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REVIEW

Acquired resistance to cancer immunotherapy

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Abstract

In recent times, advances in cancer immunotherapy have yielded impressive, durable clinical responses in patients with varied subtypes of cancer. However, a significant proportion of patients who initially demonstrate encouraging tumor regression develop resistance and progress over time. The identification of novel therapeutic approaches to overcome resistance may result in significantly improved clinical outcomes and remains an area of high scientific priority. This review aims to summarize the current knowledge regarding the role of both tumor-intrinsic and tumor-extrinsic factors in the development of resistance to cancer immunotherapy and to discuss current and possible future therapeutic strategies targeting these mechanisms.

Keywords Acquired resistance · Cancer immunotherapy · Checkpoint inhibitors · Immune evasion · Immune escape

Introduction

Recent advances in cancer immunotherapy, including the introduction of immune checkpoint inhibitors (ICI), have resulted in a paradigm shift in the treatment landscape of advanced cancer [1–3]. To date, these agents have displayed greatest activity in metastatic melanoma (MM) [4–8], advanced non-small-cell lung cancer (NSCLC) [9–11], urothelial cancers [12–14], head and neck squamous carcinoma [15–17], renal cell carcinoma [18], classical Hodgkin's lymphoma [19–21], Merkel cell carcinoma [22, 23], and solid tumors characterized by microsatellite instability and mismatch repair deficiency [16, 24]. Despite the impressive results of the last decade, the ever-increasing number of immunotherapy-based clinical trials has highlighted the emergence of a significant proportion of patients that acquire resistance to immunotherapy (Fig. 1). Approximately 30% of MM patients treated with ICI who obtain an initial objective response will progress within 3 years [1, 2]. The potential mechanisms underlying acquired resistance are numerous and not completely understood, overlapping at least in part with mechanisms associated with primary resistance. In this review, we discuss the most comprehensively described mechanisms associated with acquired resistance and emerging approaches serving to restore effective immunosurveillance.

Current cancer immunotherapies and the immune checkpoints

Effective activation of tumor-specific T cells is the result of a set of complex interactions occurring at the immunological synapse, consisting of (i) recognition of a major histocompatibility complex (MHC)-bound tumor epitope via the T cell receptor (TCR); (ii) effective co-stimulation, i.e., interaction of receptors/ligands such as CD28 on T cells and B7 on antigen-presenting cells [25]; (iii) a relative lack of co-inhibition, i.e., interaction between negative regulators of T cells (immune checkpoints) such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death protein 1 (PD-1) and their ligands [26].

The physiological role of immune checkpoints is to maintain self-tolerance and to control inflammation, yet they also

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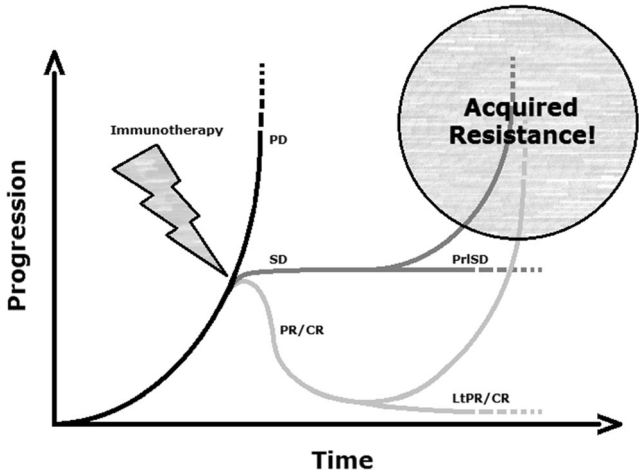

