2	NCT02428192
		Ipilimumab	Advanced or Metastatic Melanoma/Advanced or Metastatic NSCLC	Phase 4	NCT03673332
		Abatacept	Recurrent/Refractory Plasma Cell Myeloma	Phase 2	NCT03457142
	4-1BB agonist	Utomilumab	Neoplasms	Phase 1	NCT02315066
		Utomilumab	Advanced Solid Tumors	Phase 1	NCT02179918
		Utomilumab			NCT02444793
		Utomilumab	Lymphoma/Head and Neck Squamous Cell Carcinoma/NSCLC/Renal Cell Carcinoma/Malignant Melanoma	Phase 1	NCT01307267
		Utomilumab	Acute Myeloid Leukemia	Phase 2	NCT03390296
		Utomilumab	Breast Cancer	Phase 2	NCT03414658
		Utomilumab	Advanced Cancer	Phase 2	NCT02554812
		Urelumab	Advanced Solid Tumors/ B-Cell Non-Hodgkin Lymphoma	Phase 1&2	NCT02253992
	OX40 agonist	Vonlerolizumab	Neoplasms	Phase 1	NCT02410512
		PF-04518600			NCT02315066
		PF-04518600	Acute Myeloid Leukemia	Phase 2	NCT03390296
		PF-04518600	Advanced Cancer	Phase 2	NCT02554812
		MEDI0562	Head and Neck Cancer/Melanoma	Phase 1	NCT03336606
		MEDI6469	Advanced Solid Tumors/Aggressive B-cell Lymphomas	Phase 1&2	NCT02205333
		BMS 986178	B-Cell Non-Hodgkin Lymphoma/Follicular Lymphoma	Phase 1	NCT03410901
		MEDI6383	Recurrent or Metastatic Solid Tumors	Phase 1	NCT02221960
	CD27 agonist	Varlilumab	Glioma/Malignant Glioma/Astrocytoma, Grade II	Phase 1	NCT02924038
		Varlilumab	Glioblastoma	Phase 2	NCT03688178
		Varlilumab	Solid Tumors	Phase 1&2	NCT02543645
		Varlilumab	Squamous Cell Carcinoma of the Head and Neck/Ovarian Carcinoma/Colorectal Cancer (CRC)/Renal Cell Carcinoma/Glioblastoma (Phase ll Only)	Phase 1&2	NCT02335918
		Varlilumab	Melanoma	Phase 2	NCT02302339
		MDX-1203(CD27 ligand antibody)	Renal Cell Carcinoma/Non-hodgkin's Lymphoma	Phase 1	NCT00944905
		ARGX-110(CD27 ligand antibody)	Advanced Cancers	Phase 1&2	NCT01813539
	GITR agonist	MEDI1873	Advanced Solid Tumors	Phase 1	NCT02583165
		BMS-986156			NCT03335540
		MK-1248			NCT02553499
		INCAGN01876	Advanced and Metastatic Solid Tumors	Phase 1/2	NCT03277352
		INCAGN01876			NCT02697591
		INCAGN01876			NCT03126110
		OMP-336B11	Locally Advanced Malignant Neoplasm / Metastatic Cancer	Phase 1	NCT03295942
		OMP-336B11			
		TRX518	Solid Tumors	Phase 1	NCT02628574
		GWN323			NCT02740270
		MK-4166			NCT02132754
		BMS-986156	Solid Tumors	Phase 1/2	NCT02598960
		MK-4166	Glioblastoma /Glioblastoma Multiforme	Phase 1	NCT03707457

[65,70], suggesting that blockade of this axis would target not only innate immune cells, but also tumor cells.

The engulfing activity of phagocytes can be regulated by modulating the expression of components of the phagocytic machinery (e.g., phagocytic receptors) and/or the signaling pathways responsible for cytoskeletal rearrangement (e.g., RhoA and Rac1). For example, nuclear receptor liver X receptor (LXR) is known to increase the expression of Mer (a ligand of the "eat me" signal) upon its contact with an apoptotic cell to enhance phagocytic action [71]. The peroxisome proliferator-activated receptors (PPARs) represent another type of nuclear receptor; among them, the gamma type increases the expression CD36 and enhances phagocytosis by facilitating binding to the apoptotic cell [72]. Various agonists of PPARγ, including rosiglitazone, pioglitazone, and lobeglitazone, are currently in clinical use for the treatment of type 2 diabetes mellitus [73].

Table 4
Phagocytosis enhancers

Phagocytosis enhancer	Target	Subtypes	Drugs	Ref
CD47	CD47 : SIRPα	Tethering signal	Anti-CD47, Anti-SIRPα SIRPαFc	[52–55,57,58,116,262,263]
β2M of MHC 1	β2M of MHC 1 : LILRB1	Tethering signal	Anti-LILRB1	[60]
CD46		Tethering signal		[61]
CD31	CD31 : CD31	Tethering signal		[62]
ROCK inhibitor	ROCK	Tickling signal	Fasudil, Y27632	[63,64]
HMG-CoA reductase inhibitors	RhoA	Tickling signal	Statin	[69,264]
LXR agonists	LXR	Engulfment signal	GW3965	[71]
PPARγ activators	PPARγ	Engulfment signal	Thiazolidinediones (TDZs) GW9662	[72]

2.4. DC migration to lymph node and maturation

Draining lymph nodes (dLNs) serve to organize immune responses by bringing APCs and T cells together spatially and temporally to promote T cell proliferation. When DCs discern alerting signals, they quickly undergo activation, migration from the tissue to the dLNs, and maturation. Therefore, strategies to induce strong inflammation can be considered to support DC maturation and augment DC migration.

$CD103^+$ DCs in the TME, which are required for $CD8^+$ T cell cross-priming, can migrate from the tumor to dLNs after tumor antigen uptake [74]. This process requires the chemokine receptor, CCR7: recent reports showed that CCR7-deficient mice lack $CD103^+$ DC-mediated antigen transport to the dLNs [74,75] and increased expression of CCR7 has been reported to promote the migration of DCs from peripheral tissues into the dLNs [76]. CCR7 is also responsible for a strong anti-tumor $CD8^+$ T cell immune response that is correlated with $CD8^+$ T cell infiltration and patient outcomes [74,77]. Therefore, therapeutic strategies to drive DCs into the dLNs could conceivably improve the cross-priming of anti-tumor T cells. For example, the engagement of FcγR by IgG immune complexes has been reported to increase the CCR7 expression and matrix metalloproteinase (MMP) production of DCs, thereby promoting the CCR7-dependent migration of DCs from peripheral tissues into the dLNs [75]. In addition, previous studies have demonstrated that TLR4 agonist such as lipopolysaccharide or angelan is important for inducing DC migration [78,79].

As mentioned above, FLT3 ligand injections dramatically expand $CD103^+$ DC progenitors in the bone marrow. However, it has been also reported that immature form of $CD103^+$ DCs cannot efficiently prime T cells, and they inhibit tumor immunity by priming naïve T cell to $Foxp3^+$ Treg cells [40,80,81]. Thus, to activate anti-tumor T cell immunity, relevant strategies for maturation of $CD103^+$ DCs should be required. Among the APCs, $CD103^+$ DCs (and their human counterpart, $CD141^+$ DCs) uniquely express TLR3 [82,83]. TLR3 recognizes double-stranded RNA of virus and its synthetic analog, polyriboinosinic: polyribocytidylic acid (poly I:C) and induces DC maturation and type I IFN production [84]. Production of type I IFN by the $CD103^+$ DC lineage is required for the priming of T cells against tumor antigens. In accordance with the previous study, the combination of FLT3 ligands with TLR3 ligand has been shown to activate $CD103^+$ DC progenitors in tumors, promote B16 tumor regression, and enhance the response to PD-L1 immune checkpoint blockade [40].

The interaction of PAMPs with TLRs enhances the immune response by engaging TLRs. For example, imiquimod, a TLR7 agonist that was first approved by the FDA in 1997, is currently being used to treat basal cell carcinoma (a skin cancer) [85,86]. Imiquimod stimulates the release of pro-inflammatory cytokines, such as IFN-α, IL-6, and TNF-α, and activates DC maturation through TLR7 [87,88]. Another TLR agonist, bacillus Calmette-Guérin (BCG; attenuated *Mycobacterium bovis* used for vaccination), interacts with innate immune cells via diverse PRRs, including TLR2 and 4 [89]. Accumulated clinical reports suggest that intravesical BCG injection is the preferred first-line treatment for non-muscle invasive bladder cancer [90,91].

2.5. DC-T cell interaction

Increasing attention has recently focused on T cell priming as a positive predictor for the responsiveness to blockade of PD-1 or PD-L1 [92,93]. T cell priming is a sophisticated process that requires multiple APC-originating stimulatory signals. The binding of TCR to MHC/antigenic peptide complex (signal 1) offers specificity to T cell priming, but further co-stimulatory signals (signal 2) are also required. For example, CD28 can activate T cells by binding to CD80 or CD86 on APCs to trigger the production of interleukin-2 (IL-2). Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is homologous to CD28 and binds CD80 or CD86 with high affinity [94]. During the course of immune reaction, CTLA-4 is upregulated and outcompetes CD28, inhibiting of T cell proliferation and reducing IL-2 production [95,96]. The identification of CTLA-4 led to the development of the anti-CTLA-4 antibody, which was the first immune checkpoint blockade approved by the FDA [97].

CD40 is a member of the tumor necrosis factor (TNF) receptor superfamily that is generally expressed on DCs, and macrophages, and B lymphocytes. Signaling via CD40 induces the maturation of DCs, which play a crucial role in activating CTLs. CD40 ligand (also called CD154) is expressed on activated T cells. Engagement of CD40 on APCs induces positive signaling that leads to the expression of CD80/86, the production of IL-12, and the stimulation of antigen-presentation [98]. In the mouse model for pancreatic ductal adenocarcinoma (PDAC), treatment with an agonistic anti-CD40 antibody is associated with massive infiltration of CTLs into PDAC tumors and subsequent tumor regression [99]. Recent work has shown that CD40 agonists demonstrate synergistic activity in combination with PD1:PDL1 immune checkpoint blockades, and that this propagates durable anti-tumor immune responses [100]. CD40 immunotherapy in combination with gemcitabine and nab-paclitaxel has significant anti-tumor activity in an orthotopic pancreatic cancer mouse model that shows almost no response to immune checkpoint blockade [101]. A phase I study of the use of a CD40 agonist in combination with gemcitabine in patients with PDAC has also yielded anti-tumor activity [102,103].

Other TNF receptors, including 4-1BB, OX40, CD27, and glucocorticoid-induced TNF receptor (GITR), also contribute effective co-stimulatory signals that are required to improve the differentiation and functions of T cells [104,105]. OX40 is a co-stimulatory receptor that binds to the OX40 ligand to initiate cellular signaling events required for full activation of T cells. Agonists that mimic the effect of OX40L can boost OX40 signaling and potentially overcome the suppression of the anti-tumor immune response in patients with cancer [106,107]. Recently, modulation of the GITR/GITR ligand axis has been reported to provide the desired biological outcome of inhibiting Treg cell's function while activating $CD8^+$ T effector cells in preclinical

tumor models [108–111]. In order to harness this co-stimulatory signaling, many TNFR agonists have been developed and are currently being tested in phase I/II clinical trials in combination with anti-PD-1 or anti-PD-L1 antibodies (NCT02179918, NCT02845323, NCT02253992, NCT02335918, NCT03038672, NCT02553499, NCT02132754, NCT02740270, NCT02598960, NCT03029832, NCT02528357).

2.6. Examples of intrinsic cancer vaccination

Inducing "intrinsic cancer vaccination" by utilizing the initial stage (steps 1-3) of the cancer-immunity cycle is expected to trigger a full-fledged anti-cancer immune response. Some chemotherapeutics, such as doxorubicin, mitoxantrone, and oxaliplatin, have been reported to induce ICD of cancer cells, leading to activation of anti-tumor immune responses [11–14,16,18,112]. However, the use of ICD inducers (e.g., doxorubicin) alone appears insufficient to induce anti-tumor immunity in cancer patients and spontaneous tumor mouse models with an immunosuppressive TME [113]. In addition, chemotherapy has also reported to have toxicity on immune cells and potential direct immunosuppressive effects. For example, higher dosages of cyclophosphamide induce immune suppression by the complete eradication of hematopoietic cells and rather enhance the accumulation of myeloid-derived suppressor cells in the TME [114]. Likewise, daunorubicin belonging to the anthracycline group has been shown to provoke leukopenia by inducing cell death in both resting and active peripheral blood lymphocytes [115]. Moreover, some solid tumors have been shown to resist the enhancers of phagocytosis, including CD47 blockade and ROCK inhibitors [60,70,116]. To overcome these limited effects of monotherapies, it is necessary to trigger immunogenic clearance at the early stages of the tumor immune response, as this will convert the immunosuppressive TME to an immunogenic microenvironment and propagate immunity against cancer. Therefore, we suggest that inducing the immunogenic killing of tumor cells (Table 2) in conjunction with improving DC function (e.g., enhancing phagocytosis, Table 4) would be a suitable combined strategy to effectively awaken intrinsic tumor immunity.

Recently, the combined application of ROCK blockade (Y27632) and doxorubicin was reported to elicit anti-tumor immunity in various tumor models [57]. This combination strategy markedly enhanced the DC-mediated phagocytosis of immunogenic dying cells and the cross-presentation of specific tumor antigens, compared to each monotherapy. Notably, combining doxorubicin with ROCK blockade significantly increased T cell priming and intratumoral $CD8^+$ T cell infiltration even in spontaneous breast tumor mouse models. These results highlight the ability of intrinsic cancer vaccination to awaken our body's immune response against immunosuppressive tumors to augment tumor-specific immunity. In addition, this synergism was not seen in cells treated with cisplatin (which does not induce ICD) and a ROCK inhibitor, suggesting that ICD by doxorubicin is essential for strong anti-tumor immunity in this system.

In addition, intratumoral administration of G100, a synthetic TLR4 agonist, was reported to induce turning cold tumors to hot, resulted in facilitating meaningful immune responses in patients with advanced Merkel cell carcinoma [117]. Note that TLR4 agonist glucopyranosyl lipid adjuvant–stable emulsion (GLA-SE) combined with radiation therapy is currently being studied in patients with metastatic sarcoma in the phase 1 clinical trial (NCT02180698).

Other studies have combined oncolytic viruses with chemotherapeutic drugs to induce ICD in preclinical models and human patients [32,118]. These combination therapies were found to trigger the release of HMGB1 and ATP to the extracellular environment as well as expose surface CRT [32]. A study combining hTert-Ad (human telomerase reverse transcriptase promoter-regulated adenovirus) with the proteasome inhibitor, bortezomib, found that the use of this combined treatment *in vitro* triggered features of enhanced ER stress, unfolded protein response (UPR) activation and associated apoptotic cell death, and that this translated into *in vivo* anti-tumor activity [119]. Moreover, $CD8^+$ T cell depletion was found to abolish the therapeutic benefit of the combination treatment. Another combinatorial therapy using oncolytic herpes simplex virus-1 and the ICD-inducing drug, mitoxantrone, was reported to enhance anti-tumor therapeutic efficacy in a preclinical murine breast cancer model [120]. Because oncolytic virus-driven PAMPs can activate DCs to cross-prime T cells, these combination therapies can also be examples of the intrinsic cancer vaccination strategy.

