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## REVIEW

# Resistance to anticancer immunity in cancer patients: potential strategies to reverse resistance

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In the 1990s, the application of immunotherapy approaches to target cancer cells resulted in significant clinical responses in patients with advanced malignancies who were refractory to conventional therapies. While early immunotherapeutics were focused on T cell-mediated cytotoxic activity, subsequent efforts were centered on targeted antibody-mediated anticancer therapy. The initial success with antibody therapy encouraged further studies and, consequently, there are now more than 25 FDA-approved antibodies directed against a range of targets. Although both T cell and antibody therapies continue to result in significant clinical responses with minimal toxicity, a significant subset of patients does not respond to immunotherapy and another subset develops resistance following an initial response. This review is focused on describing examples showing that cancer resistance to immunotherapies indeed occurs. In addition, it reviews the mechanisms being used to overcome the resistance to immunotherapies by targeting the tumor cell directly and/or the tumor microenvironment.

**Key words:** cancer, checkpoint inhibitors, cytotoxic T cells, immunotherapy, overcoming resistance

## Introduction

While conventional cancer treatments, such as surgery, chemotherapy, and radiation have extended survival for many patients, they have had limited success in certain tumor types and in patients with late stage diseases. Consequently, the search for more effective and less toxic cancer therapeutics continues. For many years, researchers have explored the idea that the immune system could be harnessed with the aim of inducing an anti-tumor immune response. It has been recognized that tumors are often poorly immunogenic for both humoral antibody and T cell-mediated responses. Several mechanisms have been characterized that alter the immune responses to tumors [1], including immune editing [2], tumor-derived suppressor factors [3], suppressor factors derived from the tumor microenvironment (TME) [4,5], the induction of suppressor T-cells [3] and the development of myeloid-derived suppressor cells (MDSCs) [6].

The innate immune system plays a role in the initial anti-tumor response and, as such, it has been considered as a therapeutic target. However, in the majority of cases, when the tumor develops mechanisms of resistance to cell death, both the innate

and adaptive immune responses become ineffective and are unable to eradicate the tumor. Interestingly, a deeper understanding of these mechanisms is providing new means to circumvent or alter the resistance of the immune response to tumors. Consequently, immunotherapy has emerged as a significant therapeutic strategy in the eradication of many tumor types.

The role of the immune system in the regression of tumors was first highlighted by the FDA-approved administration of IL-2 in renal cancer in 1992 and in metastatic melanoma in 1998 [7]. This was followed by the use of *ex vivo* IL-2 to generate and expand autologous T-cells and tumor infiltrating lymphocytes (TILs) for adoptive T-cell (ATC) transfer and treatment of cancer patients. ATC has shown promising results in the treatment of advanced cancer and, in particular, for a subset of patients refractory to standard therapy [8–12]. These findings, while not applicable to all tumors, led to the development of novel methods to introduce anti-tumor TCRs into autologous lymphocytes and the engineering of tumor-specific chimeric antigen receptors (CARs) into normal lymphocytes for therapeutic use [8, 13–15].

During the last two decades, in addition to cell-mediated immunotherapy, we have also seen the emergence of antibody-

mediated targeted therapies directed against tumor cells or their microenvironment. The first chimeric monoclonal antibody (mAb), rituximab (anti-CD20 mAb), was FDA-approved in 1997 for the treatment of low grade and follicular NHL [16, 17]. Subsequently, over 25 mAbs have been approved for the treatment of a variety of cancers [18–20].

Although the advent of new immunotherapy approaches has improved the survival of many patients with advanced malignancies, the prevalence of non-responders, especially in common malignancies such as breast, colon and prostate cancers, also provides a strong reminder that we possess only a partial understanding of the events underlying the immune resistance of tumors. It should be noted that the success of preclinical studies in mice contrasts with the current situation in the clinic [21–24]. The ultimate goal of most T cell-mediated anti-cancer immunotherapy strategies is to induce a strong cytotoxic T lymphocyte (CTL) response, with the prevailing view being that induced CTLs will eradicate tumor cells. However, this view has been challenged by clinical observations showing that even a strong and sustained cytotoxic response may only translate to a partial response in patients. This is due to a number of complex issues, such as an unfavorable TME (resulting in impaired lymphocyte migration and recruitment), tumor evasion, immune editing, and selection of immunoresistant tumor cell variants [25]. In addition, regulatory T cells (Tregs), macrophages, MSDCs, and neutrophils constitute major components of the immune infiltrate within the tumor tissue that curtails anti-tumor immunity [26]. A better understanding of the underlying molecular mechanisms of tumor escape remains a vital step in the development of strategies to overcome this process.

