

Immunological Mechanisms Underneath the Efficacy of Cancer Therapy

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Abstract

Accumulating preclinical and clinical evidence indicates that the success of several anticancer agents—including some conventional chemotherapeutics, targeted anticancer agents as well as specific forms of radiotherapy—depends (at least in part) on their ability to stimulate anticancer immune responses. Such immunostimulatory effects can be "on-target," i.e., they originate within cancer cells, or "off-target," i.e., they develop from

a heretofore unsuspected interaction between cancer therapy and the immune system. Here, we briefly discuss the immunologic mechanisms that underlie the efficacy of some forms of cancer therapy, as we highlight the rationale for combining these treatment modalities with immunotherapy to achieve superior therapeutic effects. *Cancer Immunol Res*; 4(11); 895–902. ©2016 AACR.

Introduction

In a seminal *Cell* paper from 2000, Hanahan and Weinberg summarized more than one century of preclinical and clinical cancer research as they proposed six common hallmarks of malignancy: (i) self-sufficiency in growth signals, (ii) insensitivity to antiproliferative cues, (iii) resistance to regulated cell death, (iv) limitless replicative potential, (v) prominent proangiogenic activity, and (vi) invasive and metastatic behavior (1). This model has been highly instrumental for subsequent investigation, possibly as it identified for the first time a limited amount of cellular features shared by most (if not all) tumors. Retrospectively, however, it also celebrated the view of cancer as a cell-autonomous disease, a sort of "endogenous infection" driven by the unrestrained expansion of a malignant precursor bearing genetic or epigenetic alterations (2). Perhaps the most unfortunate consequence of such a reductionistic vision, which (in different flavors) has permeated cancer research throughout the 20th century, is that tumors have long been approached (both in preclinical and clinical settings) much alike bacterial diseases. Thus, multiple anticancer therapeutics have been developed based on the concept that tumors should be eradicated with

powerful cytotoxic agents targeting malignant cells and sparing (as much as possible) their normal counterparts (3). Today, the limitations of such an approach leap to the eye. First, it is now clear that most of the molecular, biochemical, and metabolic features that characterize malignant cells (e.g., high rates of aerobic glycolysis) are less specific than originally thought, and *de facto* define other cells with a similar conduct (e.g., highly proliferating T cells; refs. 4, 5). Second (and most important in this context), the advent of the 21st century has brought about a renovated vision of cancer as a disease that arises, progresses, and responds to therapeutic challenges in the context of an intimate, bidirectional cross-talk with its microenvironment, including not only stromal and endothelial components, but also various populations of immune cells (6–8).

Based on these considerations, it is quite surprising to note that some anticancer agents developed throughout the 20th century according to the aforementioned paradigm, i.e., as if cancer were mostly a cell-autonomous disease, have demonstrated (at least some degree of) clinical efficacy and are still used for the treatment of various neoplasms (3). Even more surprising, these interventions include not only molecules with a superior specificity, such as targeted anticancer agents but also relatively non-selective approaches, like some conventional chemotherapeutics and radiotherapy (3). Thus, specificity may not constitute a common determinant of clinical efficacy in this context (although the importance of some degree of specificity as a means to limit the side effects of treatment is undeniable; ref. 9). Rather, several anticancer agents clinically used for the treatment of solid tumors (irrespective of type) appear to share the ability to activate novel or reactivate existent adaptive immune responses specific for malignant cells, even though they have never been selected for this property. Taken together, these observations suggest that the anticancer regimens that were not discarded at preclinical or clinical development based on safety issues or lack of efficacy and reached the clinical practice are enriched in agents with immunostimulatory activity. Obviously, similar considerations cannot be made for therapeutic regimens commonly used against hematologic neoplasms. Thus, high-dose cytarabine and the so-called CHOP regimen (high-dose cyclophosphamide, doxorubicin,

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vincristine, and prednisolone), which are routinely used for the management of some forms of leukemia and lymphoma (10, 11), are intrinsically immunosuppressive as part of their ability to kill malignant cells, which in this scenario are aberrant immune cell populations or progenitors thereof.