Currently, nano-formulation has been emerged as an engineered platform for the encapsulation and delivering of immunotherapeutic drugs (e.g., antigens, adjuvants, phagocytosis enhancers, and immune checkpoint blockades) to specific site, thereby protecting the cargos from their rapid elimination and increasing the uptake efficiency by target cells, resulting in enhanced immune responses. For these reasons, commercial nanoplatforms, Doxil and Abraxane have been approved in clinic. In particular, nanoplatform enables to successfully co-deliver intrinsic cancer vaccination inducers via various chemical- or physical modification techniques, leading to elicit anti-tumor immunity. In this section, we provide several examples of nano-immunotheraputics currently being developed, capable of improving efficacy of intrinsic cancer vaccination.

The co-delivery of an ICD inducer with a CD47 antagonist into the TME was shown to trigger the emission of danger signals from dying cancer cells and initiate a cellular immune response [121]. In this work, the authors modified human ferritin to contain a Sirpα variant (FHSirpα) that is capable of binding and antagonizing CD47 (a "don't eat me" signaling molecule) to enhance the phagocytosis of cancer cells by bone marrow-derived macrophages (BMDMs) and DCs (BMDCs). Nanocages containing doxorubicin (FHSirpα-dox) were shown to dramatically improve tumor regression and anti-tumor immunity in various tumor models. In addition, no tumor development was observed in treated mice re-challenged with the same tumor cells, indicating that a persistent tumor-specific immunity had been generated.

Nanoparticles for co-delivery of ICD inducer and TLR agonist has been also employed for improving an anti-tumor immune response. Paclitaxel (PTX) is clinically approved chemical reagent that can induce ICD. Seth at al. demonstrated that combination strategy using low dose PTX and TLR7 agonist, imiquimod, synergistically induced effective anti-tumor response. By using water soluble polymer (γ-glutamic acid; γ-PGA), PTX and imiquimod formed crystalline microstructure and co-delivered for treatment of B16F10 melanoma. This nano-formulated reagent showed significant tumor cell killing effect and promoted DC proliferation and activation [122]. PLGA (poly-lactic-co-glycolic acid) biodegradable microparticles loaded with doxorubicin and CpG oligodeoxynucleotides provoked tumor specific T cell immunity which lead to the entire eradication of lymphoma [123]. Recently, Liu et al., designed a dual pH-responsive multifunctional nanoparticle system based on poly(L-histidine) and hyaluronic acid for combining doxorubicin and resiquimod (R848, TLR7/8 agonist). They showed that these nanoparticles mediated simultaneous and targeted delivery of chemotherapy and immune regulator, leading to significantly inhibit tumor growth by regulating anti-tumor immunity [124].

Lu et al., reported the combination therapy with inducing ICD and inhibiting immunosuppressive indoleamine 2,3-dioxygenase (IDO) pathway as another example of the intrinsic cancer vaccination strategy. They developed the self-assembling lipid nanovesicle constructed by phospholipid-conjugated prodrug, indoximod (IND, an IDO pathway inhibitor to improve T cell function in cancer) and trapped oxaliplatin in the mesoporous silica. This drug triggered significant expression of CRT and HMGB-1 in the tumor site and increased expression of TLR4 of $CD45^+/CD11b^+/CD11c^+$ population in the PDAC syngenic mouse model [125]. Further, they also developed doxorubicin-encapsulated IND-liposomes that induced ICD in breast cancer cells (4T1) by increasing surface CRT and releasing ATP and HMGB1. They showed that doxorubicin encapsulated IND-liposomes enhanced DC activation ($CD80^+$, $CD86^+$, $CD103^+$), $CD8^+$ T cell infiltration into the tumor tissue,

inhibited significant tumor growth, and prolonged survival rate in the 4T1 mouse model [126].

Furthermore, designed nanoparticles for combining photothermal/photodymanic therapy with ICD inducers or adjuvants have reported to trigger robust anti-cancer immune responses and reduce the risk of tumor recurrence [127,128].

To efficient delivery of tumor antigens and poly(I:C) to immune cells, biodegradable poly(lactic-co-glycolic acid) nanoparticle coated with an agonistic anti-CD40 monoclonal antibody has also been developed. Targeting nanoparticle to CD40 led to selective delivery of nanovaccine to DCs, improved T cell priming against tumor associated antigens, and enhanced tumor control [129].

Collectively, various types of nanoparticles have been developed and tuned for the cancer immunotherapy. Although challenges continues to exist in the field of nanoparticles, especially in achieving clinical applications in human, current studies clearly show that nanoplatform holds the potential promising as a new class of immunotherapy.

3. The benefits of intrinsic cancer vaccination strategy

3.1. Moving beyond current cancer vaccines

Therapeutic cancer vaccines have been developed for various types of cancer using a known non-self single antigen, a combination of single antigens, tumor derived peptides or total tumor cell lysates [130–132]. Initially, whole-cell lysate preparations of gamma-irradiated cancer cells (GVAX®), were administered with granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjuvant; however, this strategy failed to propagate an anti-tumor effect in the initial clinical phase [133]. Furthermore, whole-cell vaccines, tumor associated antigens and peptide-based cancer vaccination have also shown limited efficacy in sufficient induction of T cell immunity [132,134].

To bypass the first step of targeting tumor cells *in vivo*, *ex vivo* manipulated DCs have been used as therapeutic cancer vaccines. In such strategies, autologous DCs are expanded, pulsed with an antigen *ex vivo* and reinjected back into the patient [135]. Sipuleucel-T (provenge®) is an example of a DC-based vaccine; it contains antigen prostatic acid phosphatase (PAP) and GM-CSF, has been approved by FDA for the treatment of advanced prostate cancer [136]. However, it should be noted that the complex and costly *ex vivo* manipulation procedures using autologous DCs may alter the function of re-administered cells.

For the current cancer vaccines to work, the target tumor antigen must be expressed constantly. Clones that do not express that particular antigen are resistant to the treatment, accounting for tumor relapse and low therapeutic benefit [3,132,137]. For example, a phase III clinical trial of Tecemotide (Merck) in patients with non-small cell lung cancer has failed due to low clinical efficacy [138,139], and GlaxoSmithKline discontinued clinical trials of cancer vaccination with melanoma-associated antigen A3 (MAGE A3) based on unsatisfactory clinical outcomes in melanoma and non-small cell lung cancer [138,140].

"Immunoediting" is a dynamic interaction between tumor cells and the immune system that includes the immune escape mechanism of tumor cells, which enables them to progress against the immunosurveillance of the immune system [141]. It is thought that tumor immunoediting also occurs during vaccination therapy of established tumors and contributes to tumor progression or relapse. Vaccination therapy requires appropriate processing of TAAs and their display on the surface of APCs via MHC class I molecules [142,143]. However, tumor cells can change themselves by altering the antigen processing/presenting machinery, downregulating the expression of MHC class I molecules, losing antigens, and/or inducing anti-apoptotic mechanisms. In addition, chronic exposure to TAAs and the lack of co-stimulatory molecules on most solid tumors may cause activated T cells to be anergized [137,144,145]. However, intrinsic cancer vaccination strategies can promote T cell priming, block the immune escape mechanism of tumor cells and increase tumor-infiltrated T cells within TME. Because these strategies intrinsically awaken our own immune system by ameliorating immunosuppressive TME and activating DCs to generate polyclonal tumor-specific T cells so that these cells will amplify and become effector T cells. It may allow for the clinical translation of broadly applicable cancer vaccines that overcome the immune-tolerance pathways in the TME (Table 3).

3.2. Abscopal effect

The abscopal effect is the regression of an untreated distant tumor following localized treatment [146,147]. It has been shown that systemic and durable anti-cancer-immunity can be induced through a stepwise immune response triggered by local application of an ICD inducer, such as radiation therapy or photodynamic therapy (PDT) [128,148–150]. Given the immune suppressive nature of the TME, intrinsic cancer vaccination therapy directed to the tumor site is also likely to induce an abscopal effect by fully activating tumor-specific immunity. Potent anti-tumor T cells formed at one tumor site must be capable of attacking distant tumor lesions, because completely activated cytotoxic T cells do not require co-stimulatory signals to kill their targets and are insensitive to inhibitory signals. [151–153]. Therefore, an effective *in situ* intrinsic vaccination strategy should yield a T cell-mediated systemic response in the setting of localized treatment, similar to the abscopal effect derived from radiotherapy [154].

3.3. Long-term memory

Although extensive efforts have been made to develop a cancer vaccine, the available options do not yield beneficial anti-tumor effects in most cancer patients [137]. Even vaccines that use an immunogenic epitope capable of inducing an impressive CTL response have reportedly failed to generate a consistent clinical response, suggesting that tumor-specific $CD8^+$ T cells alone are insufficient to induce potent anti-tumor immune responses [155–158]. Recent studies have also demonstrated the critical importance of $CD8^+$ T cell memory achieve a sustainable and consistent anti-tumor immune response [155,159,160].

Following the initial exposure to a pathogen, T cells are primed, differentiate into effectors, and undergo a rapid expansion of the cell population. This is followed by a contraction phase that leaves behind a population of antigen-experienced T cells that further differentiate into memory pool that can exist for long periods. Immunologic memory is a hallmark of the adaptive immune response and guarantees that the host will be able to rapidly activate that efficiently removes the pathogen upon re-exposure. It is generally accepted that the initial CD8+ T cells surviving at contraction phase exhibit an effector-memory cell (Tem) phenotype, whereas memory CD8+ T cell populations found long after clearance of infection consist frequently of central memory T cells (Tcms).

Classically, the Tem and Tcm $CD8^+$ T cells subsets can be distinguished by their expression of certain surface molecules: Tcms express higher levels of the homing receptors, CD62L and CCR7, while Tems express low levels of CD62L and CCR7. Tems are mainly located in the peripheral tissues and cause an immediate immune response upon exposure of the external antigen, while Tcms can migrate to the T cell zone, where they contribute to inducing a systemic immune response [155].

Memory $CD8^+$ T cells can be exhausted by chronic antigen exposure in the TME, and/or their function can be inhibited by immune suppressive factors, such as TGF-β secreted from DCs and Treg cells [161]. Therefore, in the chronic antigen exposure state, conventional therapeutic cancer vaccines that target a single antigen, may fail to amplify T cell memory population [155]. In order to overcome these problems and generate sustainable $CD8^+$ T cell memory, proper antigen uptake of DCs and their surface expression of co-stimulatory signals are

essential, as is the helper T cell-mediated secretion of IL-2, IL-7, and IL-15 [162,163]. Combined strategies to increase neoantigen/DAMP release and enhance phagocytosis have been found to improve the activity of DCs (e.g., antigen processing and co-stimulatory molecule expression) to produce anti-tumor-specific T cells [57]. Remarkably, innate immune cells activated with exposure to various antigens by combinational strategy of intrinsic cancer vaccination may boost naive T cell to vigorous proliferate and differentiate into effector T cells as well as Tems and Tcms [164–166]. Thus, intrinsic cancer vaccination would be expected to provide long-term tumor-free survival through continuous surveillance and elimination of malignant cells.

4. Combination cancer therapy with immune checkpoint blockade

Monoclonal antibodies targeting the co-inhibitory immune checkpoint have demonstrated clinical responses in various malignancies, including metastatic melanoma, non-small cell lung cancer, and Hodgkin lymphoma. Ipilimumab, an antibody against CTLA-4, represents the first attempted immune checkpoint blockade and is undergoing clinical trials for various solid tumors, including advanced melanoma [96,167–170]. Ipilimumab has been demonstrated to prolong overall survival in patients with solid tumors. In a comprehensive analysis of 12 studies, the 3-year survival rate of patients with ipilimumab-treated advanced melanoma was 26%, while the 10-year survival rate of all patients treated with the drug was approximately 20% [171]. The successes of the anti-CTLA-4 clinical trials have encouraged the development of other immune checkpoint blockades. Strategies aimed at blocking PD-1/PD-L1 signaling, which inhibits T cells, have been assessed in clinical trials [172–174]. The anti-PD-1 agents, nivolumab and pembrolizumab, have shown less toxicity, better overall survival rates, and higher objective response rates than ipilimumab for a wide range of cancers, including melanoma, non-small cell lung carcinoma, renal cell carcinoma, Hodgkin lymphoma, and ovarian cancer [175–177]. In one study, the overall response rate was 11% for chemotherapy but 32% for the anti-PD-1 agent, nivolumab, among melanoma patients who did not respond to anti-CTLA-4 therapy [178]. Combined treatment with anti-CTLA-4 and anti-PD-1 might show synergistic therapeutic potential because they regulate T cell activation via distinct mechanisms. Surprisingly, recently published clinical results indicate that combination therapy with nivolumab and ipilimumab in advanced melanoma showed better overall survival than either single treatment, yielding an objective response rate of 58% [179].

However, some patients, even those with melanoma, have failed to respond at all (innate resistance) or showed an initial response that was followed by relapse (acquired resistance) [180–182]. Failure of immune checkpoint inhibition therapy can result from defects in the process of (re-)activation and failure of the clonal expansion of tumor-reactive $CD8^+$ T cells in the immunosuppressive TME [4,5,183]. Even when cross-presentation and cross-priming of T cell is successful, the expanded clones of cytotoxic T cells may face a hostile TME that precludes adequate T cell function, hindering the therapeutic efficacy of immune checkpoint inhibitors [4,184]. The TME contains a wide range of immunosuppressive leukocytes, including M2-polarized tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), Th2 $CD4^+$ T cells, and Treg cells [185–187]. They have been shown to influence the efficacy of immune checkpoint inhibitor therapy in pre-clinical models [5,188]. The complex structure of the TME, which comprises capillaries, collagen, glycosaminoglycan, glycoproteins, and immunosuppressive cells, not only inhibits the infiltration of immune cells into tumor tissue, but also interferes with the therapeutic function of a cancer vaccine by promoting tumorigenic cytokine secretion. For example, stromal cells (e.g., cancer-associated fibroblasts and tumor-associated macrophages) release a number of cytokines (e.g., IL-10, TGF-β, vascular endothelial growth factor, and indoleamine-pyrrole 2,3 dioxygenase) that promote tumor growth and thereby enhance immune suppression [185–187]. Inadequate T cell function can also arise through the expression of alternative co-inhibitory immune checkpoints (e.g., CTLA-4, LAG-3, VISTA, and TIM-3) [4,5,189]. In addition, IFN-γ secreted by activated T cells can induce the loss of function of JAK1 and JAK2, thereby triggering acquired resistance [190,191]. Therefore, we need to better understand tumor-immune interactions and tumor immunoediting mechanisms if we hope to develop effective cancer immunotherapies. We should also look to develop combination strategies aimed at improving the efficacy of immune checkpoint inhibition therapy.