Several novel strategies have been successfully used in the reversal of resistance including checkpoint inhibitors, new monoclonal antibody-drug conjugates (ADCs), engineered T cells, agents targeting the TME, combination therapies and immunosensitizing agents, among others. Accumulating evidence indicates that immunosurveillance represents only one dimension of the complex relationship between the immune system and cancer [27]. It has become clear that the host immune system is involved in both eliminating tumors and sculpting the immunogenic phenotypes of tumors that eventually form in immunocompetent hosts, indicating that immunity plays a dual role in the complex interactions between tumors and the host. In fact, the immune system can suppress tumor growth by destroying cancer cells but can also promote tumor progression by establishing conditions within the TME that facilitate tumor outgrowth.

Resistance to immunotherapy strategies in various cancers has been the subject of numerous recent reviews with little discussion concerning whether this resistance is a dogma or a proven phenomenon [28, 29]. This review focuses on the recent approaches that have been used to overcome resistance by manipulating the effector cells and antibodies that are directed to the tumor cells or to the TME.

## Innate, adaptive and tumor microenvironment influences on tumor immunity

Both the innate and adaptive immune responses have been implicated in the antitumor activities.

### Innate immunity

Arguably the most important cytotoxic effector cells in the innate immune response to tumors are the natural killer (NK) cells. These cells are directly cytotoxic, IFN- $\gamma$ -producing cells and mediate cytotoxic activity against antibody-coated tumor cells. Mature NK cells exhibit a broad spectrum of phenotypic and functional diversity. Human NK cells can be divided into two subsets: CD56<sup>bright</sup> CD16<sup>-</sup> (high cytokine producers predominantly found in lymph nodes and tonsils) and the CD56<sup>dim</sup> and CD16<sup>+</sup> NK cells (highly cytotoxic, found in peripheral blood and spleen) [30]. The responsiveness of tumor cells to NK cells is modulated by a complex spectrum of inhibitory and activating receptor-mediated signals for target and accessory cells and their pro- and anti-inflammatory microenvironment. NK cells mediate their cytotoxic activity by the granzyme pathway as well as by the TNF- $\alpha$ , Fas-L and TRAIL ligands expressed on their cell surface [31]. The antitumoral role of NK cells is supported by observations in cancer patients in the clinic. A study looking at the association between cytotoxic activity of peripheral-blood lymphocytes and cancer incidence in Japan showed that individuals with low NK cytotoxic activity had a higher incidence of cancer [32]. Coca et al. [33] reported that in patients with colorectal carcinoma, the analysis of the intratumoral infiltrates of NK cells showed that the extent of NK infiltration correlated with a favorable outcome and was of prognostic significance. Ishigami et al. [34] analysed NK infiltrates in gastric carcinoma and found that high NK infiltrates correlated with fewer metastasis and less lymphatic invasion when compared to patients with low levels of NK infiltrates. They concluded that patients with high NK infiltrates have a better prognosis than patients with low NK infiltrates. Villegas et al. [35] reported on the significance of NK infiltration in patients with squamous cell lung cancer. They examined a subset of tumor infiltrates by looking at NK cells expressing CD57 in surgical specimens. Their findings supported the conclusion that the level of tumor infiltrated by NK cells is of prognostic significance in the survival of patients with squamous cell lung carcinoma. In haploidentical hematopoietic cell transplants, alloreactive NK cells support graft versus tumor effects and reduced leukemia occurrences in patients with AML [36].

In addition to the direct response of NK cells against tumor cells, a robust NK-mediated antibody-dependent cellular cytotoxicity (ADCC) is elicited against autologous tumor cells [118]. The clinical response to antibody-based immunotherapies has been reported to positively correlate with NK cell activation, cytotoxicity, and tumor infiltration in certain cancers [30].

NK cells are *ex vivo* activated for ACT [37]. Adoptive transfer of haploidentical NK cells has resulted in favorable responses in patients with hematological malignancies [38]. At present, genetically engineered CAR NK cells are being explored as a way to more specifically direct NK cell cytotoxicity towards cancer cells [39].

### Adaptive immunity

There are many facets with which the immune system interacts with cancer cells [40, 41]. These interactions can protect the body from the development of tumors and can also shape the characteristics of emerging lesions and are composed of three phases, namely, elimination, equilibrium, and escape [27]. In cancer

immune editing both innate and adaptive immune responses detect and destroy early tumors before they can become clinically visible. Elimination is defined by the immune rejection of tumors by the host innate and adaptive immune responses [42]. The equilibrium phase is not very well characterized molecularly but it relates to immune-mediated tumor dormancy [27]. The escape phase is a process by which the tumor escapes from immune elimination and several mechanisms have been reported to be involved in this phase [43]. During escape, the immune system fails to restrict tumor growth and the emergence of tumor cells and thus results in clinical disease.