Multiple conventional chemotherapeutics and some targeted anticancer agents routinely used in patients affected by solid tumors, as well as selected forms of radiotherapy, have been shown to mediate robust immunostimulatory effects that are relevant for therapeutic responses (in both preclinical and clinical settings; ref. 12). Moreover, several immunological correlates of treatment, such as therapy-driven tumor infiltration by CD8⁺ cytotoxic T lymphocytes (CTLs) over CD4⁺CD25⁺FOXP3⁺ regulatory T (Treg) cells, or the activation of a type I interferon (IFN) response, have been associated with robust prognostic value in cohorts of patients affected by different neoplasms (13), including (but not limited to) breast (14–16), lung (17, 18), and colorectal carcinoma (19, 20).

The immunostimulatory effects of anticancer therapy can be "on-target," meaning that they originate from the interaction between therapy and cancer cells (although they may involve a molecular target that differs from the one underlying the cytotoxicity of treatment). So far, "on-target" immunostimulation by cancer therapy has been ascribed to two mutually nonexclusive mechanisms: increased antigenicity or adjuvanticity (12). Alternatively, the immunostimulatory effects of anticancer interventions can be "off-target," meaning that they stem from the interaction between therapy and the immune system. The "off-target" immunostimulatory activity of cancer therapy may result from the activation of immune effector cells (direct immunostimulation) as well as from the inhibition of immunosuppressive cell populations (indirect immunostimulation; ref. 12).

Here, we briefly present the immunological mechanisms that underlie the efficacy of anticancer interventions originally selected for their preferential cytotoxicity against malignant cells (Fig. 1), highlighting the rationale for combining these agents with immunotherapy to achieve superior therapeutic effects.

Increased Antigenicity

For being recognized by the adaptive arm of the immune system, any cell must expose antigenic peptides that have not been previously considered as harmless (and hence have not elicited central or peripheral tolerance mechanisms), in association with MHC class I molecules (21). As compared with healthy tissues, tumors generally are a good source of such neoantigens, mostly as a consequence of the high incidence of somatic mutations that affect the relatively instable genome of malignant cells (22). However, neoplastic cells tend to downregulate MHC class I molecules as a means to hide from the adaptive immune system (23–27). Of note, the complete loss of MHC class I expression underlies the only form of transmissible cancer known to date, the Tasmanian devil facial tumor disease (DFTD; ref. 28). Owing to the lack of MHC class I molecules from their surface, DFTD cells not only escape immune recognition by the primary host but also fail to elicit normal allograft rejection when they come in contact with a secondary host (28). This peculiar case exemplifies the importance of MHC class I expression for the antigenicity of cancer cells.

In mice and humans, the complete loss of MHC class I molecules favors the activation of natural killer (NK) cells upon the

de-inhibition of NK-cell receptors like killer cell lectin like receptor C1 (KLRC1, best known as NKG2A) and members of the killer-cell immunoglobulin-like receptor (KIR) family (29, 30). Thus, mouse and human malignant cells generally retain low levels of MHC class I molecules on their surface as they express decreased levels of ligands for activatory NK-cell receptors, such as killer cell lectin like receptor K1 (KLRK1, best known as NKG2D) and natural cytotoxicity triggering receptor 3 (NCR3, best known as NKp30), simultaneously escaping adaptive and innate immunity (31–33). Although neoplastic cells are more immunogenic than they normal counterparts *a priori*, they evolve under the selective pressure of the immune system, resulting in the selection of poorly immunogenic variants (in the context of a process that is commonly known as immunoediting; refs. 6, 7). Conventional chemotherapeutics, including 5-fluorouracil (one of the most frequently used anticancer drugs) and gemcitabine (a mainstay of the therapeutic armamentarium against pancreatic carcinoma; refs. 34–36), targeted anticancer agents such as the hypomethylating drug decitabine (which is routinely used in patients with myelodysplastic syndrome or acute myeloid leukemia; refs. 37, 38), the EGFR inhibitor gefitinib (which is approved in some countries for the therapy of non-small cell lung carcinoma; refs. 39, 40), the BRAF^{V600E}-specific molecule dabrafenib and the MEK inhibitor trametinib (both of which are approved for the treatment of melanoma patients bearing BRAF mutations; ref. 41), as well as radiotherapy (42, 43), have been shown to boost the antigenicity of human or mouse cancer cells cultured *in vitro* or grown in immunocompetent hosts, mostly as a consequence of restored MHC class I expression. Other anticancer agents that (directly or indirectly) promote genomic instability (i.e., they further increase the mutational load of malignant cells)—such as the PARP1 inhibitor olaparib (which is nowadays used for the treatment of ovarian carcinoma patients with germline BRCA1/BRCA2 mutations)—are also expected to increase the antigenicity of neoplastic cells (44, 45). However, this hypothesis has never been formally tested, neither in preclinical nor in clinical settings. Moreover, it remains unclear whether the restoration of antigenicity in the course of treatment has prognostic significance in cancer patients.