The lack of benefit from checkpoint inhibitors parallels the lack of effective CD8+ T cells in TME, which is related with resistance of immune checkpoint therapy. The generation of tumor-reactive $CD8^+$ T cells requires the successful processing and presentation of tumor-associated antigenic peptides by APCs, such as DCs. However, a lack of sufficient neoantigens, impaired neoantigen processing and/or presentation can both lead to an insufficient generation of anti-tumor T cells [5,192]. Mutation burden is a tumor-intrinsic factor that correlates with the anti-tumor response of immune checkpoint inhibitor therapy. Tumor types harboring high levels of nonsynonymous mutations (e.g., melanoma, lung cancer, and bladder cancer) exhibit some of the highest response rates to immune checkpoint inhibitors. Consistently, DNA-mismatch repair deficiency leading to genome instability is associated with an enhanced response to PD-1 blockade [193]. Loss or mutation of β2M of MHC class I on tumor cells can also induce an innate resistance mechanism [194,195].

As the critical mechanism for limitation of immune checkpoint blockades is dysfunctional APCs defective in the priming of tumor-reactive CD8+ T cells, clinical utilities of conventional cancer treatments including cytotoxic chemotherapy, radiotherapy and targeted therapy in combination with immune checkpoint blockades have been currently explored, aiming to achieve synergetic effects with improved and durable clinical response. We also note that intrinsic cancer vaccination that activates our immune system to recognize cancer as a non-self, is expected to be a promising strategy to overcome the resistance to PD-1 therapy (Fig. 3). Strategies to promote ICD or to enhance antigen presentation by improving the phagocytic function of DCs may promote the formation of suitable neoantigens and DAMPs in non-inflamed tumors, and enhance DC functions (maturation and cross-presentation of DCs), leading to adequate T cell priming and clonal expansion [57]. For example, radio- or chemotherapies that elicit ICD are known to release DAMPs and neoantigens, which activate DCs to cross-present tumor antigens to lymphocytes [11,196]. Studies have shown that the therapeutic effects of CD47 blockade depend on the DC-mediated cross-priming of T cell responses [55]. CD47 blockade was also combined with anti-PD-L1, for dual targeting of innate and adaptive checkpoints on tumor cells. Liu at al. engineered bispecific heterodimer, anti-PD-L1-Sirpα and showed that they robustly increased DC mediated cross prime ability and anti-tumor T cell response, leading to significantly inhibit tumor growth. Moreover, combination of the bispecific reagent and doxorubicin was found to report to induce ICD, exerting a stronger tumor specific immune response for tumor eradication [197].

Recently, the Lin group developed nanoscale coordination polymer core-shell nanoparticles that carry oxaliplatin and the photosensitizer pyropheophorbide-lipid conjugate (NCP@pyrolipid) for effective treatment of advanced colorectal cancer. The designed NCP@pyrolipid could provoke ICD of cancer cell and resulted in antitumor vaccination and an abscopal effect. Moreover, the immunogenic nanoparticles enhanced the anti-tumor efficacy of the antibodies inhibiting the PD-1/PD-L1 axis [198].

Further studies will be required to evaluate the ability of intrinsic cancer vaccination to overcome acquired resistance to immune checkpoint blockade. Intriguingly, the ICD inducer, cyclophosphamide, has been shown to selectively target Treg cells at a low dose *in vivo* [199], suggesting that induction of ICD can convert an immunosuppressive cold tumor into an immune-activated hot tumor. In addition, the induction and secretion of DAMPs during ICD causes the release of pro-

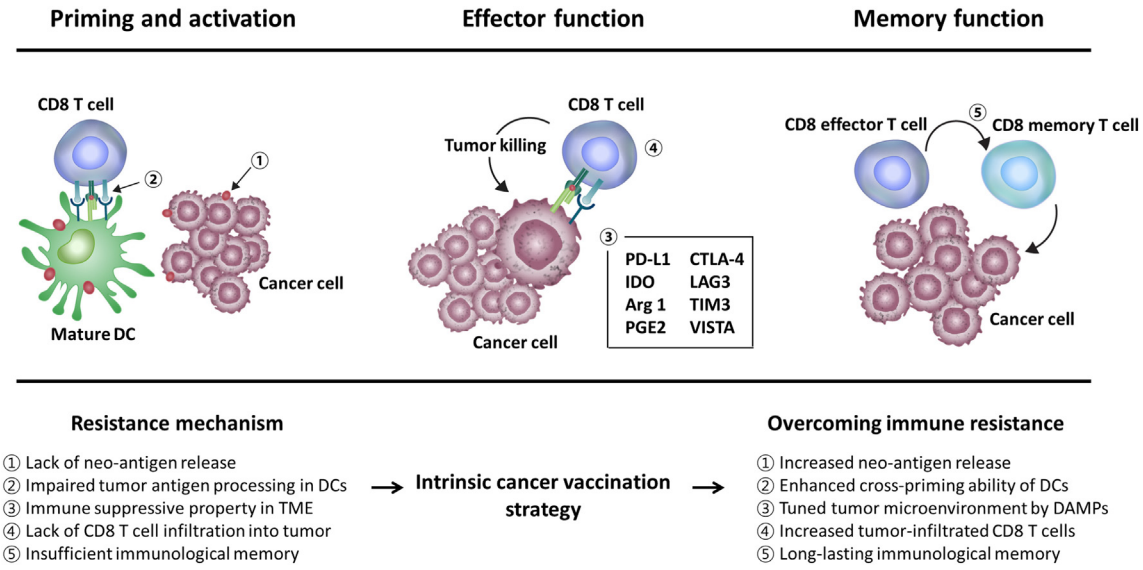

Fig. 3. Overcoming resistance to PD-1 therapy. Upper panel: schematic diagram that represents the priming and activation of tumor-specific $CD8^+$ T cells, effector $CD8^+$ T cell function, and memory $CD8^+$ T cell function. Lower panel: resistance mechanisms to PD-1 therapy (left) and possible approaches through which an intrinsic cancer vaccination strategy could overcome this resistance (right).

inflammatory cytokines and chemokines and the activation/maturation of APCs to produce a robust innate immune response.

For long-term immunologic memory, a subset of effector T cells must differentiate into Tems [155,200] under the guidance of $CD4^+$ helper T cells and DCs [155]. The impaired formation of Tems may lead to tumor relapse following discontinuation of therapy. The cellular and molecular mechanisms of Tem expansion following PD-1 blockade are not fully understood, but reacquisition of the memory T cell response has been reported to occur in cancer patients with a higher mutation burden. Therefore, we expect that an intrinsic cancer vaccination strategy that primes new populations of T cells or seeks to augment existing T cell responses may be needed to produce durable T cell memory against tumor.

5. Conclusions and future perspectives

In cancer patients, the cancer-immunity cycle does not work properly for following reasons: 1) Tumor antigens may not be detected. 2) DCs and T cells may consider tumor antigens as self rather than non-self (foreign), thereby stimulating the response of Treg cell rather than effector responses. 3) T cells may not accordingly infiltrate and home to tumors. 4) The tumor may escape immune surveillance and cell death by expressing activating and inhibitory ligands that interact with receptors found on the surface of immune cells. 5) Factors in the TME might suppress the produced effector T cells [3,132,144,145,201]. Although the clinical efficacy and durable responses seen with immune checkpoint blockades have spurred dramatic changes in our approach to treating cancer, the results from large clinical trials clearly show that only a fraction of patients respond and many will relapse. Therefore, we urgently need to develop a novel immunotherapeutic strategy that meets the following five requirements: 1) targetability to selectively recognize the neoantigens of cancer cells; 2) adaptability to the antigen variability that arises from mutation of cancer cells; 3) self-propagation within the immune system itself, to enhance anti-cancer-immunity; 4) penetration of immune cells to tumor tissues; and 5) durability of the immune effect.

In this review, we discuss new concept of "intrinsic cancer vaccination", which we believe will amplify a sufficient and robust immune response in the early stage of the cancer-immunity cycle. To awaken intrinsic immunity against tumors, this strategy involves killing tumor cells in a manner that exposes new antigens to immune cells via ICD, while also enhancing phagocytosis in order to prime T cells capable of specifically recognizing cancer cells. Intrinsic cancer vaccination-mediated induction of T cell immunity may enable to enhance the clinical response rates of anticancer treatments. However, it will be crucial to extend these findings to the clinical situation.

We also describe the utilizing of nano-formulation for targeted and/or co- delivery of immunotherapeutic drugs. Although the nanoplatform provide great opportunity for improving efficacy of intrinsic cancer vaccination strategy, their own immunogenicity that affect immune responses need to be considered for design and engineering of nanoparticles. In addition, tuning of the general properties of nanoparticles such as size, shape, surface modification, and spatiotemporal drug release is necessary to reduce unwanted immune reactions. As the safety evaluation of nanoplatform is required for the successful clinical applications, the network between nanoparticles and immune system should be considered in the nano-immunotherapy field.

Note that while intrinsic cancer vaccination is an important strategy of $CD8^+$ T cell-associated anti-cancer immune responses, this is not the only means to facilitate an immune response against cancer [202–204]. Knowledge of the concepts and mechanisms that underlie intrinsic cancer vaccination-induced T cell activation could provide shed light on new strategies for combining this strategy with novel immunotherapeutic approaches. For example, within the TME, PD-L1 is constitutively expressed in response to oncogenic signaling or induced in response to inflammatory cytokines (e.g., IFN-γ). As discussed in the review, the intrinsic cancer vaccination-mediated induction of T cell immunity overcomes resistance to immune checkpoint inhibitor therapies. Similarly, PD-L1 expression is increased upon intrinsic cancer vaccination treatment, providing a rationale for combined cancer treatment using this strategy and αPD-L1. The combination of intrinsic cancer vaccination with immune checkpoint blockade may yield significantly improved anti-tumor responses by releasing the state of immunosuppressive microenvironment and augmenting tumor-reactive T cell responses.

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Additional information

The authors declare that there is no competing financial interest.