Many immunotherapy approaches have centered around manipulating the T lymphocyte system because of the diversity and high specificity of CTLs and the potential for a long-term effect due to the formation of memory T cells. Two signals are required to generate anti-tumor CTLs: (signal 1) activation of naïve T-cells by antigen presenting cells (APCs) in combination with MHC bound to tumor peptides resulting in HLA complexes which are recognized by the TCR and (signal 2) binding to costimulatory molecules (B7 on APC, and CD8 on T cells). In addition to the activation signals, there are also inhibitory molecules, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and Programmed cell death protein 1 (PD1) on T cells, which induce negative signaling when bound to their ligands. Depending on the balance of the activating and inhibitory signaling, there may be killing or no killing, respectively [44].

The cancer immunoediting model incorporates both immune surveillance and the dynamic interactions of the tumor with the adaptive and the innate branches of the immune system that edit and sculpt the intra-tumoral landscape [45]. In addition, a number of studies in murine models have suggested that the immune system may edit different tumors by altering their expression profiles to allow them to evade immune reactions [46, 47]. Following therapy, resistant tumor clones, that may have already been present at low numbers prior to the therapy, are selected in addition to newly mutated clones induced by the therapy.

Several mechanisms of immune-suppression have been reported, including expansion and accumulation of T-reg cells [48], formation of MDSCs [49] and secretion of various inhibitors (e.g. IDO, VEGF and PD-L1) by tumor cells and the TME [49, 50]. T cells also express receptors that negatively regulate the induction of an anti-tumor response, such as CTLA-4 [51], and receptors that regulate cytotoxic activity like PD1, LAG-3, FIM-3 and BTLA [52]. The polarization of macrophages to type II (M2), which secrete chemokines to recruit T-regs, also contributes to immune-suppression [53].

Cancer stem cells (CSCs) are thought to be responsible for resistance and tumor relapses in some situations [54, 55]. The activation of different signaling pathways (such as NOTCH and WNT/Beta Catenin, TGF- $\beta$ , Hedgehog, PI-3K/AKT/mTOR and JAK/Stat) are involved in the resistance of CSCs to immune reactivity [56–59].

Antitumor CTLs may undergo a massive expansion upon antigenic stimulation. However, homeostasis is maintained by a subsequent contraction of the cells via activation-induced cell death (AICD) and programmed cell death. Premature death of antitumor CTLs by AICD is a major drawback in CTL anticancer-mediated immunotherapy [60, 61]. AICD is induced

by caspase-dependent and independent pathways [61]. The persistence of viable antitumor CTLs is a hallmark of successful T cell-mediated immunotherapy and the prevention of AICD is critical to achieve significant clinical results. Schulte et al. [62] have reported that FasL is involved in AICD of CTLs overexpressing FasL, and FasL has also been detected in the sera of cancer patients and has been shown to interact with Fas-expressing CTLs for AICD. Schultz et. al demonstrated that ADAM10 is involved in shedding of FasL and its inhibition can reduce AICD. Recently, Cao et al. [63] reported that histone deacetylase inhibitors (HDACs) specifically inhibit apoptosis in CD4+ T-cells within tumors and enhance the antitumor response, thus suppressing melanoma growth.

## Tumor microenvironment

Tregs and MDSCs are normally present in the TME and inhibit cancer specific T-cell functions and induce immune suppression [64]. The TME changes as a function of tumor progression. A dysregulated TME impacts tumorigenesis as tissues subjected to chronic inflammation exhibit a higher cancer incidence [65]. Factors that contribute to tumor growth in the TME include tumor-associated macrophages (TAMs), Tregs, MDSCs, cancer-associated fibroblasts (CAFs), ECM (extracellular microenvironment) and tumor vasculature. Activated CTLs must enter the TME where they encounter a large number of negative signals that affect their functions. These regulatory signals are derived from both the tumor [66] and the stromal cells (immune cells, fibroblast, endothelial cells, and inflammatory cells) [67, 68].