Increased Adjuvanticity

Antigenicity is required but not sufficient for the elicitation of an adaptive immune response (regardless of its target). As a matter of fact, an increased availability of antigenic epitopes in the absence of appropriate immunostimulatory signals rather supports the establishment of peripheral tolerance (46). In the context of infections, such immunostimulatory signals are provided by highly conserved microbial structures commonly known as "microbe-associated molecular patterns" (MAMP), including bacterial lipopolysaccharide or viral double-stranded RNA (47). In the context of cancer therapy, a similar function is provided by "damage-associated molecular patterns" (DAMP), which are endogenous molecules that mediate robust immunomodulatory effects upon release (or exposure on the surface of) stressed or dying cancer cells (48). Similar to MAMPs, DAMPs act by binding to pattern recognition receptors (PRR) expressed on both myeloid and lymphoid components of the host immune system (48). Thus, DAMPs alert the organism of a state of danger much alike MAMPs do, and *de facto* underlie the immunogenicity of cancer cell death. Therapeutically relevant immunogenic cell

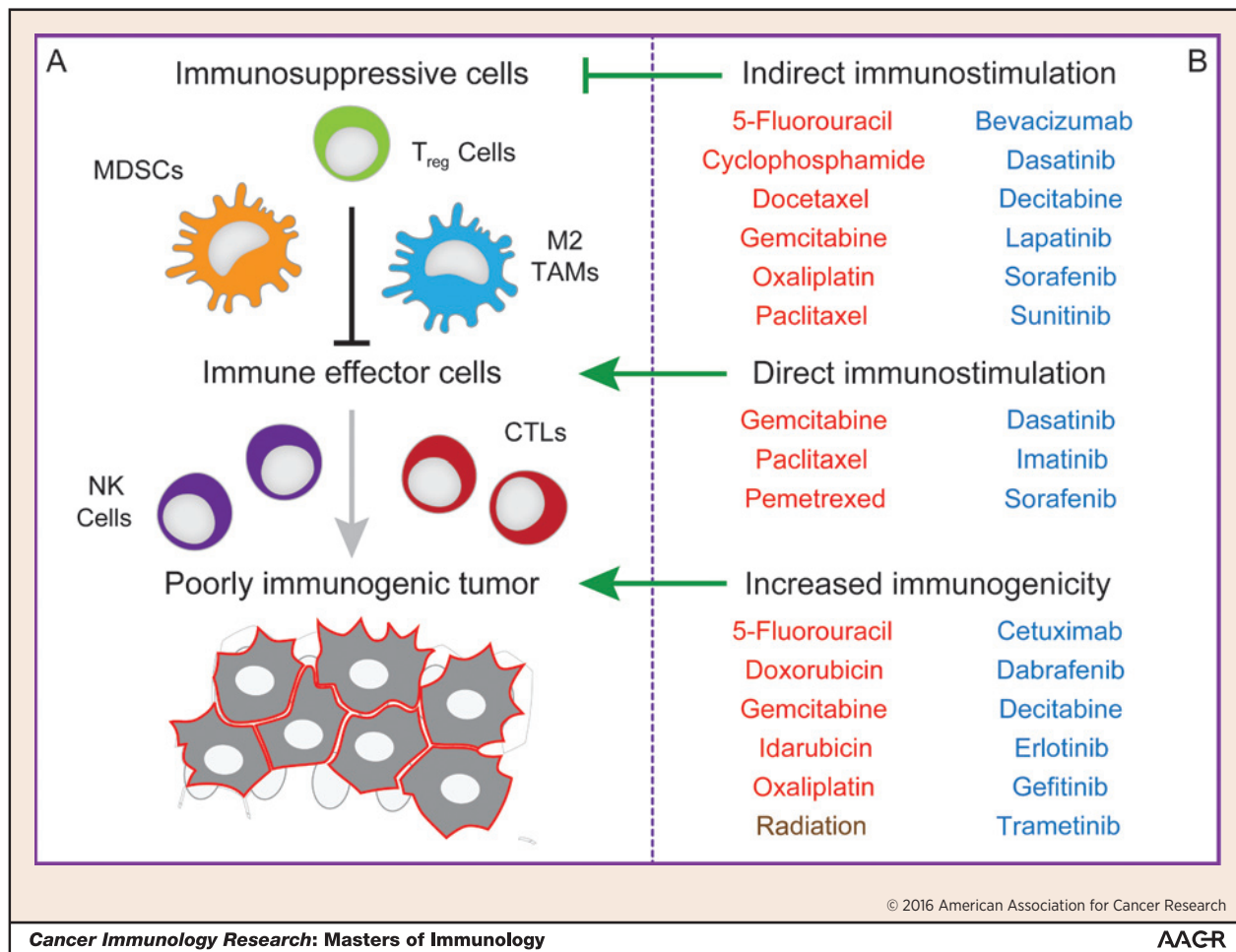


Figure 1.

Immunological effects of anticancer therapy. Human neoplasms develop in the context of an intimate, bidirectional relationship with the host immune system, which eventually results in the selection of tumor variants displaying reduced antigenicity and adjuvanticity, as well as in the establishment of local and systemic immunosuppressive networks (A). The clinical success of several treatments currently used against solid malignancies (including conventional chemotherapeutics, in