References

[1] S. Farkona, E.P. Diamandis, I.M. Blasutig, Cancer immunotherapy: the beginning of the end of cancer? BMC Med 14 (2016) 73.
[2] J. Couzin-Frankel, Breakthrough of the year 2013, Cancer immunotherapy 342 (2013) 1432–1433 Science.
[3] S.H. van der Burg, R. Arens, F. Ossendorp, T. van Hall, C.J. Melief, Vaccines for established cancer: overcoming the challenges posed by immune evasion, Nat Rev Cancer 16 (2016) 219–233.
[4] J.S. O'Donnell, M.J. Smyth, M.W. Teng, Acquired resistance to anti-PD1 therapy: checkmate to checkpoint blockade? Genome Med 8 (2016) 111.
[5] R.W. Jenkins, D.A. Barbie, K.T. Flaherty, Mechanisms of resistance to immune checkpoint inhibitors, Br J Cancer 118 (2018) 9–16.
[6] R.H. Vonderheide, The Immune Revolution: A Case for Priming, Not Checkpoint, Cancer Cell 33 (2018) 563–569.
[7] X. Zhao, S. Subramanian, Intrinsic Resistance of Solid Tumors to Immune Checkpoint Blockade Therapy, Cancer Res 77 (2017) 817–822.
[8] J. Rieth, S. Subramanian, Mechanisms of Intrinsic Tumor Resistance to Immunotherapy, Int J Mol Sci 19 (2018).
[9] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity 39 (2013) 1–10.
[10] J.M. Kim, D.S. Chen, Immune escape to PD-L1/PD-1 blockade: seven steps to success (or failure), Ann Oncol 27 (2016) 1492–1504.
[11] G. Kroemer, L. Galluzzi, O. Kepp, L. Zitvogel, Immunogenic cell death in cancer therapy, Annu Rev Immunol 31 (2013) 51–72.
[12] D.V. Krysko, A.D. Garg, A. Kaczmarek, O. Krysko, P. Agostinis, P. Vandenabeele, Immunogenic cell death and DAMPs in cancer therapy, Nat Rev Cancer 12 (2012) 860–875.
[13] N. Casares, M.O. Pequignot, A. Tesniere, F. Ghiringhelli, S. Roux, N. Chaput, E. Schmitt, A. Hamai, S. Hervas-Stubbs, M. Obeid, F. Coutant, D. Metivier, E. Pichard, P. Aucouturier, G. Pierron, C. Garrido, L. Zitvogel, G. Kroemer, Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death, J Exp Med 202 (2005) 1691–1701.
[14] M. Obeid, A. Tesniere, F. Ghiringhelli, G.M. Fimia, L. Apetoh, J.L. Perfettini, M. Castedo, G. Mignot, T. Panaretakis, N. Casares, D. Metivier, N. Larochette, P. van Endert, F. Ciccosanti, M. Piacentini, L. Zitvogel, G. Kroemer, Calreticulin exposure dictates the immunogenicity of cancer cell death, Nat Med 13 (2007) 54–61.
[15] I. Martins, Y. Wang, M. Michaud, Y. Ma, A.Q. Sukkurwala, S. Shen, O. Kepp, D. Metivier, L. Galluzzi, J.L. Perfettini, L. Zitvogel, G. Kroemer, Molecular mechanisms of ATP secretion during immunogenic cell death, Cell Death Differ 21 (2014) 79–91.
[16] F. Ghiringhelli, L. Apetoh, A. Tesniere, L. Aymeric, Y. Ma, C. Ortiz, K. Vermaelen, T. Panaretakis, G. Mignot, E. Ullrich, J.L. Perfettini, F. Schlemmer, E. Tasdemir, M. Uhl, P. Genin, A. Civas, B. Ryffel, J. Kanellopoulos, J. Tschopp, F. Andre, R. Lidereau, N.M. McLaughlin, N.M. Haynes, M.J. Smyth, G. Kroemer, L. Zitvogel, Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors, Nat Med 15 (2009) 1170–1178.
[17] T. Yamazaki, D. Hannani, V. Poirier-Colame, S. Ladoire, C. Locher, A. Sistigu, N. Prada, S. Adjemian, J.P. Catani, M. Freudenberg, C. Galanos, F. Andre, G. Kroemer, L. Zitvogel, Defective immunogenic cell death of HMGB1-deficient tumors: compensatory therapy with TLR4 agonists, Cell Death Differ 21 (2014) 69–78.
[18] L. Apetoh, F. Ghiringhelli, A. Tesniere, M. Obeid, C. Ortiz, A. Criollo, G. Mignot, M.C. Maiuri, E. Ullrich, P. Saulnier, H. Yang, S. Amigorena, B. Ryffel, F.J. Barrat, P. Saftig, F. Levi, R. Lidereau, C. Nogues, J.P. Mira, A. Chompret, V. Joulin, F. Clavel-Chapelon, J. Bourhis, F. Andre, S. Delaloge, T. Tursz, G. Kroemer, L. Zitvogel, Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy, Nat Med 13 (2007) 1050–1059.
[19] M. Yadav, S. Jhunjhunwala, Q.T. Phung, P. Lupardus, J. Tanguay, S. Bumbaca, C. Franci, T.K. Cheung, J. Fritsche, T. Weinschenk, Z. Modrusan, I. Mellman, J.R. Lill, L. Delamarre, Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing, Nature 515 (2014) 572–576.
[20] A. Sistigu, T. Yamazaki, E. Vacchelli, K. Chaba, D.P. Enot, J. Adam, I. Vitale, A. Goubar, E.E. Baracco, C. Remedios, L. Fend, D. Hannani, L. Aymeric, Y. Ma, M. Niso-Santano, O. Kepp, J.L. Schultze, T. Tuting, F. Belardelli, L. Bracci, V. La Sorsa, G. Ziccheddu, P. Sestili, F. Urbani, M. Delorenzi, M. Lacroix-Triki, V. Quidville, R. Conforti, J.P. Spano, L. Pusztai, V. Poirier-Colame, S. Delaloge, F. Penault-Llorca, S. Ladoire, L. Arnould, J. Cyrta, M.C. Dessoliers, A. Eggermont, M.E. Bianchi, M. Pittet, C. Engblom, C. Pfirschke, X. Preville, G. Uze, R.D. Schreiber, M.T. Chow, M.J. Smyth, E. Proietti, F. Andre, G. Kroemer, L. Zitvogel, Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy, Nat Med 20 (2014) 1301–1309.
[21] L. Zitvogel, O. Kepp, G. Kroemer, Immune parameters affecting the efficacy of chemotherapeutic regimens, Nat Rev Clin Oncol 8 (2011) 151–160.
[22] R. Zappasodi, S.M. Pupa, G.C. Ghedini, I. Bongarzone, M. Magni, A.D. Cabras, M.P. Colombo, C. Carlo-Stella, A.M. Gianni, M. Di Nicola, Improved clinical outcome in indolent B-cell lymphoma patients vaccinated with autologous tumor cells experiencing immunogenic death, Cancer Res 70 (2010) 9062–9072.
[23] W.G. Land, The Role of Damage-Associated Molecular Patterns (DAMPs) in Human Diseases: Part II: DAMPs as diagnostics, prognostics and therapeutics in clinical medicine, Sultan Qaboos Univ Med J 15 (2015) e157–e170.
[24] H.E. Barker, J.T. Paget, A.A. Khan, K.J. Harrington, The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence, Nat Rev Cancer 15 (2015) 409–425.
[25] A.R. van Vliet, T. Verfaillie, P. Agostinis, New functions of mitochondria associated membranes in cellular signaling, Biochim Biophys Acta 1843 (2014) 2253–2262.
[26] T. Kawai, S. Akira, The roles of TLRs, RLRs and NLRs in pathogen recognition, Int Immunol 21 (2009) 317–337.
[27] O. Takeuchi, S. Akira, Pattern recognition receptors and inflammation, Cell 140 (2010) 805–820.
[28] A. Alloatti, F. Kotsias, A.M. Pauwels, J.M. Carpier, M. Jouve, E. Timmerman, L. Pace, P. Vargas, M. Maurin, U. Gehrmann, L. Joannas, O.I. Vivar, A.M. Lennon-Dumenil, A. Savina, K. Gevaert, R. Beyaert, E. Hoffmann, S. Amigorena, Toll-like Receptor 4 Engagement on Dendritic Cells Restrains Phago-Lysosome Fusion and Promotes Cross-Presentation of Antigens, Immunity 43 (2015) 1087–1100.
[29] S. Pesonen, I. Diaconu, L. Kangasniemi, T. Ranki, A. Kanerva, S.K. Pesonen, U. Gerdemann, A.M. Leen, K. Kairemo, M. Oksanen, E. Haavisto, S.L. Holm, A. Karioja-Kallio, S. Kauppinen, K.P. Partanen, L. Laasonen, T. Joensuu, T. Alanko, V. Cerullo, A. Hemminki, Oncolytic immunotherapy of advanced solid tumors with a CD40L-expressing replicating adenovirus: assessment of safety and immunologic responses in patients, Cancer Res 72 (2012) 1621–1631.
[30] S.J. Russell, K.W. Peng, Measles virus for cancer therapy, Curr Top Microbiol Immunol 330 (2009) 213–241.
[31] S. Miyamoto, H. Inoue, T. Nakamura, M. Yamada, C. Sakamoto, Y. Urata, T. Okazaki, T. Marumoto, A. Takahashi, K. Takayama, Y. Nakanishi, H. Shimizu, K. Tani, Coxsackievirus B3 is an oncolytic virus with immunostimulatory properties that is active against lung adenocarcinoma, Cancer Res 72 (2012) 2609–2621.
[32] S.T. Workenhe, K.L. Mossman, Oncolytic virotherapy and immunogenic cancer cell death: sharpening the sword for improved cancer treatment strategies, Mol Ther 22 (2014) 251–256.
[33] R.J. Prestwich, F. Errington, R.M. Diaz, H.S. Pandha, K.J. Harrington, A.A. Melcher, R.G. Vile, The case of oncolytic viruses versus the immune system: waiting on the judgment of Solomon, Hum Gene Ther 20 (2009) 1119–1132.
[34] J. Nam, S. Son, L.J. Ochyl, R. Kuai, A. Schwendeman, J.J. Moon, Chemo-photothermal therapy combination elicits anti-tumor immunity against advanced metastatic cancer, Nat Commun 9 (2018) 1074.
[35] J. Fucikova, P. Kralikova, A. Fialova, T. Brtnicky, L. Rob, J. Bartunkova, R. Spisek, Human tumor cells killed by anthracyclines induce a tumor-specific immune response, Cancer Res 71 (2011) 4821–4833.
[36] W. Hou, Q. Zhang, Z. Yan, R. Chen, H.J. Zeh Iii, R. Kang, M.T. Lotze, D. Tang, Strange attractors: DAMPs and autophagy link tumor cell death and immunity, Cell Death Dis 4 (2013) e966.
[37] C. Fu, A. Jiang, Dendritic Cells and CD8 T Cell Immunity in Tumor Microenvironment, Front Immunol 9 (2018) 3059.
[38] Y. Ma, G.V. Shurin, Z. Peiyuan, M.R. Shurin, Dendritic cells in the cancer microenvironment, J Cancer 4 (2013) 36–44.
[39] H. Karsunky, M. Merad, A. Cozzio, I.L. Weissman, M.G. Manz, Flt3 ligand regulates dendritic cell development from Flt3+ lymphoid and myeloid-committed progenitors to Flt3+ dendritic cells in vivo, J Exp Med 198 (2003) 305–313.
[40] H. Salmon, J. Idoyaga, A. Rahman, M. Leboeuf, R. Remark, S. Jordan, M. Casanova-Acebes, M. Khudoynazarova, J. Agudo, N. Tung, S. Chakarov, C. Rivera, B. Hogstad, M. Bosenberg, D. Hashimoto, S. Gnjatic, N. Bhardwaj, A.K. Palucka, B.D. Brown, J. Brody, F. Ginhoux, M. Merad, Expansion and Activation of CD103(+) Dendritic Cell Progenitors at the Tumor Site Enhances Tumor Responses to Therapeutic PD-L1 and BRAF Inhibition, Immunity 44 (2016) 924–938.
[41] K. Liu, M.C. Nussenzweig, Origin and development of dendritic cells, Immunol Rev 234 (2010) 45–54.
[42] M.A. Meyer, J.M. Baer, B.L. Knolhoff, T.M. Nywening, R.Z. Panni, X. Su, K.N. Weilbaecher, W.G. Hawkins, C. Ma, R.C. Fields, D.C. Linehan, G.A. Challen, R. Faccio, R.L. Aft, D.G. DeNardo, Breast and pancreatic cancer interrupt IRF8-dependent dendritic cell development to overcome immune surveillance, Nat Commun 9 (2018) 1250.
[43] C. Pfirschke, M. Siwicki, H.W. Liao, M.J. Pittet, Tumor Microenvironment: No Effector T Cells without Dendritic Cells, Cancer Cell 31 (2017) 614–615.
[44] B. Pulendran, J. Banchereau, S. Burkeholder, E. Kraus, E. Guinet, C. Chalouni, D. Caron, C. Maliszewski, J. Davoust, J. Fay, K. Palucka, Flt3-ligand and granulocyte colony-stimulating factor mobilize distinct human dendritic cell subsets in vivo, J Immunol 165 (2000) 566–572.
[45] D.H. Munn, A.L. Mellor, The tumor-draining lymph node as an immune-privileged site, Immunol Rev 213 (2006) 146–158.
[46] N. Bertho, H. Adamski, L. Toujas, M. Debove, J. Davoust, V. Quillien, Efficient migration of dendritic cells toward lymph node chemokines and induction of T(H)1 responses require maturation stimulus and apoptotic cell interaction, Blood 106 (2005) 1734–1741.
[47] D. Alvarez, E.H. Vollmann, U.H. von Andrian, Mechanisms and consequences of dendritic cell migration, Immunity 29 (2008) 325–342.
[48] K.C. Sheng, G.A. Pietersz, M.D. Wright, V. Apostolopoulos, Dendritic cells: activation and maturation–applications for cancer immunotherapy, Curr Med Chem 12 (2005) 1783–1800.
[49] S.B. Drutman, E.S. Trombetta, Dendritic cells continue to capture and present antigens after maturation in vivo, J Immunol 185 (2010) 2140–2146.
[50] O.P. Joffre, E. Segura, A. Savina, S. Amigorena, Cross-presentation by dendritic cells, Nat Rev Immunol 12 (2012) 557–569.
[51] P. Guermonprez, J. Valladeau, L. Zitvogel, C. Thery, S. Amigorena, Antigen presentation and T cell stimulation by dendritic cells, Annu Rev Immunol 20 (2002) 621–667.