The immunosuppressive Tregs and MDSCs are the major immunosuppressive factors in the TME and inhibit CTL function [69, 70]. It has been well documented that TILs are unable to attack tumor cells and that this is thought to be due to the immunosuppressive TME [71]. CD4+ CD25<sup>hi</sup>, T-reg cells [72], CD28+ CD25+ T-reg cells [72], CD19+ CD25<sup>hi</sup> regulating B cells [72] and IL-13-producing NK-T cells [73] have been reported to be present in the TME in cancer patients. In addition, the TME conditions injected T cells to become immunosuppressive [26]. Recruitment of immature MDSCs in the TME converts these cells to mature immunosuppressive MDSCs [74]. Notably, there is crosstalk among MDSCs, Tregs and NK-T cells.

There are factors in the TME that affect T-effector cell functions and downregulate their activation and subsequent anti-tumor response. Hypoxia has been shown to inhibit T-cell receptors and CD28 activation of T-cells and suppress their response [75]. The low extracellular pH, low glucose concentration, and defective vascularization affect T-cell trafficking, infiltration, and function [76]. Even when a successful anti-tumor T-cell response is generated, tumor cells have ways of evading the response. For example, activation of anti-apoptotic pathways and inhibition of pro-apoptotic pathways in tumor cells result in the resistance of tumor cells to killing by CD8 T-cells. There are also other inhibitors that are directed at and inhibit the function of CTLs. Park et al. [77] have reported that TGF- $\beta$  inhibited T-cell-mediated antitumor immunity. TGF- $\beta$  inhibits cytotoxic activities via the inhibition of gene products involved in cytotoxicity. Huang et al. [78] reported that TLRs are expressed on tumor cells and their activation releases several factors, such as IL-6, NOS, IL-12, B7-H1,

B7-H2, which regulate CTL functions. Harimoto et al. [79] reported that tolerogenic dendritic cells inhibit the induction of CD8+ tumor-specific CTLs and inhibit their function. Tumor-derived soluble gangliosides have been shown to inhibit T-cell proliferation [80] and also induce T-cell apoptosis [81]. The cytokine IL-10 can downregulate MHC class I on tumor cells and inhibit CD8 T-cell recognition and lysis [82, 83]. PDL1, expressed either on tumor cells or in the TME, interacts with PD1 on the surface of T-cells and can result in the inhibition of T-cell effector cytotoxic functions and T-cell death. Wang et al. [4] have reported that B7-H4, the stimulatory molecule and member of the B7 family, is overexpressed in many tumors. The interaction of tumor cells with CTLs results in the inhibition of T-cell response via inhibition of expansion and cell growth and decreased cytokine secretion and induction of AICD. In addition, B7-H4 promotes the development of Treg cells. Expression of B7-H4 has been shown to be upregulated on tumor cells and inhibits T-cell effector functions [84]. An *in vitro* study has also shown that expression of FasL by tumor cells protects them from Fas-mediated killing by CTLs [85].

Although promising results have been observed in clinical trials of CAR-modified T cells for some hematological cancers and neuroblastoma [86], poor or moderate results were observed in solid cancers and some patients show no response to CAR T cells [87]. These limitations may be due to several factors such as failure of CTL activation by tumor cells or the inherent resistance of tumor cells to CAR-T killing.

While the advent of anti-CD19 CART therapy has shown promise [88], its limitations are that it requires CART expansion and engraftment [89]. Fourcade et al. [90] have reported that therapy with five cycles or more of ibritumib improved anti-CD19 T-cell expansion with decreased expression of the immunosuppressive PD-1 on T-cells of CLL patients [91]. Thus, poorly responding patients may benefit from this combination treatment. Another recent report by Newick et al. [92] reported that CART cells are not effective against solid tumors because tumor derived immunosuppressive factors (PGE2 and PKA) inhibit T-cell receptor activation. These investigators have generated a small peptide that inhibits PKA activity and thus restores the cytotoxicity of CART cells.

### Mechanisms to reverse resistance to immune destruction

As described earlier, many tumor cells are clearly resistant to destruction by the immune system. Herein we describe some of the immunotherapeutic approaches used to target this resistance.

While cell-mediated immunotherapy has resulted in significant objective clinical responses, (particularly with the use of ACT, checkpoint inhibitors and engineered T cells bearing anti-tumor TCRs), many patients do not respond initially and/or develop resistance to further treatments. Mechanisms involved in tumor resistance to CTLs include resistance to perforin/granzyme [93–95], altered expression of death receptors, alteration of the apoptotic regulator p53 [96], and lower expression of MHC-1 [97–99].

Several strategies have been considered to reverse resistance of cancer cells to CTL-mediated recognition and cytotoxicity. These

include: (i) checkpoint inhibitors, (ii) engineered cells expressing anti-tumor T-cell receptors and CART cells, (iii) anti-apoptotic inhibitors, (iv) targeting the TME, (v) antibodies as sensitizing agents, (vi) ADCs, (vii) inhibitors of AICD, and (viii) others.