red, targeted anticancer agents, in blue, and radiotherapy) depends (at least in part) on their ability to promote therapeutically relevant tumor-targeting immune responses, either as they increase the immunogenicity (antigenicity or adjuvanticity) of malignant cells ("on-target" immunostimulation), or as they interact with immune effectors or immunosuppressive cell populations ("off-target" immunostimulation; B). CTL, CD8⁺ cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cell; NK, natural killer; TAM, tumor-associated macrophage; Treg, CD4⁺CD25⁺FOXP3⁺ T.

death-associated DAMPs encompass (although they are not limited to): calreticulin (CALR), heat shock protein family A member 1A (HSP1A1; best known as HSP70), and heat shock protein 90kDa alpha family class A member 1 (HSP90AA1; best known as HSP90), three endoplasmic reticulum (ER) chaperones that stimulate phagocytosis once exposed on the cell surface (49); ATP and annexin A1 (ANXA1), which have chemotactic and immunostimulatory effects on antigen-presenting cells once secreted in the extracellular microenvironment (50, 51); type I IFN, which (amongst other effects) acts on cancer cells to favor the secretion of C-X-C motif chemokine ligand 10 (CXCL10, a chemoattractant for T cells; ref. 15); and high mobility group box 1 (HMGB1), a nuclear protein that exerts multipronged immunostimulatory activity once released by dying cancer cells (52). In addition, some DAMPs are particularly important for tumor recognition and elimination by NK cells, including several ligands for NKG2D, such as MHC class I

polypeptide-related sequence A (MICA), MICB, retinoic acid early transcript 1E (RAET1E), and various members of the UL16 binding protein (ULBP) family (33, 53).