[52] S.B. Willingham, J.P. Volkmer, A.J. Gentles, D. Sahoo, P. Dalerba, S.S. Mitra, J. Wang, H. Contreras-Trujillo, R. Martin, J.D. Cohen, P. Lovelace, F.A. Scheeren, M.P. Chao, K. Weiskopf, C. Tang, A.K. Volkmer, T.J. Naik, T.A. Storm, A.R. Mosley, B. Edris, S.M. Schmid, C.K. Sun, M.S. Chua, O. Murillo, P. Rajendran, A.C. Cha, R.K. Chin, D. Kim, M. Adorno, T. Raveh, D. Tseng, S. Jaiswal, P.O. Enger, G.K. Steinberg, G. Li, S.K. So, R. Majeti, G.R. Harsh, M. van de Rijn, N.N. Teng, J.B. Sunwoo, A.A. Alizadeh, M.F. Clarke, I.L. Weissman, The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors, Proc Natl Acad Sci U S A 109 (2012) 6662–6667.
[53] K. Weiskopf, N.S. Jahchan, P.J. Schnorr, S. Cristea, A.M. Ring, R.L. Maute, A.K. Volkmer, J.P. Volkmer, J. Liu, J.S. Lim, D. Yang, G. Seitz, T. Nguyen, D. Wu, K. Jude, H. Guerston, A. Barkal, F. Trapani, J. George, J.T. Poirier, E.E. Gardner, L.A. Miles, E. de Stanchina, S.M. Lofgren, H. Vogel, M.M. Winslow, C. Dive, R.K. Thomas, C.M. Rudin, M. van de Rijn, R. Majeti, K.C. Garcia, I.L. Weissman, J. Sage, CD47-blocking immunotherapies stimulate macrophage-mediated destruction of small-cell lung cancer, J Clin Invest 126 (2016) 2610–2620.
[54] D. Tseng, J.P. Volkmer, S.B. Willingham, H. Contreras-Trujillo, J.W. Fathman, N.B. Fernhoff, J. Seita, M.A. Inlay, K. Weiskopf, M. Miyanishi, I.L. Weissman, Anti-CD47 antibody-mediated phagocytosis of cancer by macrophages primes an effective antitumor T-cell response, Proc Natl Acad Sci U S A 110 (2013) 11103–11108.
[55] X. Liu, Y. Pu, K. Cron, L. Deng, J. Kline, W.A. Frazier, H. Xu, H. Peng, Y.X. Fu, M.M. Xu, CD47 blockade triggers T cell-mediated destruction of immunogenic tumors, Nat Med 21 (2015) 1209–1215.
[56] M.M. Xu, Y. Pu, D. Han, Y. Shi, X. Cao, H. Liang, X. Chen, X.D. Li, L. Deng, Z.J. Chen, R.R. Weichselbaum, Y.X. Fu, Dendritic Cells but Not Macrophages Sense Tumor Mitochondrial DNA for Cross-priming through Signal Regulatory Protein alpha Signaling, Immunity 47 (2017) 363–373 e365.
[57] G.H. Nam, E.J. Lee, Y.K. Kim, Y. Hong, Y. Choi, M.J. Ryu, J. Woo, Y. Cho, D.J. Ahn, Y. Yang, I.C. Kwon, S.Y. Park, I.S. Kim, Combined Rho-kinase inhibition and immunogenic cell death triggers and propagates immunity against cancer, Nat Commun 9 (2018) 2165.
[58] E. Koh, E.J. Lee, G.H. Nam, Y. Hong, E. Cho, Y. Yang, I.S. Kim, Exosome-SIRPalpha, a CD47 blockade increases cancer cell phagocytosis, Biomaterials 121 (2017) 121–129.
[59] K. Weiskopf, Cancer immunotherapy targeting the CD47/SIRPalpha axis, Eur J Cancer 76 (2017) 100–109.
[60] A.A. Barkal, K. Weiskopf, K.S. Kao, S.R. Gordon, B. Rosental, Y.Y. Yiu, B.M. George, M. Markovic, N.G. Ring, J.M. Tsai, K.M. McKenna, P.Y. Ho, R.Z. Cheng, J.Y. Chen, L.J. Barkal, A.M. Ring, I.L. Weissman, R.L. Maute, Engagement of MHC class I by the inhibitory receptor LILRB1 suppresses macrophages and is a target of cancer immunotherapy, Nat Immunol 19 (2018) 76–84.
[61] K. Elward, M. Griffiths, M. Mizuno, C.L. Harris, J.W. Neal, B.P. Morgan, P. Gasque, CD46 plays a key role in tailoring innate immune recognition of apoptotic and necrotic cells, J Biol Chem 280 (2005) 36342–36354.
[62] S. Brown, I. Heinisch, E. Ross, K. Shaw, C.D. Buckley, J. Savill, Apoptosis disables CD31-mediated cell detachment from phagocytes promoting binding and engulfment, Nature 418 (2002) 200–203.
[63] S.Y. Kim, S. Kim, D.J. Bae, S.Y. Park, G.Y. Lee, G.M. Park, I.S. Kim, Coordinated balance of Rac1 and RhoA plays key roles in determining phagocytic appetite, PLoS One 12 (2017), e0174603.
[64] A.C. Tosello-Trampont, K. Nakada-Tsukui, K.S. Ravichandran, Engulfment of apoptotic cells is negatively regulated by Rho-mediated signaling, J Biol Chem 278 (2003) 49911–49919.
[65] J. Lane, T.A. Martin, G. Watkins, R.E. Mansel, W.G. Jiang, The expression and prognostic value of ROCK I and ROCK II and their role in human breast cancer, Int J Oncol 33 (2008) 585–593.
[66] I. Teiti, B. Florie, C. Pich, R. Gence, I. Lajoie-Mazenc, P. Rochaix, G. Favre, A.F. Tilkin-Mariame, In vivo Effects in Melanoma of ROCK Inhibition-Induced FasL Overexpression, Frontiers in oncology 5 (2015) 156.
[67] K. Yamashita, Y. Kotani, Y. Nakajima, M. Shimazawa, S. Yoshimura, S. Nakashima, T. Iwama, H. Hara, Fasudil, a Rho kinase (ROCK) inhibitor, protects against ischemic neuronal damage in vitro and in vivo by acting directly on neurons, Brain Res 1154 (2007) 215–224.
[68] G. Martin, H. Duez, C. Blanquart, V. Berezowski, P. Poulain, J.C. Fruchart, J. Najib-Fruchart, C. Glineur, B. Staels, Statin-induced inhibition of the Rho-signaling pathway activates PPARalpha and induces HDL apoA-I, J Clin Invest 107 (2001) 1423–1432.
[69] K. Morimoto, W.J. Janssen, M.B. Fessler, K.A. McPhillips, V.M. Borges, R.P. Bowler, Y.Q. Xiao, J.A. Kench, P.M. Henson, R.W. Vandivier, Lovastatin enhances clearance of apoptotic cells (efferocytosis) with implications for chronic obstructive pulmonary disease, J Immunol 176 (2006) 7657–7665.
[70] N. Rath, M.F. Olson, Rho-associated kinases in tumorigenesis: re-considering ROCK inhibition for cancer therapy, EMBO Rep 13 (2012) 900–908.
[71] A.G. N, S.J. Bensinger, C. Hong, S. Beceiro, M.N. Bradley, N. Zelcer, J. Deniz, C. Ramirez, M. Diaz, G. Gallardo, C.R. de Galarreta, J. Salazar, F. Lopez, P. Edwards, J. Parks, M. Andujar, P. Tontonoz, A. Castrillo, Apoptotic cells promote their own clearance and immune tolerance through activation of the nuclear receptor LXR, Immunity 31 (2009) 245–258.
[72] G. Majai, Z. Sarang, K. Csomos, G. Zahuczky, L. Fesus, PPARgamma-dependent regulation of human macrophages in phagocytosis of apoptotic cells, Eur J Immunol 37 (2007) 1343–1354.
[73] J. Waugh, G.M. Keating, G.L. Plosker, S. Easthope, D.M. Robinson, Pioglitazone: a review of its use in type 2 diabetes mellitus, Drugs 66 (2006) 85–109.
[74] E.W. Roberts, M.L. Broz, M. Binnewies, M.B. Headley, A.E. Nelson, D.M. Wolf, T. Kaisho, D. Bogunovic, N. Bhardwaj, M.F. Krummel, Critical Role for CD103(+)/CD141(+) Dendritic Cells Bearing CCR7 for Tumor Antigen Trafficking and Priming of T Cell Immunity in Melanoma, Cancer Cell 30 (2016) 324–336.
[75] M.R. Clatworthy, C.E. Aronin, R.J. Mathews, N.Y. Morgan, K.G. Smith, R.N. Germain, Immune complexes stimulate CCR7-dependent dendritic cell migration to lymph nodes, Nat Med 20 (2014) 1458–1463.
[76] M. Tomura, A. Hata, S. Matsuoka, F.H. Shand, Y. Nakanishi, R. Ikebuchi, S. Ueha, H. Tsutsui, K. Inaba, K. Matsushima, A. Miyawaki, K. Kabashima, T. Watanabe, O. Kanagawa, Tracking and quantification of dendritic cell migration and antigen trafficking between the skin and lymph nodes, Sci Rep 4 (2014) 6030.
[77] P. Correale, M.S. Rotundo, C. Botta, M.T. Del Vecchio, P. Tassone, P. Tagliaferri, Tumor infiltration by chemokine receptor 7 (CCR7)(+) T-lymphocytes is a favorable prognostic factor in metastatic colorectal cancer, Oncoimmunology 1 (2012) 531–532.
[78] S. Grobner, R. Lukowski, I.B. Autenrieth, P. Ruth, Lipopolysaccharide induces cell volume increase and migration of dendritic cells, Microbiol Immunol 58 (2014) 61–67.
[79] N. Seyfizadeh, R. Muthuswamy, D.A. Mitchell, S. Nierkens, N. Seyfizadeh, Migration of dendritic cells to the lymph nodes and its enhancement to drive anti-tumor responses, Crit Rev Oncol Hematol 107 (2016) 100–110.
[80] V.K. Raker, M.P. Domogalla, K. Steinbrink, Tolerogenic Dendritic Cells for Regulatory T Cell Induction in Man, Front Immunol 6 (2015) 569.
[81] J. Waithman, D. Zanker, K. Xiao, S. Oveissi, B. Wylie, R. Ng, L. Togel, W. Chen, Resident CD8(+) and migratory CD103(+) dendritic cells control CD8 T cell immunity during acute influenza infection, PLoS One 8 (2013), e66136.
[82] A.N. Desch, G.J. Randolph, K. Murphy, E.L. Gautier, R.M. Kedl, M.H. Lahoud, I. Caminschi, K. Shortman, P.M. Henson, C.V. Jakubzick, CD103+ pulmonary dendritic cells preferentially acquire and present apoptotic cell-associated antigen, J Exp Med 208 (2011) 1789–1797.
[83] F.E. Pearson, K. Chang, Y. Minoda, I.M.L. Rojas, O.L. Haigh, G. Daraj, K.M. Tullett, K.J. Radford, Activation of human CD141(+) and CD1c(+) dendritic cells in vivo with combined TLR3 and TLR7/8 ligation, Immunol Cell Biol 96 (2018) 390–400.
[84] M. Matsumoto, T. Seya, TLR3: interferon induction by double-stranded RNA including poly(I:C), Adv Drug Deliv Rev 60 (2008) 805–812.
[85] K.R. Beutner, J.K. Geisse, D. Helman, T.L. Fox, A. Ginkel, M.L. Owens, Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream, Journal of the American Academy of Dermatology 41 (1999) 1002–1007.
[86] I. Ahmed, J. Berth-Jones, Imiquimod: a novel treatment for lentigo maligna, The British journal of dermatology 143 (2000) 843–845.
[87] R.P. Burns Jr., B. Ferbel, M. Tomai, R. Miller, A.A. Gaspari, The imidazoquinolines, imiquimod and R-848, induce functional, but not phenotypic, maturation of human epidermal Langerhans' cells, Clinical immunology (Orlando, Fla.) 94 (2000) 13–23.
[88] H. Hemmi, T. Kaisho, O. Takeuchi, S. Sato, H. Sanjo, K. Hoshino, T. Horiuchi, H. Tomizawa, K. Takeda, S. Akira, Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway, Nat Immunol 3 (2002) 196–200.
[89] S. Tsuji, M. Matsumoto, O. Takeuchi, S. Akira, I. Azuma, A. Hayashi, K. Toyoshima, T. Seya, Maturation of human dendritic cells by cell wall skeleton of Mycobacterium bovis bacillus Calmette-Guerin: involvement of toll-like receptors, Infection and immunity 68 (2000) 6883–6890.
[90] R.J. Sylvester, M.A. van der, D.L. Lamm, Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials, The Journal of urology 168 (2002) 1964–1970.
[91] R.J. Sylvester, A.P. van der Meijden, J.A. Witjes, K. Kurth, Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials, The Journal of urology 174 (2005) 86–91 discussion 91-82.
[92] S.B. Coffelt, K.E. de Visser, Revving Up Dendritic Cells while Braking PD-L1 to Jump-Start the Cancer-Immunity Cycle Motor, Immunity 44 (2016) 722–724.
[93] R. van de Ven, A.N. Niemeijer, A.G.M. Stam, S.M.S. Hashemi, C.G. Slockers, J.M. Daniels, E. Thunnissen, E.F. Smit, T.D. de Gruijl, A.J. de Langen, High PD-1 expression on regulatory and effector T-cells in lung cancer draining lymph nodes, ERJ open research (2017) 3.
[94] P.S. Linsley, J.L. Greene, W. Brady, J. Bajorath, J.A. Ledbetter, R. Peach, Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors, Immunity 1 (1994) 793–801.
[95] L. Chen, S. Ashe, W.A. Brady, I. Hellstrom, K.E. Hellstrom, J.A. Ledbetter, P. McGowan, P.S. Linsley, Costimulation of antitumor immunity by the B7 counterreceptor for the T lymphocyte molecules CD28 and CTLA-4, Cell 71 (1992) 1093–1102.
[96] M.F. Krummel, J.P. Allison, CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells, J Exp Med 183 (1996) 2533–2540.
[97] E.J. Lipson, C.G. Drake, Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma, Clinical cancer research : an official journal of the American Association for Cancer Research 17 (2011) 6958–6962.
[98] M. Cella, D. Scheidegger, K. Palmer-Lehmann, P. Lane, A. Lanzavecchia, G. Alber, Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances T cell stimulatory capacity: T-T help via APC activation, J Exp Med 184 (1996) 747–752.
[99] R.H. Vonderheide, D.L. Bajor, R. Winograd, R.A. Evans, L.J. Bayne, G.L. Beatty, CD40 immunotherapy for pancreatic cancer, Cancer Immunol Immunother 62 (2013) 949–954.
[100] M. Singh, C. Vianden, M.J. Cantwell, Z. Dai, Z. Xiao, M. Sharma, H. Khong, A.R. Jaiswal, F. Faak, Y. Hailemichael, L.M.E. Janssen, U. Bharadwaj, M.A. Curran, A. Diab, R.L. Bassett, D.J. Tweardy, P. Hwu, W.W. Overwijk, Intratumoral CD40