### Checkpoint inhibitors

It is becoming clear that the immune system can recognize tumors and, in some cases, can control tumor progression and even eliminate them. Thus, many strategies have been developed to increase the immune system's efficacy by addressing mechanisms responsible for its failure. One such strategy has been to block molecules involved in the regulation of immune checkpoints.

This has been shown to restore T-cell activation leading to amplification of the anti-tumor response [21–23, 100]. A number of mAbs targeting proteins involved in immune checkpoints have now entered the clinic and have shown significant objective responses in patients. For example, Ipilimumab is an anti-CTLA4 antibody which can block the co-inhibitory receptor on CTLs and enhances the induction of the CTL response. Peggs and Quezada [101] and Hodi et al. [102] have reported that patients with melanoma who failed on other treatments improved their survival when treated with ipilimumab. The study evaluated the use of ipilimumab alone and in combination with a gp100 peptide vaccine. In comparison with those receiving vaccine alone, overall survival was prolonged significantly by the combination treatment. Recently, ipilimumab has also been used in combination with conventional therapies such as etoposide and platinum [103] and in combination with different checkpoint blocking antibodies, resulting in the potentiation of anti-tumor immune responses [21–23, 104].

In the TME, the failure of anti-tumor CTLs to kill tumor cells is due to the inhibitory effect of the PD1-PD-L1 pathway, which consists of PD1, a cell surface receptor expressed on T cells and pro-B cells, and its ligands PDL1 (B7-H1) and PDL2 (B7-DC). This pathway functions as an immune checkpoint and can mediate immunosuppression in the TME [105–108]. Blocking this checkpoint with mAbs, either against PD1 or PDL1, has been shown to restore anti-tumor activity of T cells and the use of these checkpoint inhibitors in the clinic has resulted in significant objective responses in many advanced cancers. Two such mAbs have been approved by the FDA for melanoma and lung cancer [106, 107] and the approval for their use in other cancers [109–111]. Checkpoint inhibitors have also been clinically investigated in renal carcinoma (the US Food and Drug Administration approved of Opdivo (nivolumab) to treat patients with advanced (metastatic) renal cell carcinoma, a form of kidney cancer, who have received a certain type of prior therapy) [112, 113], urothelial cancer (the US Food and Drug Administration approved Tecentriq (atezolizumab), a programmed death-ligand 1 (PD-L1) blocking antibody, to treat the most common type of bladder cancer, called urothelial carcinoma) [114] and non-Hodgkin lymphoma [the US Food and Drug Administration granted accelerated approval to nivolumab (Opdivo, marketed by Bristol–Myers Squibb) for the treatment of patients with classical Hodgkin's Lymphoma (cHL) that have relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin (Adcetris)] [115,

116]. These mAbs show good tolerability in patients, are suitable for outpatient administration and can be used alone or in combination with other therapies.

Many additional inhibitory receptors that regulate T-cell responses have been identified (e.g. LAG3, 2B4, BTLA, IL-10R, TIM3 [T-cell immunoglobulin mucine 3], and NKG2A). Studies targeting some of these inhibitory pathways in combination with CTLA4 and PD1/PDL1 blockades are in progress and have shown promising results [90, 108, 117]. Combinations of immunotherapy approaches are considered to be required for long-term remissions in most cancer patients and the combination of checkpoint blocking mAbs with radiotherapy [118, 119], chemotherapy, cancer vaccines [120, 121], and sensitizing agents are being evaluated clinically [122].

Antibody-mediated checkpoint blockade of killer cell immunoglobulin-like receptor (KIR) is mediated by an anti-KIR blocking antibody (Lirilumab), which is in clinical trials [123]. It has also been shown that ADCC induced by both rituximab and trastuzumab is augmented *in vivo* by cross linking the activated CD-137 receptor which is induced on NK cells upon ADCC [124, 125]. In response to antibody therapy, NK cells contribute to the generation of an anticancer adaptive immune response through IFN-gamma release and triggering DC activation for antigen presentation. Strategies to disrupt NK cell immunosuppression include the development of means to facilitate their infiltration along with the disruption of resistant factors. A recent review by Wang et al. [4] discusses the role of NK-induced ADCC and approaches to augment it in cancer immunotherapy.

### Engineered T cells and CAR T cells

In hematological malignancies, cancer-associated antigens (CAA) are non-mutated with germ line sequence. Such CAAs can serve as therapeutic targets; examples include CD20 on most B cell lymphomas [16] and CD52 in CLL and some lymphomas [126]. An additional therapeutic approach has been the use of CD19-targeted CAR-T cells for treatment of lymphoma and leukemia [127, 128].