Fig. 1 Graphical representation of acquired resistance to cancer immunotherapy. PD, progressive disease; SD, stable disease; PrlSD, prolonged stable disease; PR, partial response; CR, complete response; LtPR, long-term partial response; LtCR, long-term complete response

represent one of the most common mechanisms of cancer-mediated immune evasion [26, 27]. Indeed, the primary goal of ICI therapy is to restore and maintain the activity of tumor-specific T cells by blocking immune checkpoint-mediated suppression [28]. CTLA-4 is a competitive antagonist of CD28 and can suppress T cell responses when expressed on effector T cells [29]. Ipilimumab, an anti-CTLA-4 fully human monoclonal antibody, was the first checkpoint inhibitor approved by the US Food and Drug Administration (FDA), as a monotherapy for the treatment of advanced melanoma in 2011 [8, 30]. Long-term survival data from clinical trials of ipilimumab has demonstrated durable disease control lasting over 5 years in approximately 20% of patients [31]. Another checkpoint inhibitor expressed by activated T cells is PD-1. The expression of its ligands, PD-L1/PD-L2, varies by tumor type and can be constitutive or induced by activated T cell-produced IFN gamma (IFNγ). Clinical targeting of this protein and its ligands via ICI has further improved the response rate of patients with metastatic cancer [5–7, 32]. Two anti-PD-1 human monoclonal antibodies, nivolumab and pembrolizumab, and three new human monoclonal antibodies directed against PD-L1, durvalumab, atezolizumab, and avelumab, have received FDA approval for the treatment of selected tumor types [1, 33, 34].

Other types of immunotherapy, thus far evaluated predominantly in clinical trials, include (i) adoptive transfer of T cells, either expanded from the tumor-microenvironment (tumor-infiltrating lymphocytes, or TILs [35]) or genetically modified (i.e., chimeric-antigen receptor or CAR-T cells [36, 37] and TCR-engineered T cells [38, 39]); (ii) therapeutic cancer vaccines, including those stimulating the adaptive immune system to generate an immune response against patient-specific tumor neoantigens [40, 41]; and (iii) oncolytic virotherapy, in particular T-VEC, alone or in combination with ICI [42, 43].

Mechanisms of acquired immune resistance

Most human tumors develop in an immunologically competent environment; thus, some level of immune escape and resistance is intrinsic to any established malignancy [3]. Acquired resistance to cancer immunotherapy can develop via genetic and epigenetic heritable traits that pre-exist in the tumor prior to treatment and then emerge following immune selection. However, acquired resistance can also arise from de novo alterations at a single-cell level [2]. When under attack, cancer cells and other components of the tumor microenvironment (TME) can alter their transcriptome in response to interactions with immune cells and their products [2, 44]. Genomic instability can further boost the emergence of immune-resistant cancer cell clones.

Tumor cells can protect themselves and evade the immune system through *intrinsic resistance* mechanisms such as loss/downregulation of target antigen expression, defective antigen presentation, insensitivity to immune effector molecules, up-regulation of alternative immune checkpoints and epigenetic alterations or through *extrinsic resistance* mechanisms mediated by non-cancerous cells in the TME, such as tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) [45–49]. As described, all such mechanisms can exist prior to cancer immunotherapy exposure and overlap with primary immune resistance. It is therefore most likely that the co-existence of multiple primary and/or acquired immune evasion mechanisms within the same tumor leads to acquired resistance in the clinical setting. In the next sections, we will discuss the current knowledge on the major resistance mechanisms associated with acquired resistance to cancer immunotherapy which have been identified to date in solid tumors.

Tumor-intrinsic factors

Defective presentation of tumor-antigens

Tumor cell recognition by the adaptive immune system represents an essential step in obtaining tumor regression. For an antigen on tumor cells to be recognized by T cells, it must be processed and presented in association with MHC molecules [50]. Therefore, immune evasion can be mediated via defects in the antigen presentation pathway. These defects can be categorized into two groups: (i) loss of antigenic molecules (either at a DNA, RNA, or post-translational level) or (ii) impaired antigen processing and presentation ability.