activation and checkpoint blockade induces T cell-mediated eradication of melanoma in the brain, Nat Commun 8 (2017) 1447.
[101] K.T. Byrne, R.H. Vonderheide, CD40 Stimulation Obviates Innate Sensors and Drives T Cell Immunity in Cancer, Cell Rep 15 (2016) 2719–2732.
[102] G.L. Beatty, E.G. Chiorean, M.P. Fishman, B. Saboury, U.R. Teitelbaum, W. Sun, R.D. Huhn, W. Song, D. Li, L.L. Sharp, D.A. Torigian, P.J. O'Dwyer, R.H. Vonderheide, CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans, Science 331 (2011) 1612–1616.
[103] G.L. Beatty, D.A. Torigian, E.G. Chiorean, B. Saboury, A. Brothers, A. Alavi, A.B. Troxel, W. Sun, U.R. Teitelbaum, R.H. Vonderheide, P.J. O'Dwyer, A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma, Clinical cancer research : an official journal of the American Association for Cancer Research 19 (2013) 6286–6295.
[104] M. Croft, C.A. Benedict, C.F. Ware, Clinical targeting of the TNF and TNFR superfamilies, Nat Rev Drug Discov 12 (2013) 147–168.
[105] E.R. Sturgill, T.N.F.R. Agonists, A Review of Current Biologics Targeting OX40, 4-1BB, CD27, and GITR, American Journal of Hematology/Oncology®, 2017 13.
[106] B.D. Curti, M. Kovacsovics-Bankowski, N. Morris, E. Walker, L. Chisholm, K. Floyd, J. Walker, I. Gonzalez, T. Meeuwsen, B.A. Fox, T. Moudgil, W. Miller, D. Haley, T. Coffey, B. Fisher, L. Delanty-Miller, N. Rymarchyk, T. Kelly, T. Crocenzi, E. Bernstein, R. Sanborn, W.J. Urba, A.D. Weinberg, OX40 is a potent immune-stimulating target in late-stage cancer patients, Cancer Res 73 (2013) 7189–7198.
[107] S. Aspeslagh, S. Postel-Vinay, S. Rusakiewicz, J.C. Soria, L. Zitvogel, A. Marabelle, Rationale for anti-OX40 cancer immunotherapy, Eur J Cancer 52 (2016) 50–66.
[108] I.K. Kim, B.S. Kim, C.H. Koh, J.W. Seok, J.S. Park, K.S. Shin, E.A. Bae, G.E. Lee, H. Jeon, J. Cho, Y. Jung, D. Han, B.S. Kwon, H.Y. Lee, Y. Chung, C.Y. Kang, Glucocorticoid-induced tumor necrosis factor receptor-related protein co-stimulation facilitates tumor regression by inducing IL-9-producing helper T cells, Nat Med 21 (2015) 1010–1017.
[109] D. Coe, S. Begom, C. Addey, M. White, J. Dyson, J.G. Chai, Depletion of regulatory T cells by anti-GITR mAb as a novel mechanism for cancer immunotherapy, Cancer Immunol Immunother 59 (2010) 1367–1377.
[110] A.D. Cohen, D.A. Schaer, C. Liu, Y. Li, D. Hirschhorn-Cymmerman, S.C. Kim, A. Diab, G. Rizzuto, F. Duan, M.A. Perales, T. Merghoub, A.N. Houghton, J.D. Wolchok, Agonist anti-GITR monoclonal antibody induces melanoma tumor immunity in mice by altering regulatory T cell stability and intra-tumor accumulation, PLoS One 5 (2010), e10436.
[111] D.A. Knee, B. Hewes, J.L. Brogdon, Rationale for anti-GITR cancer immunotherapy, Eur J Cancer 67 (2016) 1–10.
[112] A. Tesniere, F. Schlemmer, V. Boige, O. Kepp, I. Martins, F. Ghiringhelli, L. Aymeric, M. Michaud, L. Apetoh, L. Barault, J. Mendiboure, J.P. Pignon, V. Jooste, P. van Endert, M. Ducreux, L. Zitvogel, F. Piard, G. Kroemer, Immunogenic death of colon cancer cells treated with oxaliplatin, Oncogene 29 (2010) 482–491.
[113] M. Ciampricotti, C.S. Hau, C.W. Doornebal, J. Jonkers, K.E. de Visser, Chemotherapy response of spontaneous mammary tumors is independent of the adaptive immune system, Nat Med 18 (2012) 344–346 author reply 346.
[114] M. Ahlmann, G. Hempel, The effect of cyclophosphamide on the immune system: implications for clinical cancer therapy, Cancer Chemother Pharmacol 78 (2016) 661–671.
[115] C. Ferraro, L. Quemeneur, S. Fournel, A.F. Prigent, J.P. Revillard, N. Bonnefoy-Berard, The topoisomerase inhibitors camptothecin and etoposide induce a CD95-independent apoptosis of activated peripheral lymphocytes, Cell Death Differ 7 (2000) 197–206.
[116] J.T. Sockolosky, M. Dougan, J.R. Ingram, C.C. Ho, M.J. Kauke, S.C. Almo, H.L. Ploegh, K.C. Garcia, Durable antitumor responses to CD47 blockade require adaptive immune stimulation, Proc Natl Acad Sci U S A 113 (2016) E2646–E2654.
[117] S. Bhatia, N.J. Miller, H. Lu, N.V. Longino, D. Ibrani, M.M. Shinohara, D.R. Byrd, U. Parvathaneni, R. Kulikauskas, J. Ter Meulen, F.J. Hsu, D.M. Koelle, P. Nghiem, Intratumoral G100, a TLR4 Agonist, Induces Antitumor Immune Responses and Tumor Regression in Patients with Merkel Cell Carcinoma, Clinical cancer research : an official journal of the American Association for Cancer Research 25 (2019) 1185–1195.
[118] I. Liikanen, L. Ahtiainen, M.L. Hirvinen, S. Bramante, V. Cerullo, P. Nokisalmi, O. Hemminki, I. Diaconu, S. Pesonen, A. Koski, L. Kangasniemi, S.K. Pesonen, M. Oksanen, L. Laasonen, K. Partanen, T. Joensuu, F. Zhao, A. Kanerva, A. Hemminki, Oncolytic adenovirus with temozolomide induces autophagy and antitumor immune responses in cancer patients, Mol Ther 21 (2013) 1212–1223.
[119] B. Boozari, B. Mundt, N. Woller, N. Struver, E. Gurlevik, P. Schache, A. Kloos, S. Knocke, M.P. Manns, T.C. Wirth, S. Kubicka, F. Kuhnel, Antitumoural immunity by virus-mediated immunogenic apoptosis inhibits metastatic growth of hepatocellular carcinoma, Gut 59 (2010) 1416–1426.
[120] S.T. Workenhe, G. Simmons, J.G. Pol, B.D. Lichty, W.P. Halford, K.L. Mossman, Immunogenic HSV-mediated oncolysis shapes the antitumor immune response and contributes to therapeutic efficacy, Mol Ther 22 (2014) 123–131.
[121] E.J. Lee, G.H. Nam, N.K. Lee, M. Kih, E. Koh, Y.K. Kim, Y. Hong, S. Kim, S.Y. Park, C. Jeong, Y. Yang, I.S. Kim, Nanocage-Therapeutics Prevailing Phagocytosis and Immunogenic Cell Death Awakens Immunity against Cancer, Adv Mater (2018) 30.
[122] A. Seth, M.B. Heo, Y.T. Lim, Poly (gamma-glutamic acid) based combination of water-insoluble paclitaxel and TLR7 agonist for chemo-immunotherapy, Biomaterials 35 (2014) 7992–8001.
[123] A. Makkouk, V.B. Joshi, A. Wongrakpanich, C.D. Lemke, B.P. Gross, A.K. Salem, G.J. Weiner, Biodegradable microparticles loaded with doxorubicin and CpG ODN for in situ immunization against cancer, The AAPS journal 17 (2015) 184–193.
[124] Y. Liu, L. Qiao, S. Zhang, G. Wan, B. Chen, P. Zhou, N. Zhang, Y. Wang, Dual pH-responsive multifunctional nanoparticles for targeted treatment of breast cancer by combining immunotherapy and chemotherapy, Acta biomaterialia 66 (2018) 310–324.
[125] J. Lu, X. Liu, Y.P. Liao, F. Salazar, B. Sun, W. Jiang, C.H. Chang, J. Jiang, X. Wang, A.M. Wu, H. Meng, A.E. Nel, Nano-enabled pancreas cancer immunotherapy using immunogenic cell death and reversing immunosuppression, Nat Commun 8 (2017) 1811.
[126] J. Lu, X. Liu, Y.P. Liao, X. Wang, A. Ahmed, W. Jiang, Y. Ji, H. Meng, A.E. Nel, Breast Cancer Chemo-immunotherapy through Liposomal Delivery of an Immunogenic Cell Death Stimulus Plus Interference in the IDO-1 Pathway, ACS Nano 12 (2018) 11041–11061.
[127] Q. Chen, L. Xu, C. Liang, C. Wang, R. Peng, Z. Liu, Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy, Nat Commun 7 (2016), 13193.
[128] J. Xu, L. Xu, C. Wang, R. Yang, Q. Zhuang, X. Han, Z. Dong, W. Zhu, R. Peng, Z. Liu, Near-Infrared-Triggered Photodynamic Therapy with Multitasking Upconversion Nanoparticles in Combination with Checkpoint Blockade for Immunotherapy of Colorectal Cancer, ACS Nano 11 (2017) 4463–4474.
[129] R.A. Rosalia, L.J. Cruz, S. van Duikeren, A.T. Tromp, A.L. Silva, W. Jiskoot, T. de Gruijl, C. Lowik, J. Oostendorp, S.H. van der Burg, F. Ossendorp, CD40-targeted dendritic cell delivery of PLGA-nanoparticle vaccines induce potent anti-tumor responses, Biomaterials 40 (2015) 88–97.
[130] J. Banchereau, K. Palucka, Immunotherapy: Cancer vaccines on the move, Nat Rev Clin Oncol 15 (2018) 9–10.
[131] C. Guo, M.H. Manjili, J.R. Subjeck, D. Sarkar, P.B. Fisher, X.Y. Wang, Therapeutic cancer vaccines, past, present, and future, Adv Cancer Res 119 (2013) 421–475.
[132] C.L. Chiang, G. Coukos, L.E. Kandalaft, Whole Tumor Antigen Vaccines: Where Are We? Vaccines (Basel) 3 (2015) 344–372.
[133] J. Nemunaitis, Vaccines in cancer: GVAX, a GM-CSF gene vaccine, Expert Rev Vaccines 4 (2005) 259–274.
[134] M. Yarchoan, B.A. Johnson 3rd, E.R. Lutz, D.A. Laheru, E.M. Jaffee, Targeting neoantigens to augment antitumour immunity, Nat Rev Cancer 17 (2017) 209–222.
[135] K. Palucka, J. Banchereau, Dendritic-cell-based therapeutic cancer vaccines, Immunity 39 (2013) 38–48.
[136] E. Anassi, U.A. Ndefo, Sipuleucel-T (provenge) injection: the first immunotherapy agent (vaccine) for hormone-refractory prostate cancer, P T 36 (2011) 197–202.
[137] B. Bodey, B. Bodey Jr., S.E. Siegel, H.E. Kaiser, Failure of cancer vaccines: the significant limitations of this approach to immunotherapy, Anticancer Res 20 (2000) 2665–2676.
[138] A. Thomas, G. Giaccone, Why has active immunotherapy not worked in lung cancer? Ann Oncol 26 (2015) 2213–2220.
[139] C. Butts, M.A. Socinski, P.L. Mitchell, N. Thatcher, L. Havel, M. Krzakowski, S. Nawrocki, T.E. Ciuleanu, L. Bosquee, J.M. Trigo, A. Spira, L. Tremblay, J. Nyman, R. Ramlau, G. Wickart-Johansson, P. Ellis, O. Gladkov, J.R. Pereira, W.E. Eberhardt, C. Helwig, A. Schroder, F.A. Shepherd, S.t. team, Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial, Lancet Oncol 15 (2014) 59–68.
[140] J.F. Vansteenkiste, B.C. Cho, T. Vanakesa, T. De Pas, M. Zielinski, M.S. Kim, J. Jassem, M. Yoshimura, J. Dahabreh, H. Nakayama, L. Havel, H. Kondo, T. Mitsudomi, K. Zarogoulidis, O.A. Gladkov, K. Udud, H. Tada, H. Hoffman, A. Bugge, P. Taylor, E.E. Gonzalez, M.L. Liao, J. He, J.L. Pujol, J. Louahed, M. Debois, V. Brichard, C. Debruyne, P. Therasse, N. Altorki, Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small-cell lung cancer (MAGRIT): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Oncol 17 (2016) 822–835.
[141] R.D. Schreiber, L.J. Old, M.J. Smyth, Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion, Science 331 (2011) 1565–1570.
[142] J.D. Comber, R. Philip, MHC class I antigen presentation and implications for developing a new generation of therapeutic vaccines, Ther Adv Vaccines 2 (2014) 77–89.
[143] G. Moron, G. Dadaglio, C. Leclerc, New tools for antigen delivery to the MHC class I pathway, Trends Immunol 25 (2004) 92–97.
[144] D.S. Vinay, E.P. Ryan, G. Pawelec, W.H. Talib, J. Stagg, E. Elkord, T. Lichtor, W.K. Decker, R.L. Whelan, H. Kumara, E. Signori, K. Honoki, A.G. Georgakilas, A. Amin, W.G. Helferich, C.S. Boosani, G. Guha, M.R. Ciriolo, S. Chen, S.I. Mohammed, A.S. Azmi, W.N. Keith, A. Bilsland, D. Bhakta, D. Halicka, H. Fujii, K. Aquilano, S.S. Ashraf, S. Nowsheen, X. Yang, B.K. Choi, B.S. Kwon, Immune evasion in cancer: Mechanistic basis and therapeutic strategies, Semin Cancer Biol 35 (Suppl) (2015) S185–S198.
[145] G.L. Beatty, W.L. Gladney, Immune escape mechanisms as a guide for cancer immunotherapy, Clinical cancer research : an official journal of the American Association for Cancer Research 21 (2015) 687–692.
[146] M.A. Postow, M.K. Callahan, C.A. Barker, Y. Yamada, J. Yuan, S. Kitano, Z. Mu, T. Rasalan, M. Adamow, E. Ritter, C. Sedrak, A.A. Jungbluth, R. Chua, A.S. Yang, R.A. Roman, S. Rosner, B. Benson, J.P. Allison, A.M. Lesokhin, S. Gnjatic, J.D. Wolchok, Immunologic correlates of the abscopal effect in a patient with melanoma, N Engl J Med 366 (2012) 925–931.
[147] R.H. Mole, Whole body irradiation; radiobiology or medicine? Br J Radiol 26 (1953) 234–241.
[148] Z.I. Hu, H.L. McArthur, A.Y. Ho, The Abscopal Effect of Radiation Therapy: What Is It and How Can We Use It in Breast Cancer? Curr Breast Cancer Rep 9 (2017) 45–51.
[149] X. Duan, C. Chan, N. Guo, W. Han, R.R. Weichselbaum, W. Lin, Photodynamic Therapy Mediated by Nontoxic Core-Shell Nanoparticles Synergizes with Immune Checkpoint Blockade To Elicit Antitumor Immunity and Antimetastatic Effect on Breast Cancer, J Am Chem Soc 138 (2016) 16686–16695.