The importance of danger signaling for the elicitation of therapeutically relevant tumor-targeting immune responses is corroborated by an ever-increasing amount of preclinical and clinical findings. In mice, multiple chemotherapeutics and radiotherapy display suboptimal efficacy if either the emission of specific DAMPs by malignant cells or normal detection of DAMPs by the host is genetically inactivated (reviewed in 54). Thus, mouse tumors growing in syngeneic hosts lacking purinergic receptor P2×7 (*P2rx7*, which encodes one of the main receptors for extracellular ATP; ref. 55), Toll-like receptor 4 (*Tlr4*, which is involved in extracellular HMGB1 signaling; ref. 52), or formyl peptide receptor 1 (*Fpr1*, which codes for an ANXA1 receptor; ref. 51) exhibit limited therapeutic responses to anticancer agents

that kill malignant cells in an immunogenic manner (see below), as compared with the same tumors established in wild-type mice. In cancer patients, biomarkers of deficient DAMP emission in tumor biopsies as well as polymorphisms affecting PRR signaling have been associated with dismal clinical outcome in multiple independent cohorts of cancer patients (13). For instance, loss-of-function alleles of *P2RX7* (55), *TLR4* (52, 56), *FPR1* (51, 56), and Toll-like receptor 3 (*TLR3*, which is involved in type I IFN signaling; ref. 56) have all been associated with decreased time-to-metastasis and/or reduced overall survival in cohorts of breast carcinoma patients receiving neoadjuvant or adjuvant anthracycline-based chemotherapy.

Conventional chemotherapeutics including doxorubicin and idarubicin (two anthracyclines routinely used for the treatment of breast carcinoma; ref. 57) and oxaliplatin (which is frequently used against colorectal carcinoma; ref. 58), targeted anticancer agents like the EGFR-specific monoclonal antibody cetuximab (also part of the current therapeutic armamentarium against colorectal carcinoma; ref. 59), and radiotherapy (60) are particularly efficient at killing malignant cells in a way that is compatible with the optimal release of DAMPs and the consequent activation of a therapeutically relevant anticancer immune response. 5-Fluorouracil (34), gemcitabine (35, 36), gefitinib (39, 40), erlotinib (yet another clinically used EGFR inhibitor; ref. 40), and radiotherapy (61) have all been shown to promote the exposure of NKG2D ligands on some mouse or human cancer cells cultured *in vitro* or grown in immunocompetent hosts, although such an immunostimulatory activity is not universal and exhibits a considerable degree of context dependency. Of note, the proper exposure or release of DAMPs by dying cancer cells obligatorily rely on the pre-mortem activation of intracellular mechanisms of adaptation to stress, such as the ER stress response (62), autophagy (50, 63), and the DNA-damage response (33). This has far-reaching implications for the development of combinatorial strategies that endow otherwise non-immunostimulatory chemotherapeutics with the ability to boost cancer cell adjuvanticity (64).

Direct Immunostimulation

Premalignant lesions escape immunosurveillance and form clinically manifest tumors not only because preneoplastic cells are immunoedited based on their surface features but also because progressing tumors establish robust immunosuppressive networks that operate locally and systemically (8, 65). Such immunosuppressive mechanisms involve virtually all components of the adaptive immune system, hence endowing progressing cancers with a robust shield against the (re)activation of the immune system (it should be kept in mind that cell death, and hence the release of potentially antigenic peptides and DAMPs, is a very common occurrence in both hematologic and solid tumors, even in the absence of therapy; refs. 8, 65). As an example, tumor-infiltrating dendritic cells (DC) are relatively immature and express high levels of the immunosuppressive enzyme indoleamine 2,3-dioxygenase 1 (IDO1) as compared with their tissue-resident counterparts, hence exhibiting a rather tolerogenic, rather than immunogenic, phenotype (66). Along similar lines, circulating or tumor-infiltrating NK cells from cancer patients often exhibit (at least some degree of) functional impairment as compared with their normal counterparts (67, 68). Amongst other conventional chemotherapeutics, the following molecules direct-