Cancer neoantigens, i.e. those arising from somatic tumor mutations, have been shown to be critical targets for eliciting immune responses and immune-mediated tumor killing [25]. In a pioneering study, Brown et al. [51] analyzed RNA-sequencing data to predict potentially immunogenic mutations

in 515 patients from six different cancer types. The predicted immunogenic mutational counts demonstrated a strong correlation with increased overall survival, providing initial evidence of the importance of neoantigens in human cancer immune recognition. Using large-scale genomic data sets generated from biopsies of 18 different subtypes of solid tumor, Rooney et al. [52] demonstrated that the number of predicted neoantigens was positively associated with in situ immunological activity ("cytolytic activity") across numerous tumor types. Moreover, neoantigen depletion in certain tumor types supported the hypothesis of an immune-mediated pressure to eliminate immunogenic neoantigens. More recently, Rizvi et al. [53] reported that a higher somatic nonsynonymous mutational burden correlates with improved clinical outcomes following ICI therapy in patients with NSCLC. Similar results were obtained by Snyder et al. [54] and van Allen et al. [55] in advanced melanoma. In a recent publication by Riaz et al. [56], the genomic changes in tumors from 68 patients with advanced melanoma, who progressed or were naïve to anti-CTLA-4 therapy, were assessed before and after anti-PD-1 therapy. A reduction in mutation and neoantigen load was observed in association with a response to anti-PD-1 therapy independent of prior immune therapy exposure, suggesting clonal evolution as result of treatment-dependent immunoediting. These studies provided clear evidence that cancer neoantigens represent important targets for the human immune system and appear to play an important role in tumor elimination following treatment with ICI.

Loss of antigenic molecules Recently, Anagnostou et al. [57] demonstrated that loss of expression of 7 to 18 putative mutation-associated neoantigens can result in acquired resistance to ICI therapy. The analyses were conducted on matched pre-treatment and resistant tumors from patients with NSCLC undergoing ICI therapy and demonstrated that neoantigen loss occurred via the elimination of tumor subclones and chromosomal loss of truncal alterations. This was the first study demonstrating that an evolving landscape of mutations can be linked to acquired resistance to ICI. Moreover, the majority of eliminated mutations were typically highly expressed and encoded for neoantigens that were predicted to have high MHC binding affinity or to induce stronger TCR mediated responses. A separate study, conducted by Verdegaal et al. [58], suggested that the dynamic interactions between T cells and cancer cells can induce T cell-mediated neoantigen immunoediting, resulting in partial or total neoantigen loss. In contrast, in a separate study investigating a single patient case in which a complete response to adoptive T cell therapy (ACT) was achieved, acquired resistance occurred without loss of target neoantigens [4]. However, in a mouse model of ACT against murine melanoma, tumor progression after initial regression was associated with a loss of the gene encoding the target tumor antigen [59]. These data demonstrate that downregulation/loss of neoantigens may occur in patients treated with immunotherapy, yet this is not a universal mechanism of acquired immune resistance.

It is likely that proinflammatory cytokines can contribute to immune escape by inducing loss of antigen expression [44]. In a mouse model of ACT [60], melanoma has been shown to acquire resistance through TNFα-induced epithelial-to-mesenchymal de-differentiation. This process, resulting in a loss of melanocytic antigens, causes a switch to a less immunogenic tumor phenotype that can more easily evade immune surveillance. Other cytokines produced by tumor-infiltrating cells, such as IL-6 or TGFβ, have been shown to induce epithelial-to-mesenchymal transition in mouse models of several types of cancer, indicating that inflammation may promote acquired resistance in numerous types of histologically varied cancer [61, 62]. Further work is needed to determine the role of this process in clinical practice.

Impaired antigen processing and presentation machinery Clinical evidence of defective antigen presentation induced by immunotherapy was recently reported by Tran et al. [63]. This group reported the case of a patient with metastatic colorectal cancer treated with an infusion of HLA-C*08:02-restricted TILs targeting mutant KRAS G12D. Loss of the chromosome 6 haplotype encoding the HLA-C*08:02 class I MHC molecule caused the progression of a single lesion 9 months after ACT. Lack of surface expression of class I MHC molecules can also be induced by alterations in genes encoding components of the antigen presentation machinery. Mutations in the β2-microglobulin (*B2M*) gene have been shown to mediate acquired resistance to IL-2 or ACT [64]. B2M is associated with MHC class I and is essential for its folding and transport to the T cell surface [47, 65]. Recently, Zaretsky et al. [66] reported a case of late acquired resistance to anti-PD-1 therapy in a patient with MM. In this study, loss of MHC surface expression was associated with the acquisition of a new homozygous truncating mutation in the *B2M* gene. Further studies [67, 68] have supported the role of *B2M* loss in the development of anti-PD-1 therapy resistance in melanoma and lung cancer. Chang et al. [69] demonstrated a combination of structural and epigenetic defects in MHC class I antigen processing and presentation machinery in MM after immunotherapy. These defects included loss of tapasin (a MHC class I antigen processing molecule) due to a germline frameshift in *TAPBP* exon 3 in association with somatic loss of the other allele, selective epigenetic silencing of the HLA-A3 antigen, and loss of one HLA haplotype. An additional case, documented by our group [70], provided further evidence of alterations to the MHC class I antigen processing and presentation machinery as a mechanism of acquired resistance after T cell-based immunotherapy in MM. To summarize, these mechanisms allow previously antigenic mutations