[150] M.E. Rodriguez-Ruiz, I. Rodriguez, S. Garasa, B. Barbes, J.L. Solorzano, J.L. Perez-Gracia, S. Labiano, M.F. Sanmamed, A. Azpilikueta, E. Bolanos, A.R. Sanchez-Paulete, M.A. Aznar, A. Rouzaut, K.A. Schalper, M. Jure-Kunkel, I. Melero, Abscopal Effects of Radiotherapy Are Enhanced by Combined Immunostimulatory mAbs and Are Dependent on CD8 T Cells and Crosspriming, Cancer Res 76 (2016) 5994–6005.
[151] M. Suresh, J.K. Whitmire, L.E. Harrington, C.P. Larsen, T.C. Pearson, J.D. Altman, R. Ahmed, Role of CD28-B7 interactions in generation and maintenance of CD8 T cell memory, J Immunol 167 (2001) 5565–5573.
[152] C.A. London, M.P. Lodge, A.K. Abbas, Functional responses and costimulator dependence of memory CD4+ T cells, J Immunol 164 (2000) 265–272.
[153] H. Gudmundsdottir, A.D. Wells, L.A. Turka, Dynamics and requirements of T cell clonal expansion in vivo at the single-cell level: effector function is linked to proliferative capacity, J Immunol 162 (1999) 5212–5223.
[154] S.C. Formenti, S. Demaria, Systemic effects of local radiotherapy, Lancet Oncol 10 (2009) 718–726.
[155] C.A. Klebanoff, L. Gattinoni, N.P. Restifo, CD8+ T-cell memory in tumor immunology and immunotherapy, Immunol Rev 211 (2006) 214–224.
[156] T. Boon, P.G. Coulie, B.J. Van den Eynde, P. van der Bruggen, Human T cell responses against melanoma, Annu Rev Immunol 24 (2006) 175–208.
[157] N.P. Restifo, S.A. Rosenberg, Use of standard criteria for assessment of cancer vaccines, Lancet Oncol 6 (2005) 3–4.
[158] S.A. Rosenberg, J.C. Yang, N.P. Restifo, Cancer immunotherapy: moving beyond current vaccines, Nat Med 10 (2004) 909–915.
[159] S.A. Rosenberg, R.M. Sherry, K.E. Morton, W.J. Scharfman, J.C. Yang, S.L. Topalian, R.E. Royal, U. Kammula, N.P. Restifo, M.S. Hughes, D. Schwartzentruber, D.M. Berman, S.L. Schwarz, L.T. Ngo, S.A. Mavroukakis, D.E. White, S.M. Steinberg, Tumor progression can occur despite the induction of very high levels of self/tumor antigen-specific CD8+ T cells in patients with melanoma, J Immunol 175 (2005) 6169–6176.
[160] F. Pages, A. Berger, M. Camus, F. Sanchez-Cabo, A. Costes, R. Molidor, B. Mlecnik, A. Kirilovsky, M. Nilsson, D. Damotte, T. Meatchi, P. Bruneval, P.H. Cugnenc, Z. Trajanoski, W.H. Fridman, J. Galon, Effector memory T cells, early metastasis, and survival in colorectal cancer, N Engl J Med 353 (2005) 2654–2666.
[161] M. Kronenberg, A. Rudensky, Regulation of immunity by self-reactive T cells, Nature 435 (2005) 598–604.
[162] D.L. Barber, E.J. Wherry, R. Ahmed, Cutting edge: rapid in vivo killing by memory CD8 T cells, J Immunol 171 (2003) 27–31.
[163] E.J. Wherry, V. Teichgraber, T.C. Becker, D. Masopust, S.M. Kaech, R. Antia, U.H. von Andrian, R. Ahmed, Lineage relationship and protective immunity of memory CD8 T cell subsets, Nat Immunol 4 (2003) 225–234.
[164] V.A. Pedicord, W. Montalvo, I.M. Leiner, J.P. Allison, Single dose of anti-CTLA-4 enhances CD8+ T-cell memory formation, function, and maintenance, Proc Natl Acad Sci U S A 108 (2011) 266–271.
[165] L. Huang, H. Xu, G. Peng, TLR-mediated metabolic reprogramming in the tumor microenvironment: potential novel strategies for cancer immunotherapy, Cell Mol Immunol 15 (2018) 428–437.
[166] K.T. Byrne, R.H. Vonderheide, CD40 therapy and surgery: a potential immunologic partnership, J Immunother 36 (2013) 359–361.
[167] P.S. Linsley, W. Brady, M. Urnes, L.S. Grosmaire, N.K. Damle, J.A. Ledbetter, CTLA-4 is a second receptor for the B cell activation antigen B7, J Exp Med 174 (1991) 561–569.
[168] H. Schneider, J. Downey, A. Smith, B.H. Zinselmeyer, C. Rush, J.M. Brewer, B. Wei, N. Hogg, P. Garside, C.E. Rudd, Reversal of the TCR stop signal by CTLA-4, Science 313 (2006) 1972–1975.
[169] J.L. Riley, M. Mao, S. Kobayashi, M. Biery, J. Burchard, G. Cavet, B.P. Gregson, C.H. June, P.S. Linsley, Modulation of TCR-induced transcriptional profiles by ligation of CD28, ICOS, and CTLA-4 receptors, Proc Natl Acad Sci U S A 99 (2002) 11790–11795.
[170] O.S. Qureshi, Y. Zheng, K. Nakamura, K. Attridge, C. Manzotti, E.M. Schmidt, J. Baker, L.E. Jeffery, S. Kaur, Z. Briggs, T.Z. Hou, C.E. Futter, G. Anderson, L.S. Walker, D.M. Sansom, Trans-endocytosis of CD80 and CD86: a molecular basis for the cell-extrinsic function of CTLA-4, Science 332 (2011) 600–603.
[171] D. Schadendorf, F.S. Hodi, C. Robert, J.S. Weber, K. Margolin, O. Hamid, D. Patt, T.T. Chen, D.M. Berman, J.D. Wolchok, Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma, J Clin Oncol 33 (2015) 1889–1894.
[172] Y. Ishida, Y. Agata, K. Shibahara, T. Honjo, Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death, EMBO J 11 (1992) 3887–3895.
[173] G.J. Freeman, A.J. Long, Y. Iwai, K. Bourque, T. Chernova, H. Nishimura, L.J. Fitz, N. Malenkovich, T. Okazaki, M.C. Byrne, H.F. Horton, L. Fouser, L. Carter, V. Ling, M.R. Bowman, B.M. Carreno, M. Collins, C.R. Wood, T. Honjo, Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation, J Exp Med 192 (2000) 1027–1034.
[174] M.E. Keir, S.C. Liang, I. Guleria, Y.E. Latchman, A. Qipo, L.A. Albacker, M. Koulmanda, G.J. Freeman, M.H. Sayegh, A.H. Sharpe, Tissue expression of PD-L1 mediates peripheral T cell tolerance, J Exp Med 203 (2006) 883–895.
[175] C. Robert, J. Schachter, G.V. Long, A. Arance, J.J. Grob, L. Mortier, A. Daud, M.S. Carlino, C. McNeil, M. Lotem, J. Larkin, P. Lorigan, B. Neyns, C.U. Blank, O. Hamid, C. Mateus, R. Shapira-Frommer, M. Kosh, H. Zhou, N. Ibrahim, S. Ebbinghaus, A. Ribas, K.-. investigators, Pembrolizumab versus Ipilimumab in Advanced Melanoma, N Engl J Med 372 (2015) 2521–2532.
[176] C. Robert, G.V. Long, J. Schachter, A. Arance, J.J. Grob, L. Mortier, A. Daud, M.S. Carlino, C.M. McNeil, M. Lotem, J.M.G. Larkin, P. Lorigan, B. Neyns, C.U. Blank, T.M. Petrella, O. Hamid, H. Zhou, B.H. Moreno, N. Ibrahim, A. Ribas, Long-term outcomes in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab (pembro) treatment, Journal of Clinical Oncology 35 (2017) 9504.
[177] J. Naidoo, D.B. Page, B.T. Li, L.C. Connell, K. Schindler, M.E. Lacouture, M.A. Postow, J.D. Wolchok, Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies, Ann Oncol 27 (2016) 1362.
[178] B. Chmielowski, O. Hamid, D.R. Minor, S.P. D'Angelo, G.K. Pennock, K. Grossmann, P.A. Ascierto, A. Daud, R. Dummer, F.S. Hodi, C. Lebbé, C. Robert, J.A. Sosman, A. Yang, A. Lambert, J.S. Weber, A phase III open-label study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus investigator's choice in advanced melanoma patients progressing post anti-CTLA-4 therapy, Journal of Clinical Oncology 31 (2013) TPS9105.
[179] J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.J. Grob, C.L. Cowey, C.D. Lao, J. Wagstaff, D. Schadendorf, P.F. Ferrucci, M. Smylie, R. Dummer, A. Hill, D. Hogg, J. Haanen, M.S. Carlino, O. Bechter, M. Maio, I. Marquez-Rodas, M. Guidoboni, G. McArthur, C. Lebbe, P.A. Ascierto, G.V. Long, J. Cebon, J. Sosman, M.A. Postow, M.K. Callahan, D. Walker, L. Rollin, R. Bhore, F.S. Hodi, J. Larkin, Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma, N Engl J Med 377 (2017) 1345–1356.
[180] P. Sharma, S. Hu-Lieskovan, J.A. Wargo, A. Ribas, Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy, Cell 168 (2017) 707–723.
[181] J.M. Zaretsky, A. Garcia-Diaz, D.S. Shin, H. Escuin-Ordinas, W. Hugo, S. Hu-Lieskovan, D.Y. Torrejon, G. Abril-Rodriguez, S. Sandoval, L. Barthly, J. Saco, B. Homet Moreno, R. Mezzadra, B. Chmielowski, K. Ruchalski, I.P. Shintaku, P.J. Sanchez, C. Puig-Saus, G. Cherry, E. Seja, X. Kong, J. Pang, B. Berent-Maoz, B. Comin-Anduix, T.G. Graeber, P.C. Tumeh, T.N. Schumacher, R.S. Lo, A. Ribas, Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma, N Engl J Med 375 (2016) 819–829.
[182] S.L. Topalian, F.S. Hodi, J.R. Brahmer, S.N. Gettinger, D.C. Smith, D.F. McDermott, J.D. Powderly, R.D. Carvajal, J.A. Sosman, M.B. Atkins, P.D. Leming, D.R. Spigel, S.J. Antonia, L. Horn, C.G. Drake, D.M. Pardoll, L. Chen, W.H. Sharfman, R.A. Anders, J.M. Taube, T.L. McMiller, H. Xu, A.J. Korman, M. Jure-Kunkel, S. Agrawal, D. McDonald, G.D. Kollia, A. Gupta, J.M. Wigginton, M. Sznol, Safety, activity, and immune correlates of anti-PD-1 antibody in cancer, N Engl J Med 366 (2012) 2443–2454.
[183] W. Hugo, J.M. Zaretsky, L. Sun, C. Song, B.H. Moreno, S. Hu-Lieskovan, B. Berent-Maoz, J. Pang, B. Chmielowski, G. Cherry, E. Seja, S. Lomeli, X. Kong, M.C. Kelley, J.A. Sosman, D.B. Johnson, A. Ribas, R.S. Lo, Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma, Cell 165 (2016) 35–44.
[184] J.S. O'Donnell, G.V. Long, R.A. Scolyer, M.W. Teng, M.J. Smyth, Resistance to PD1/PDL1 checkpoint inhibition, Cancer Treat Rev 52 (2017) 71–81.
[185] M. Wang, J. Zhao, L. Zhang, F. Wei, Y. Lian, Y. Wu, Z. Gong, S. Zhang, J. Zhou, K. Cao, X. Li, W. Xiong, G. Li, Z. Zeng, C. Guo, Role of tumor microenvironment in tumorigenesis, J Cancer 8 (2017) 761–773.
[186] T.L. Whiteside, The tumor microenvironment and its role in promoting tumor growth, Oncogene 27 (2008) 5904–5912.
[187] F.R. Balkwill, M. Capasso, T. Hagemann, The tumor microenvironment at a glance, J Cell Sci 125 (2012) 5591–5596.
[188] A. Mantovani, F. Marchesi, A. Malesci, L. Laghi, P. Allavena, Tumour-associated macrophages as treatment targets in oncology, Nat Rev Clin Oncol 14 (2017) 399–416.
[189] S. Koyama, E.A. Akbay, Y.Y. Li, G.S. Herter-Sprie, K.A. Buczkowski, W.G. Richards, L. Gandhi, A.J. Redig, S.J. Rodig, H. Asahina, R.E. Jones, M.M. Kulkarni, M. Kuraguchi, S. Palakurthi, P.E. Fecci, B.E. Johnson, P.A. Janne, J.A. Engelman, S.P. Gangadharan, D.B. Costa, G.J. Freeman, R. Bueno, F.S. Hodi, G. Dranoff, K.K. Wong, P.S. Hammerman, Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints, Nat Commun 7 (2016), 10501.
[190] A. Garcia-Diaz, D.S. Shin, B.H. Moreno, J. Saco, H. Escuin-Ordinas, G.A. Rodriguez, J.M. Zaretsky, L. Sun, W. Hugo, X. Wang, G. Parisi, C.P. Saus, D.Y. Torrejon, T.G. Graeber, B. Comin-Anduix, S. Hu-Lieskovan, R. Damoiseaux, R.S. Lo, A. Ribas, Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression, Cell Rep 19 (2017) 1189–1201.
[191] K. Abiko, N. Matsumura, J. Hamanishi, N. Horikawa, R. Murakami, K. Yamaguchi, Y. Yoshioka, T. Baba, I. Konishi, M. Mandai, IFN-gamma from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer, Br J Cancer 112 (2015) 1501–1509.
[192] T.N. Gide, J.S. Wilmott, R.A. Scolyer, G.V. Long, Primary and Acquired Resistance to Immune Checkpoint Inhibitors in Metastatic Melanoma, Clinical cancer research : an official journal of the American Association for Cancer Research 24 (2018) 1260–1270.
[193] D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, L.A. Diaz Jr., PD-1 Blockade in Tumors with Mismatch-Repair Deficiency, N Engl J Med 372 (2015) 2509–2520.
[194] T.E. Angell, M.G. Lechner, J.K. Jang, J.S. LoPresti, A.L. Epstein, MHC class I loss is a frequent mechanism of immune escape in papillary thyroid cancer that is reversed by interferon and selumetinib treatment in vitro, Clinical cancer research : an official journal of the American Association for Cancer Research 20 (2014) 6034–6044.
[195] M. Bernal, F. Ruiz-Cabello, A. Concha, A. Paschen, F. Garrido, Implication of the beta2-microglobulin gene in the generation of tumor escape phenotypes, Cancer Immunol Immunother 61 (2012) 1359–1371.
[196] L. Galluzzi, A. Buque, O. Kepp, L. Zitvogel, G. Kroemer, Immunogenic cell death in cancer and infectious disease, Nat Rev Immunol 17 (2017) 97–111.