On 1 July 2014, the US FDA granted a 'breakthrough therapy' designation for CTL019, an anti-CD19 CART therapy, in patients with B-cell malignancies [129–131] and complete molecular remissions in patients with leukemia have been reported with this agent. In addition, Dolnikov et al. [132] have reported efficacy of this therapy in chemoresistant pediatric patients with ALL.

### Anti-apoptotic inhibitors (sensitizing agents)

NF- $\kappa$ B is hyperactivated in the majority of cancers and participates in the regulation of cell survival, cell proliferation, invasion, and resistance [133]. Inhibition of NF- $\kappa$ B may reverse tumor immune resistance [134]. Tumor cells develop cross-resistance to various cytotoxic stimuli (e.g. chemotherapy, immunotherapy, radiation and hormonal therapy) by developing mechanisms to resist drug-induced apoptosis [135]. NF- $\kappa$ B transcriptionally regulates several genes that regulate and suppress cell death by necrosis or apoptosis [136, 137] and, therefore, the inhibition of NF- $\kappa$ B may reverse this antitumor resistance mechanism.

The role of the dysregulated NF- $\kappa$ B/SNAIL/YY1/RKIP loop in the regulation of resistance to immunotherapy in cancer cells has

been reported [138]. The presence of this dysregulated loop in various cancer cell models has also been shown to regulate the epithelial–mesenchymal transition and metastasis [139]. Each gene product in the loop has been shown to be directly involved in the regulation of tumor cell resistance to immunotherapy mediated by cytotoxic ligands (Fas-L, TRAIL) expressed on cytotoxic T-cells and NK cells. Interventions to disrupt this loop-mediated resistance has been successful in reversing resistance. For example, treatment of cancer cells with Nitric Oxide donors, proteasome inhibitors and/or inhibiting each gene product of the loop individually have all resulted in reversal of resistance and sensitization to immunotherapy-mediated stimuli [140].

The intrinsic anti-apoptotic regulation of the Bcl-2 family of proteins maintains the integrity of the mitochondrial membrane. Alterations in the expression of Bcl-2 family members contribute to neoplastic transformation and cancer cell resistance to both chemotherapy and immunotherapy [141]. The inhibitors of apoptosis proteins (IAP) are a family of proteins that bind directly to active caspases, inhibiting their activation. They can be negatively regulated by RAF-1, HTRA2, and JMAC to release the apoptotic breaks. Many inhibitors of Bcl-2 family proteins have reached the clinic [142–144].

### Targeting the TME

The TME changes as a function of tumor progression [145]. A deregulated TME impacts tumorigenesis as tissues subjected to chronic inflammation exhibit a higher cancer incidence [65]. A variety of factors contribute to tumor growth in the TME, including tumor-associated macrophages (TAMs), Tregs, MDSCs, cancer-associated fibroblasts (CAFs), ECM and tumor vasculature.

Some TME-targeted therapies, such as Ipilimumab (anti-CTLA-4 mAb), have been shown to work in some patients [146]. IDO derived from tumor cells, macrophages and DCs is a major contributor to immunosuppression and dual targeting of CTLA-4 and IDO is effective in reversing resistance to immunotherapy [147]. Spranger et al. [148] examined the effects of combining antibodies against CTLA4, PDL1, and the IDO inhibitor INCB23843 on tumor rejection using a murine B16 melanoma model. The three combinations (anti-CTLA-4 mAb + anti-PDL1 mAb, anti-CTLA-4 mAb + INCB23843 and anti-PDL1 mAb + INCB23843) showed a significant anti-tumor effects *in vivo* [59] and activated the T-cell response. Furthermore, An et al. [149] reported that the combination of an anti-PDL1 antibody and the IDO inhibitor partly overcame lysis of CTLs in multiple myeloma. Spranger et al. [59] reported that the combination of either two agents such as CTLA-4, anti PD-1, anti PD-L1, or IDO inhibitor resulted in the proliferation of CD8 T-cells at the tumor microenvironment and resulted in tumor rejection.

During the last decade, we have witnessed the development of novel targeted therapies and a new era of precision medicine. Zitvogel et al. [150] have recently reviewed the off-target effects of targeted therapies on the immune system. For example, significant clinical responses observed with imatinib mesylate (Gleevec), which is approved by the FDA for the treatment of patients with Philadelphia chromosome CML and gastrointestinal stromal tumors, were found to be primarily due to the targeted effects but also involved the immune system. The tyrosine kinase

inhibitor Sunitinib, a first line treatment for renal carcinoma, has been reported to decrease Treg cell number [151]. The combination of bevacizumab (VEGF inhibitor) and imatinib was shown to be effective in metastatic melanoma [116, 152].