to become effectively invisible to the immune system, due to the loss of antigen presentation ability.

Insensitivity to immune effector molecules

It has been demonstrated that immunotherapy can induce resistance to T cell-mediated tumor regression by altering the normally vulnerable pathways targeted by T cells [65]; the IFNγ pathway is emerging as a key mediator of this process [71, 72]. After secretion by activated T cells, IFNγ binds to its receptor (IFNGR) on cancer cells and recruits both Janus kinase 1 and 2 (JAK1/JAK2). This recruitment can subsequently induce phosphorylation, dimerization, and activation of the transcription factor STAT1, whose translocation to the nucleus activates the transcription of IFNγ-inducible genes [72]. The process culminates in tumor cell growth inhibition, induction of apoptosis, further T cell infiltration, and upregulation of MHC class I and PD-L1 [66, 71–73]. In the previously described study by Zaretsky et al. [66], whole-exome sequencing was used to compare the DNA of paired baseline and relapsing lesions from four MM patients who exhibited disease progression after an initial response to anti-PD-1. The core aim of the analyses was to identify the genetic basis of this change in phenotype, and it resulted in the detection of truncating loss-of-function mutations in both JAK1 and JAK2, with an accompanying loss of heterozygosity, in two of the patients. This inactivation of JAK1 and JAK2 presumably caused the acquired insensitivity to IFNγ and impacted upon class I expression, immune surveillance and tumor cell proliferation. It has been previously suggested that a lack of T cell infiltrate may be caused by JAK1/JAK2 mutations, as the IFNγ pathway regulates the expression of chemokines, such as CXCL9, CXCL10, and CXCL11, with potent chemoattractant effects on T cells [72]. To further support this, both CD8+ T cell infiltration and PD-L1 expression were present in the baseline biopsies, whereas relapses were associated with the restriction of CD8+ T cells and PD-L1 expression to the tumor margin. In the context of anti–PD-1 therapy, a lack of effective interferon signaling becomes a highly advantageous immune escape strategy, as the potential protection afforded to tumors via PD-L1 is nullified by the treatment. Interferon insensitivity through other mechanisms, such as the expression of negative regulators or epigenetic silencing of JAKs, may have a similar impact and has already been documented in other forms of cancer [74–76].

Further studies are required in order to identify additional IFNγ-resistance mechanisms. Genomic alterations affecting IFNγ-pathway genes, such as the loss of *IFNGR1*, *IFNGR2*, *IRF1*, *IFIT1*, *IFIT2*, *IFIT3*, *MTAP*, *miR31* or amplification of the suppressor genes *SOCS1* and *PIAS4*, have already been reported as potential mechanisms of primary resistance to multiple ICI therapies [77]. Discerning the role of these defects as drivers of acquired resistance to immunotherapy is immensely important for developing strategies to overcome such obstacles.