ly stimulate the effector activity of myeloid or lymphoid cells: cyclophosphamide (an alkylating agent approved for the treatment of hematologic and solid neoplasms), which favored T_H17 and T_H1 memory responses, NK-cell and $CD8^+$ DC expansion in multiple mouse tumor models (69, 70); gemcitabine, which restored defective cross-presentation in a model of transplantable murine mesothelioma (71); oxaliplatin, which promoted the tumoricidal activity of macrophages and neutrophils in mice bearing several transplantable syngeneic tumors (72); paclitaxel (a taxane used for the treatment of several solid tumors), which not only stimulated DC maturation and cross-priming in mice with syngeneic mammary carcinoma (73), but also tumor infiltration by NK cells in a cohort of breast carcinoma patients (74); as well as pemetrexed (an antimetabolite routinely used against pleural mesothelioma and non-small cell lung carcinoma), which stimulated the IFN γ -secretory activity of NK cells in pancreatic cancer patients (75). In addition, imatinib and dasatinib (two BCR-ABL1 inhibitors mainly used for the treatment of chronic myelogenous leukemia) reportedly favored the expansion of circulating NK cells and CTLs and stimulated their ability to secrete IFN γ in patients with chronic myelogenous leukemia or gastrointestinal stromal tumors (76–78), while sorafenib (a multitarget tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma and hepatocellular carcinoma) promoted the accumulation of peripheral $CD4^+NKG2D^+$ T cells in melanoma patients (79). These observations suggest that multiple conventional chemotherapeutics and targeted anticancer agents selected for their preferential cytotoxicity against malignant cells also mediate immunostimulatory effects by interacting with immune effector cells (12). Of note, a similar mechanism of action underlies the activity of multiple immunotherapeutic interventions, including monoclonal antibodies that trigger OX40, CD137, or GITR signaling, recombinant cytokines like GM-CSF, and Toll-like receptor (TLR) agonists such as the TLR7-targeting drug imiquimod (which is approved for use in patients with superficial basal cell carcinoma; ref. 80). Future clinical trials should assess whether these immunotherapeutic regimens synergize with anticancer agents that mediate direct immunostimulatory effects or whether such a combinatorial approach does not provide superior therapeutic benefits.

Indirect Immunostimulation

Cancer-driven immunosuppression is an active process that involves the expansion of immunosuppressive cells including Treg cells, myeloid-derived suppressor cells (MDSC), and M2-polarized tumor-associated macrophages (TAM; refs. 8, 65). These cells interact physically or functionally (via metabolic, paracrine, or autocrine circuitries) with immune effectors to cause their inhibition. Indeed, virtually all cells involved in the elicitation and execution of immune responses are equipped with a set of inhibitory receptors that play a critical part in the physiologic extinction of immune responses (and hence in the prevention of potentially detrimental autoimmune phenomena; refs. 8, 65). Perhaps the best characterized of such immunological breaks operates on CTLs via two plasma membrane receptors: cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PDCD1, best known as PD-1). Upon binding to their respective ligands, CTLA4 and PD-1 mediate robust immunosuppressive effects to prevent excessive activation (81). The immune checkpoints controlled by CTLA4 and PD-1 are so