Other interventions to inhibit suppressive cells and/or to differentiate them have been reported [26, 153]. An extensive review has recently been published on the inhibition of suppressor cells [154]. The strategies described included the elimination of suppressor cells or the inhibition of their accumulation in the TME. The elimination can be achieved by low doses of chemotherapy or by peptibodies. MDSCs can be functionally deactivated by targeting their suppressive machinery. All-trans retinoic acid has also been shown to deplete MDSCs and DCs [153]. Low doses of cyclophosphamide selectively reduce Tregs and a cytotoxic protein consisting of parts of the diphtheria toxin and the binding domain of IL-2 (Denileukin Diftox/Ontak) has been used to eliminate suppressor cells. Blocking of Treg recruitment was achieved by antagonizing the chemokine (C-C) ligand 22 and the ligation of TLR8 on Tregs has also been effective in the depletion of Tregs and restoring CTL antitumor activity [155]. Success has also been observed by blocking CTLA-4 [89] or TGF $\beta$  [156, 157].

Changes in tumor antigenicity as a function of their growth and the consequent regulation of suppressor cells have been reported [158]. The suppression in the TME of MDSCs, Tregs and production of IDO and secretion of suppressive factors (IL-10, TGF $\beta$ , VEGF) derived from the TME and tumor have been reported to be effective strategies for immunotherapy [41].

### Antibody-mediated sensitization to immunotherapy

We have reported that tumor cells resistant to TRAIL-induced apoptosis can be sensitized to NK-mediated apoptosis through TRAIL expression on the NK cell membranes following exposure to monoclonal antibodies [159]. We speculated that this mechanism of sensitization, namely the ability of the sensitizer antibody to inhibit the constitutively anti-apoptotic pathways and render the resistant cells sensitive to the cytotoxic cells/factors, may take place *in vivo* in cancer patients treated with monoclonal antibodies in addition to the mechanisms of complement-dependent cytotoxicity (CDC) [159]. The Fc fragment of the antibody interacts with Fc receptors on cytotoxic cells (NK, monocytes) and triggers the cytolytic mechanism to kill the tumor cells via ADCC. Vega et al. [159] reported that treatment with rituximab sensitized B-NHL tumor cells to TRAIL-mediated tumor rejection by NK cells *in vivo*. These findings were corroborated by Daniel et al. [160], who reported that the combination of rituximab and TRAIL resulted in the potentiation of apoptosis *in vivo* in mice bearing tumor xenografts.

Treatment failures in cancer may be due to the development of both intrinsic and acquired resistance [24]. We have reported that rituximab sensitizes B-NHL cells to Fas-L induced apoptosis and the mechanism of sensitization was due to the activation of the Type II mitochondrial pathway [70]. We have also reported that rituximab-mediated sensitization to TRAIL apoptosis of B-NHL cell lines was mediated by rituximab-induced inhibition of the anti-apoptotic NF- $\kappa$ B pathway and the downstream DR5 transcription repressor YY1 [38].

The inhibition of NF- $\kappa$ B by DHMEQ (dehydroxymethylleptopyruvic acid; a small molecule inhibitor of NF- $\kappa$ B) and proteasome inhibitors sensitized rituximab-resistant (RR) B-NHL clones to chemotherapy-induced apoptosis [159]. In addition, HDAC inhibitors sensitized multiple myeloma cells to drug-induced apoptosis [161].

Likewise, treatment with the HDAC inhibitors valproic acid and romideisin increased CD20 expression and enhanced rituximab-induced CDC activity [162]. The combination of the Bcl2 inhibitor oblimersen with rituximab was effective in patients refractory to rituximab [163]. The fusion protein anti-CD20-hIFN- $\alpha$  sensitized RR B-NHL clones to drug-induced apoptosis [164].