Upregulation of immune-suppressive pathways

Activation of alternative immunosuppressive pathways in the TME may promote resistance to immunotherapy through impact upon T cell function [45, 65]. Numerous alternative immune checkpoints, such as T cell immunoglobulin and mucin-3 (TIM-3), lymphocyte activation gene 3 (LAG-3), V-domain Ig-containing suppressor of T cell activation (VISTA), and indoleamine-2,3-dioxygenase (IDO), have been characterized in recent years. These are often upregulated during ICI therapy with anti-PD1/PD-L1 or anti-CTLA-4 antibodies due to either the activation of the IFNγ-pathway or miscellaneous cellular signals [78, 79]. Thommen et al. [80] reported that acquired resistance to anti-PD1 therapy in patients affected by NSCLC was associated with the co-expression of PD-1, TIM-3, CTLA-4, LAG-3, and B and T lymphocyte attenuator (BTLA). Their research demonstrated that expression of these five molecules on the surface of effector T cells was associated with reduced proliferation, migration, and cytokine production. Upregulation of these, as well as multiple other inhibitory checkpoints, has been documented in response to ICI therapy in a diverse range of pre-clinical cancer models [79, 81–84]. Recently, TIM-3 upregulation was observed in lung adenocarcinoma patients who developed acquired resistance to anti-PD1 treatment [83]. In addition, a recent study from Balko et al. [85] illustrated that LAG-3 upregulation post-relapse in anti-PD1 treated tumors was associated with MHC II expression, indicating that MHC II+ tumors might derive increased benefit from anti-LAG3 therapy. Combinational therapy utilizing anti-PD-1 antibodies in association with LAG-3 inhibitors [86] or TIM-3 inhibitors [87] has already demonstrated notable efficacy in pre-clinical models and a phase I clinical trial. Indeed a study evaluating the combination of PD-1 blockade with LAG-3 blockade in patients with melanoma previously treated with anti-PD1/anti-PD-L1 monotherapy, reported an objective response rate of 16% [88]. Currently, there are numerous ongoing clinical trials evaluating the possibility of incorporating novel agents targeting alternative immune checkpoints, both as a monotherapy and in combination.

A recent pre-clinical study by Bertrand et al. [89] suggested that TNFα expression in an inflamed TME correlates positively with PD-L1 and TIM-3 expression upon anti-PD1 therapy in melanoma mouse models. Indeed, this study provides the first evidence that the TNFR1-dependent TNFα signaling pathway may be an immune evasion mechanism conferring resistance to anti-PD1 therapy. In addition, it was demonstrated that TNFα impairs the accumulation of CD8+ TILs and triggers activation-induced cell death of CD8+ T cells in mouse melanoma. Accordingly, TNFα blockade prevented

PD-L1 and TIM3 expression, and anti-PD1-induced TIL death. Consequently, this study provides a rationale for the combination of anti-PD1 and anti-TNFα antibodies as a novel potential combinational therapy for the treatment of melanoma and other cancers. A phase 1 clinical trial testing this association is ongoing (NCT03293784).

Preliminary studies have identified a potential role of specific oncogenic signaling pathways in the acquisition of resistance to immunotherapy. Activation of the β-catenin signaling pathway has been shown to correlate with an absence of CD103+ dendritic cells and T cell exclusion from the TME. This pathway appears to be activated in at least 10% of human cancers [90]. The activation of another pathway, the PI3-kinase pathway, can inhibit T cell infiltration through loss of the tumor suppressor *PTEN* and may represent an additional mechanism of immune escape [64].

Epigenetic alterations

Emerging evidence indicates that epigenetic modification may play an important role in antigen processing and presentation; in the proliferation, differentiation and function of T cells; and in the acquisition of a memory T cell phenotype [45, 91]. Additionally, epigenetic silencing of the genes encoding CXCL9 and CXCL10 has been proposed to interfere with T cell migration into tumors [92]. Changes in the chromatin landscape could therefore be at the basis of T cell exhaustion, mediating primary resistance or contributing to relapse during ICI therapy. Epigenetic targeting drugs, such as those targeting DNA methylation, histone deacetylation, or histone methylation; have demonstrated promising activity in the pre-clinical setting [91]. Ongoing clinical trials are testing various combinations of demethylating agents, hypomethylating agents, and histone deacetylase inhibitors; in association with ICI in patients with acquired resistance to immunotherapy [47, 91]. Further results are needed to assess the role of these epigenetic modulators in clinical practice.