[197] X. Liu, L. Liu, Z. Ren, K. Yang, H. Xu, Y. Luan, K. Fu, J. Guo, H. Peng, M. Zhu, Y.X. Fu, Dual Targeting of Innate and Adaptive Checkpoints on Tumor Cells Limits Immune Evasion, Cell Rep 24 (2018) 2101–2111.
[198] C. He, X. Duan, N. Guo, C. Chan, C. Poon, R.R. Weichselbaum, W. Lin, Core-shell nanoscale coordination polymers combine chemotherapy and photodynamic therapy to potentiate checkpoint blockade cancer immunotherapy, Nat Commun 7 (2016), 12499.
[199] J. Zhao, Y. Cao, Z. Lei, Z. Yang, B. Zhang, B. Huang, Selective depletion of CD4+CD25+Foxp3+ regulatory T cells by low-dose cyclophosphamide is explained by reduced intracellular ATP levels, Cancer Res 70 (2010) 4850–4858.
[200] R. Perret, F. Ronchese, Memory T cells in cancer immunotherapy: which CD8 T-cell population provides the best protection against tumours? Tissue Antigens 72 (2008) 187–194.
[201] A. Bhatia, Y. Kumar, Cellular and molecular mechanisms in cancer immune escape: a comprehensive review, Expert Rev Clin Immunol 10 (2014) 41–62.
[202] H.O. Alsaab, S. Sau, R. Alzhrani, K. Tatiparti, K. Bhise, S.K. Kashaw, A.K. Iyer, PD-1 and PD-L1 Checkpoint Signaling Inhibition for Cancer Immunotherapy: Mechanism, Combinations, and Clinical Outcome, Front Pharmacol 8 (2017) 561.
[203] C.H. June, R.S. O'Connor, O.U. Kawalekar, S. Ghassemi, M.C. Milone, CAR T cell immunotherapy for human cancer, Science 359 (2018) 1361–1365.
[204] A. Ribas, J.D. Wolchok, Cancer immunotherapy using checkpoint blockade, Science 359 (2018) 1350–1355.
[205] M.R. Elliott, F.B. Chekeni, P.C. Trampont, E.R. Lazarowski, A. Kadl, S.F. Walk, D. Park, R.I. Woodson, M. Ostankovich, P. Sharma, J.J. Lysiak, T.K. Harden, N. Leitinger, K.S. Ravichandran, Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance, Nature 461 (2009) 282–286.
[206] A. Iwata, V. Morgan-Stevenson, B. Schwartz, L. Liu, J. Tupper, X. Zhu, J. Harlan, R. Winn, Extracellular BCL2 proteins are danger-associated molecular patterns that reduce tissue damage in murine models of ischemia-reperfusion injury, PLoS One 5 (2010), e9103.
[207] A.D. Garg, D.V. Krysko, T. Verfaillie, A. Kaczmarek, G.B. Ferreira, T. Marysael, N. Rubio, M. Firczuk, C. Mathieu, A.J. Roebroek, W. Annaert, J. Golab, P. de Witte, P. Vandenabeele, P. Agostinis, A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death, EMBO J 31 (2012) 1062–1079.
[208] S.J. Gardai, K.A. McPhillips, S.C. Frasch, W.J. Janssen, A. Starefeldt, J.E. Murphy-Ullrich, D.L. Bratton, P.A. Oldenborg, M. Michalak, P.M. Henson, Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte, Cell 123 (2005) 321–334.
[209] J.W. Dear, K.J. Simpson, M.P. Nicolai, J.H. Catterson, J. Street, T. Huizinga, D.G. Craig, K. Dhaliwal, S. Webb, D.N. Bateman, D.J. Webb, Cyclophilin A is a damage-associated molecular pattern molecule that mediates acetaminophen-induced liver injury, J Immunol 187 (2011) 3347–3352.
[210] A.D. Garg, D.V. Krysko, P. Vandenabeele, P. Agostinis, Hypericin-based photodynamic therapy induces surface exposure of damage-associated molecular patterns like HSP70 and calreticulin, Cancer Immunol Immunother 61 (2012) 215–221.
[211] R. Spisek, A. Charalambous, A. Mazumder, D.H. Vesole, S. Jagannath, M.V. Dhodapkar, Bortezomib enhances dendritic cell (DC)-mediated induction of immunity to human myeloma via exposure of cell surface heat shock protein 90 on dying tumor cells: therapeutic implications, Blood 109 (2007) 4839–4845.
[212] G.Y. Chen, J. Tang, P. Zheng, Y. Liu, CD24 and Siglec-10 selectively repress tissue damage-induced immune responses, Science 323 (2009) 1722–1725.
[213] D. Tang, R. Kang, H.J. Zeh 3rd, M.T. Lotze, High-mobility group box 1 and cancer, Biochim Biophys Acta 1799 (2010) 131–140.
[214] S. Ahrens, S. Zelenay, D. Sancho, P. Hanc, S. Kjaer, C. Feest, G. Fletcher, C. Durkin, A. Postigo, M. Skehel, F. Batista, B. Thompson, M. Way, C. Reis e Sousa, O. Schulz, F-actin is an evolutionarily conserved damage-associated molecular pattern recognized by DNGR-1, a receptor for dead cells, Immunity 36 (2012) 635–645.
[215] E. Silk, H. Zhao, H. Weng, D. Ma, The role of extracellular histone in organ injury, Cell Death Dis 8 (2017) e2812.
[216] J. Xu, X. Zhang, M. Monestier, N.L. Esmon, C.T. Esmon, Extracellular histones are mediators of death through TLR2 and TLR4 in mouse fatal liver injury, J Immunol 187 (2011) 2626–2631.
[217] D. Yang, Y.V. Postnikov, Y. Li, P. Tewary, G. de la Rosa, F. Wei, D. Klinman, T. Gioannini, J.P. Weiss, T. Furusawa, M. Bustin, J.J. Oppenheim, High-mobility group nucleosome-binding protein 1 acts as an alarmin and is critical for lipopolysaccharide-induced immune responses, J Exp Med 209 (2012) 157–171.
[218] T. Murakami, Z. Hu, H. Tamura, I. Nagaoka, Release mechanism of high mobility group nucleosome binding domain 1 from lipopolysaccharide-stimulated macrophages, Mol Med Rep 13 (2016) 3115–3120.
[219] T. Eigenbrod, J.H. Park, J. Harder, Y. Iwakura, G. Nunez, Cutting edge: critical role for mesothelial cells in necrosis-induced inflammation through the recognition of IL-1 alpha released from dying cells, J Immunol 181 (2008) 8194–8198.
[220] A.U. Luthi, S.P. Cullen, E.A. McNeela, P.J. Duriez, I.S. Afonina, C. Sheridan, G. Brumatti, R.C. Taylor, K. Kersse, P. Vandenabeele, E.C. Lavelle, S.J. Martin, Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases, Immunity 31 (2009) 84–98.
[221] I.C. Scott, J.B. Majithiya, C. Sanden, P. Thornton, P.N. Sanders, T. Moore, M. Guscott, D.J. Corkill, J.S. Erjefalt, E.S. Cohen, Interleukin-33 is activated by allergen- and necrosis-associated proteolytic activities to regulate its alarmin activity during epithelial damage, Sci Rep 8 (2018) 3363.
[222] A. Mathew, T.A. Lindsley, A. Sheridan, D.L. Bhoiwala, S.F. Hushmendy, E.J. Yager, E.A. Ruggiero, D.R. Crawford, Degraded mitochondrial DNA is a newly identified subtype of the damage associated molecular pattern (DAMP) family and possible trigger of neurodegeneration, J Alzheimers Dis 30 (2012) 617–627.
[223] T. Vanden Berghe, M. Kalai, G. Denecker, A. Meeus, X. Saelens, P. Vandenabeele, Necrosis is associated with IL-6 production but apoptosis is not, Cell Signal 18 (2006) 328–335.
[224] Q. Zhang, M. Raoof, Y. Chen, Y. Sumi, T. Sursal, W. Junger, K. Brohi, K. Itagaki, C.J. Hauser, Circulating mitochondrial DAMPs cause inflammatory responses to injury, Nature 464 (2010) 104–107.
[225] D.V. Krysko, P. Agostinis, O. Krysko, A.D. Garg, C. Bachert, B.N. Lambrecht, P. Vandenabeele, Emerging role of damage-associated molecular patterns derived from mitochondria in inflammation, Trends Immunol 32 (2011) 157–164.
[226] M.W. Julian, G. Shao, S. Bao, D.L. Knoell, T.L. Papenfuss, Z.C. VanGundy, E.D. Crouser, Mitochondrial transcription factor A serves as a danger signal by augmenting plasmacytoid dendritic cell responses to DNA, J Immunol 189 (2012) 433–443.
[227] J.P. Little, S. Simtchouk, S.M. Schindler, E.B. Villanueva, N.E. Gill, D.G. Walker, K.R. Wolthers, A. Klegeris, Mitochondrial transcription factor A (Tfam) is a pro-inflammatory extracellular signaling molecule recognized by brain microglia, Mol Cell Neurosci 60 (2014) 88–96.
[228] Y. Shi, J.E. Evans, K.L. Rock, Molecular identification of a danger signal that alerts the immune system to dying cells, Nature 425 (2003) 516–521.
[229] D.L. Rosin, M.D. Okusa, Dangers within: DAMP responses to damage and cell death in kidney disease, J Am Soc Nephrol 22 (2011) 416–425.
[230] L. Galluzzi, O. Kepp, G. Kroemer, Mitochondria: master regulators of danger signalling, Nat Rev Mol Cell Biol 13 (2012) 780–788.
[231] A.E. Moghaddam, K.H. Gartlan, L. Kong, Q.J. Sattentau, Reactive carbonyls are a major Th2-inducing damage-associated molecular pattern generated by oxidative stress, J Immunol 187 (2011) 1626–1633.
[232] Y.I. Miller, S.H. Choi, P. Wiesner, L. Fang, R. Harkewicz, K. Hartvigsen, A. Boullier, A. Gonen, C.J. Diehl, X. Que, E. Montano, P.X. Shaw, S. Tsimikas, C.J. Binder, J.L. Witztum, Oxidation-specific epitopes are danger-associated molecular patterns recognized by pattern recognition receptors of innate immunity, Circ Res 108 (2011) 235–248.
[233] H.J. Anders, L. Schaefer, Beyond tissue injury-damage-associated molecular patterns, toll-like receptors, and inflammasomes also drive regeneration and fibrosis, J Am Soc Nephrol 25 (2014) 1387–1400.
[234] K. Kariko, H. Ni, J. Capodici, M. Lamphier, D. Weissman, mRNA is an endogenous ligand for Toll-like receptor 3, J Biol Chem 279 (2004) 12542–12550.
[235] R. Donato, RAGE: a single receptor for several ligands and different cellular responses: the case of certain S100 proteins, Curr Mol Med 7 (2007) 711–724.
[236] D. Foell, H. Wittkowski, T. Vogl, J. Roth, S100 proteins expressed in phagocytes: a novel group of damage-associated molecular pattern molecules, J Leukoc Biol 81 (2007) 28–37.
[237] I. Martins, A. Tesniere, O. Kepp, M. Michaud, F. Schlemmer, L. Senovilla, C. Seror, D. Metivier, J.L. Perfettini, L. Zitvogel, G. Kroemer, Chemotherapy induces ATP release from tumor cells, Cell Cycle 8 (2009) 3723–3728.
[238] T. Panaretakis, O. Kepp, U. Brockmeier, A. Tesniere, A.C. Bjorklund, D.C. Chapman, M. Durchschlag, N. Joza, G. Pierron, P. van Endert, J. Yuan, L. Zitvogel, F. Madeo, D.B. Williams, G. Kroemer, Mechanisms of pre-apoptotic calreticulin exposure in immunogenic cell death, EMBO J 28 (2009) 578–590.
[239] G. Schiavoni, A. Sistigu, M. Valentini, F. Mattei, P. Sestili, F. Spadaro, M. Sanchez, S. Lorenzi, M.T. D'Urso, F. Belardelli, L. Gabriele, E. Proietti, L. Bracci, Cyclophosphamide synergizes with type I interferons through systemic dendritic cell reactivation and induction of immunogenic tumor apoptosis, Cancer Res 71 (2011) 768–778.
[240] H.M. Chen, P.H. Wang, S.S. Chen, C.C. Wen, Y.H. Chen, W.C. Yang, N.S. Yang, Shikonin induces immunogenic cell death in tumor cells and enhances dendritic cell-based cancer vaccine, Cancer Immunol Immunother 61 (2012) 1989–2002.
[241] M. Cirone, L. Di Renzo, L.V. Lotti, V. Conte, P. Trivedi, R. Santarelli, R. Gonnella, L. Frati, A. Faggioni, Primary effusion lymphoma cell death induced by bortezomib and AG 490 activates dendritic cells through CD91, PLoS One 7 (2012), e31732.
[242] G. Garrido, A. Rabasa, B. Sanchez, M.V. Lopez, R. Blanco, A. Lopez, D.R. Hernandez, R. Perez, L.E. Fernandez, Induction of immunogenic apoptosis by blockade of epidermal growth factor receptor activation with a specific antibody, J Immunol 187 (2011) 4954–4966.
[243] L. Menger, E. Vacchelli, S. Adjemian, I. Martins, Y. Ma, S. Shen, T. Yamazaki, A.Q. Sukkurwala, M. Michaud, G. Mignot, F. Schlemmer, E. Sulpice, C. Locher, X. Gidrol, F. Ghiringhelli, N. Modjtahedi, L. Galluzzi, F. Andre, L. Zitvogel, O. Kepp, G. Kroemer, Cardiac glycosides exert anticancer effects by inducing immunogenic cell death, Sci Transl Med 4 (2012) 143ra199.
[244] M. Obeid, T. Panaretakis, N. Joza, R. Tufi, A. Tesniere, P. van Endert, L. Zitvogel, G. Kroemer, Calreticulin exposure is required for the immunogenicity of gamma-irradiation and UVC light-induced apoptosis, Cell Death Differ 14 (2007) 1848–1850.
[245] E.B. Golden, L. Apetoh, Radiotherapy and immunogenic cell death, Semin Radiat Oncol 25 (2015) 11–17.
[246] S.R. Gameiro, M.L. Jammeh, M.M. Wattenberg, K.Y. Tsang, S. Ferrone, J.W. Hodge, Radiation-induced immunogenic modulation of tumor enhances antigen processing and calreticulin exposure, resulting in enhanced T-cell killing, Oncotarget 5 (2014) 403–416.
[247] H. Bugaut, M. Bruchard, H. Berger, V. Derangere, L. Odoul, R. Euvrard, S. Ladoire, F. Chalmin, F. Vegran, C. Rebe, L. Apetoh, F. Ghiringhelli, G. Mignot, Bleomycin exerts ambivalent antitumor immune effect by triggering both immunogenic cell death and proliferation of regulatory T cells, PLoS One 8 (2013), e65181.
[248] C. Sun, H. Wang, S. Mao, J. Liu, S. Li, J. Wang, Reactive oxygen species involved in CT26 immunogenic cell death induced by Clostridium difficile toxin B, Immunol Lett 164 (2015) 65–71.
[249] J. Fucikova, I. Moserova, I. Truxova, I. Hermanova, I. Vancurova, S. Partlova, A. Fialova, L. Sojka, P.F. Cartron, M. Houska, L. Rob, J. Bartunkova, R. Spisek, High hydrostatic pressure induces immunogenic cell death in human tumor cells, Int J Cancer 135 (2014) 1165–1177.

[250] I. Adkins, J. Fucikova, A.D. Garg, P. Agostinis, R. Spisek, Physical modalities inducing immunogenic tumor cell death for cancer immunotherapy, Oncoimmunology 3 (2014), e968434.
[251] E.M. Weiss, S. Meister, C. Janko, N. Ebel, E. Schlucker, R. Meyer-Pittroff, R. Fietkau, M. Herrmann, U.S. Gaipl, B. Frey, High hydrostatic pressure treatment generates inactivated mammalian tumor cells with immunogeneic features, J Immunotoxicol 7 (2010) 194–204.
[252] Z. Yu, J. Geng, M. Zhang, Y. Zhou, Q. Fan, J. Chen, Treatment of osteosarcoma with microwave thermal ablation to induce immunogenic cell death, Oncotarget 5 (2014) 6526–6539.
[253] A.D. Garg, S. Elsen, D.V. Krysko, P. Vandenabeele, P. de Witte, P. Agostinis, Resistance to anticancer vaccination effect is controlled by a cancer cell-autonomous phenotype that disrupts immunogenic phagocytic removal, Oncotarget 6 (2015) 26841–26860.
[254] E.B. Golden, D. Frances, I. Pellicciotta, S. Demaria, M. Helen Barcellos-Hoff, S.C. Formenti, Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death, Oncoimmunology 3 (2014), e28518.
[255] M. Korbelik, W. Zhang, S. Merchant, Involvement of damage-associated molecular patterns in tumor response to photodynamic therapy: surface expression of calreticulin and high-mobility group box-1 release, Cancer Immunol Immunother 60 (2011) 1431–1437.
[256] P. Duewell, A. Steger, H. Lohr, H. Bourhis, H. Hoelz, S.V. Kirchleitner, M.R. Stieg, S. Grassmann, S. Kobold, J.T. Siveke, S. Endres, M. Schnurr, RIG-I-like helicases induce immunogenic cell death of pancreatic cancer cells and sensitize tumors toward killing by CD8(+) T cells, Cell Death Differ 21 (2014) 1825–1837.
[257] J. Sonnemann, S. Gressmann, S. Becker, S. Wittig, M. Schmudde, J.F. Beck, The histone deacetylase inhibitor vorinostat induces calreticulin exposure in childhood brain tumour cells in vitro, Cancer Chemother Pharmacol 66 (2010) 611–616.
[258] Y. Yang, X.J. Li, Z. Chen, X.X. Zhu, J. Wang, L.B. Zhang, L. Qiang, Y.J. Ma, Z.Y. Li, Q.L. Guo, Q.D. You, Wogonin induced calreticulin/annexin A1 exposure dictates the immunogenicity of cancer cells in a PERK/AKT dependent manner, PLoS One 7 (2012), e50811.
[259] A.D. Garg, P. Agostinis, ER stress, autophagy and immunogenic cell death in photodynamic therapy-induced anti-cancer immune responses, Photochem Photobiol Sci 13 (2014) 474–487.
[260] I. Diaconu, V. Cerullo, M.L. Hirvinen, S. Escutenaire, M. Ugolini, S.K. Pesonen, S. Bramante, S. Parviainen, A. Kanerva, A.S. Loskog, A.G. Eliopoulos, S. Pesonen, A. Hemminki, Immune response is an important aspect of the antitumor effect produced by a CD40L-encoding oncolytic adenovirus, Cancer Res 72 (2012) 2327–2338.
[261] D.Y. Wong, W.W. Ong, W.H. Ang, Induction of immunogenic cell death by chemotherapeutic platinum complexes, Angew Chem Int Ed Engl 54 (2015) 6483–6487.
[262] P.S. Petrova, N.N. Viller, M. Wong, X. Pang, G.H. Lin, K. Dodge, V. Chai, H. Chen, V. Lee, V. House, N.T. Vigo, D. Jin, T. Mutukura, M. Charbonneau, T. Truong, S. Viau, L.D. Johnson, E. Linderoth, E.L. Sievers, S. Maleki Vareki, R. Figueredo, M. Pampillo, J. Koropatnick, S. Trudel, N. Mbong, L. Jin, J.C. Wang, R.A. Uger, TTI-621 (SIRPalphaFc): A CD47-Blocking Innate Immune Checkpoint Inhibitor with Broad Antitumor Activity and Minimal Erythrocyte Binding, Clinical cancer research : an official journal of the American Association for Cancer Research 23 (2017) 1068–1079.
[263] E. Cho, G.H. Nam, Y. Hong, Y.K. Kim, D.H. Kim, Y. Yang, I.S. Kim, Comparison of exosomes and ferritin protein nanocages for the delivery of membrane protein therapeutics, J Control Release 279 (2018) 326–335.
[264] N. Tanaka, S. Abe-Dohmae, N. Iwamoto, M.L. Fitzgerald, S. Yokoyama, HMG-CoA reductase inhibitors enhance phagocytosis by upregulating ATP-binding cassette transporter A7, Atherosclerosis 217 (2011) 407–414.