### Antibody-drug conjugates

Antibody-drug conjugates are therapeutics that selectively direct a cytotoxic drug to cells expressing a cell surface antigen recognized by the antibody. Over 40 distinct ADCs are currently in clinical trials [165–167]. Two ADCs (Trastuzumab emtansine [168, 169] and brentuximab vedotin [170–173]) have been approved by the FDA. These can also be used as sensitizing agents for CTL-induced apoptosis in CTL-resistant tumor cells under appropriate conditions [174]. Brentuximab vedotin was investigated in patients with CD30 positive hematological malignancies in a phase I clinical trial [170]. The ADC was also examined in patients with relapsed refractory Hodgkin lymphoma and results showed efficacy and tolerance [171, 172]. Clinical activity and immune modulation was observed in highly pretreated patients with testicular germ cell tumor. Gandolfi et al. [173] reported that in patients with refractory/relapsed Hodgkins lymphoma treated with Brentuximab vedotin, a long-term response was seen in over half of the patients. In a phase III study, Baselga et al. [168] reported longer progression free survival and overall survival in breast cancer patients and, in contrast to HER2 directed therapies in tumors with PI3KCA, treatment with Brentuximab vedotin was more effective in PI3KCA mutated and wild type tumors. This finding was corroborated by Kim et al. [169].

### Inhibitors of activation-induced cell death

The induction of apoptosis in mature T cells after antigenic stimulation, referred to as AICD, is a controlled mechanism for terminating and controlling the expansion of activated T cells [60]. Studies of tumor-induced AICD showed that anti-tumor CTLs expressing KIR did not experience AICD [175]. It is well understood that apoptotic death of lymphocytes is an important homeostatic mechanism of peripheral tolerance to self-antigen. The induction of apoptosis in mature T cells after antigenic stimulation is an important process for terminating and controlling the expansion of activated T cells. A number of inhibitory receptors that recognize HLA-I molecules are found on NK cells. These include the KIR family of potent inhibitory receptors that recognize specific polymorphisms on the classical HLA-A, -B, and C-molecules. These receptors, expressed by a small subset of peripheral T cells in healthy individuals, appear to counterbalance TCR-mediated activation. Studies in mice indicated that transgenic expression of an inhibitory NK receptor induced the accumulation of memory T cells by inhibiting AICD [175]. More

importantly, the expression of an inhibitory KIR was found to be confined to CD8+ effector T cells, limiting their proliferative capacity. In this regard, expression of inhibitory NK receptors on effector CD8(+) T cells may explain, in part, the poor replicative capacity of T cells at that stage of differentiation. In humans, we have shown that inhibitory NK receptors belonging to the KIR family, expressed by 5–40% of CD8+ TILs, contribute to the altered cytotoxic activity of tumor-reactive CTLs [60]. We have also demonstrated that KIR engagement on tumor-specific CTLs favors their survival as a consequence of inhibition of AICD, suggesting that KIR, in addition to its inhibition of CTL lytic function, also plays a role in the control of T-cell homeostasis. Norell et al. [176] reported that ROS inhibition protected MART-1 [27,38,39,41,44,48,177,178] reactive primary CTLs from AICD impairing their functions. Cao et al. [63] reported that HDAC inhibitors inhibit CD4 T cell apoptosis within the tumor, thus potentiating the antitumor response and suppressing tumor growth *in vivo*.

### Others

In addition to checkpoint blocking antibodies, agonistic CD40 antibodies (a member of the TNF-receptor superfamily expressed on certain immune and non-immune cells) reverse immunosuppression by activating APCs, induction of T-cell response and reducing MDSCs [179]. Another approach being investigated is the targeting of immune cells that play a role in cancer-associated inflammation [180], aiming to reduce cancer-promoting chronic inflammation and, as a consequence, promote tumor rejection.

### Conclusions and future directions

We have briefly discussed the principle that anti-cancer immunity is currently the main realm of treatment in a variety of tumors, whether by therapies mediated by targeted antibodies or by targeted cell-mediated lymphocytes. Clearly, the clinical responses achieved so far have been significant, especially in cancers that have not responded to conventional therapies. The current challenge is to unravel the underlying mechanisms explaining why not all patients with the same cancer respond to immunotherapy and why certain cancer types respond better than others. Several strategic approaches have been considered to overcome immune resistance, including combination therapies, engineered high-affinity anti-cancer antibodies (used alone or conjugated with cytotoxic agents), engineered anti-tumor CTLs with TCRs targeted to the tumor, agents targeting the TME, engineered CAR T cells, checkpoint inhibitors (alone or in combination), development of other checkpoint inhibitors and various immunosensitizing agents. In addition, a variety of agents have been developed and approved to resensitize tumor cells to the cytotoxic activities of immunotherapies if they become resistant to these novel immunotherapeutic approaches. Targeting the TME, which harbors many immune-suppressive factors and cells, has also been shown to be crucial in restoring the cytotoxic activity of immunotherapies. Several successes, both in targeting the immune resistance of tumors and reversing resistance that develops in response to treatment with immunotherapies, have been observed.

However, many challenges remain in understanding how to fully harness the potential of the immune system to treat cancer.

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