powerful that the standalone inhibition of either of these receptors with specific monoclonal antibodies induces durable clinical responses in a fraction of melanoma, non-small lung carcinoma, and renal cell carcinoma patients (82). Thus, robust immunostimulation can be achieved indirectly, upon the inhibition of immunosuppressive cellular circuitries. Such an immunologic "off-target" effect is relatively common amongst conventional chemotherapeutics, perhaps suggesting that immunosuppressive cells are more sensitive to cytotoxic agents than immune effectors, at least under some circumstances. Thus, 5-fluorouracil (83, 84), cyclophosphamide (85, 86), gemcitabine (83, 87–90), oxaliplatin (91), paclitaxel (92), and docetaxel (another taxane currently used for the treatment of breast carcinoma; ref. 93) have all been shown to deplete blood-borne or tumor-infiltrating Treg cells and/or circulating MDSCs (at least in part by promoting their differentiation), not only in rodent tumor models but also in patients with various neoplasms (including non-small cell lung carcinoma, pancreatic cancer, and colorectal carcinoma; ref. 12). A similar activity has also been ascribed to some targeted anticancer agents, including dasatinib (94), decitabine (95), sorafenib (96, 97), sunitinib (a multitargeted receptor tyrosine kinase inhibitor approved by the FDA for the treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors; ref. 98), bevacizumab (a VEGF-targeting monoclonal antibody that is currently approved for the treatment of some metastatic tumors; ref. 98), as well as to hitherto experimental BRAF- and KDR-targeting molecules (99, 100). Finally, the dual tyrosine kinase inhibitor lapatinib (which is used in combination regimens against HER2-overexpressing breast carcinoma) reportedly depleted M2-polarized TAMs (101). In summary, several conventional chemotherapeutics and targeted anticancer agents appear to mediate indirect "off-target" immunostimulatory effects.

Concluding Remarks

Chemotherapy and total-body irradiation have been extensively used to achieve myelo- and lymphoablation in patients allocated to hematopoietic stem cell transplants, reflecting their ability to mediate prominent immunosuppressive effects (102). How can this notion reconcile with the immunostimulatory activity recently ascribed to conventional chemotherapeutics, targeted anticancer agents, and radiotherapy? It perfectly does so when one considers the two mainstays of modern (immuno)chemotherapy: dose and schedule. When cancer was still viewed as an infection-like disease, dose-intensive therapy was often the treatment of choice. Now we know that such an approach was doomed to fail in a majority of cases, because it was incompatible with the activation of a tumor-targeting immune response that would control disease relapse (driven by treatment-resistant cancer cells; ref. 103). Nowadays, metronomic regimens (which involve the repeated administration of low-dose chemotherapy) and fractionation (which involve the delivery of the radiation dose over multiple treatment

sessions) are being implemented into the clinical practice at increased pace, as these approaches not only are compatible with, but often stimulate, therapeutically relevant antitumor immune responses (104, 105).

It is difficult to predict which of the immunological mechanisms of action of conventional chemotherapeutics, targeted anticancer agents, and radiotherapy (if any) will be most important for the development of future treatments, for at least two reasons. First, therapeutically relevant anticancer immune responses, be they natural or driven by treatment, involve the recognition of one or several antigenic determinants (antigenicity) in the context of appropriate immunostimulatory signals (adjuvanticity), resulting in the activation of tumor-targeting immune effector cells that circumvent cancer-associated immunosuppression. This implies that all the mechanisms mentioned above play an important role and explains why some tumors with a moderate mutational burden (and hence moderate antigenicity) sometimes respond better to immunotherapy than cancers expressing high amount of neoantigens (106). Second, cancer is an extremely heterogeneous disorder, implying that each specific malignancy will have to be examined from an immunologic perspective to characterize (and hence target therapeutically) the mechanisms that are in place for the evasion of tumor-targeting immunity. Efforts to implement into the clinic an immunologic characterization of tumor for prognostic and predictive purposes are already under way (107).

Major efforts are currently being devoted to the development of combinatorial regimens that harness the immunostimulatory effects of chemotherapy and radiotherapy to boost the efficacy of multiple immunotherapeutics, including checkpoint blockers. Several lines of evidence indicate indeed that the clinical efficacy of checkpoint blockers depends on tumor antigenicity (22) and adjuvanticity (108). Thus, preconditioning the tumor microenvironment with ICD inducers may constitute a promising strategy to overcome the intrinsic resistance of some neoplasms to checkpoint blockade (108). We surmise that combinations of immunotherapy with chemotherapy and/or radiotherapy will soon enter the clinics and ameliorate quality of life for millions cancer patients worldwide.

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No potential conflicts of interest were disclosed.

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