Tumor-extrinsic factors

Aside from tumor cell-mediated mechanisms of immune suppression, there are numerous factors operating in the TME that can impact upon the efficacy of immunotherapy agents. A subset of T cells that is commonly associated with cancer progression is Tregs [93]. Tregs are known to suppress effector T cell function via the secretion of inhibitory cytokines such as IL-10 and TGFβ, or by direct cell-to-cell contact [45]. IL-10 can affect antigen presentation by reducing the expression of MHC class II and co-stimulatory molecules on dendritic cells, thereby preventing the activation of effector T cells [94]. Pre-clinical studies conducted in mouse models of cancer demonstrate that in addition to expanding effector T cells in secondary lymphoid organs, anti-CTLA-4 antibodies also act to deplete intra-tumoral Tregs via antibody-dependent cell-mediated cytotoxicity (ADCC) [95–97]. This differential activity results from higher expression of CTLA-4 on Tregs relative to effector T cell subsets and enrichment of Fc gamma receptor (FcγR)-expressing cell subsets within capacity for ADCC in the TME.

Despite its potentially depleting isotype, the contribution of ADCC and role of FcγRs in the activity of anti-CTLA-4 has remained unclear until recently. Two clinical studies have previously identified a reduction in tumor-infiltrating Tregs post anti-CTLA-4 therapy [98, 99]. Moreover, in vitro studies demonstrate that ipilimumab depletes CTLA-4-expressing Tregs in the presence of FcγR-expressing monocytes and NK cells, consistent with the predicted binding affinity for activatory FcγRs [98, 100]. Most recently, a role for Fc effector function in the activity of human anti-CTLA-4 antibodies has been confirmed [101]. Importantly, this study suggested that Treg depletion only appears relevant in the context of an inflamed TME, explaining the relatively modest response rates to anti-CTLA-4 compared to the pre-clinical setting. Further clinical studies targeting Tregs in combination with ICI are already ongoing [93]. Additionally, there is some indication that epigenetic modulation can be responsible for the accumulation of Tregs in cancers [91].

The presence of other suppressive cells, such as MDSCs and TAMs, in the TME has been associated with resistance to multiple facets of immunotherapy, including ACT, ICI, and dendritic cell vaccines. Furthermore, MDSCs have been shown to play a role in promoting angiogenesis, metastasis, and immune cell suppression. Combinational strategies targeting this cell subset in association with other immunotherapy agents may enhance the clinical benefits derived by cancer patients [45]. In a recent study, M2-polarized TAMs were shown to directly interfere with anti-PD1 therapy by removing anti-PD1 antibodies from the surface of PD-1+ T cells [102]. Previous clinical studies documented a connection between high TAM infiltration and poor prognosis [103]. Studies testing the blockade of macrophage colony-stimulating factor receptor (CSF-1R) in combination with either ICI or ACT reported improved tumor regression, indicating that a reduction of TAMs may restore immunotherapy efficacy. Clinical trials evaluating the efficacy and safety of CSF-1R blockade in association with ICI across various solid tumor types are currently ongoing [45].

Future directions and conclusions

Acquired resistance to cancer immunotherapy is often the result of multiple immune escape mechanisms. Efforts to identify universal mechanisms of acquired resistance are unlikely to be successful. Future efforts should focus upon developing

biomarker-guided strategies to counteract immune resistance mechanisms on an individual patient basis, or alternatively, combination therapies targeting multiple pathways simultaneously to prevent the development of acquired resistance. Potential strategies may include the introduction of drugs inhibiting immune-suppressive cells or proteins, blockade of pathways downregulating anti-tumor immunity, modulation of epigenetic mechanisms, and combination of checkpoint inhibition [5, 7, 88] with immune pathway stimulators, such as the stimulator of interferon gene (STING) which promotes STAT activation in a JAK2-independent manner [66].

In conclusion, although patients treated with cancer immunotherapy have the potential to derive substantial benefit, the emergence of acquired resistance poses a significant challenge for a considerable proportion of patients. An improved understanding of the mechanisms underlying acquired resistance and the identification of relevant biomarkers in each individual is required for the development of novel therapeutic strategies and improved personalized cancer immunotherapies [44]. Further studies in larger cohorts will help elucidate alternative escape pathways. Current efforts aim to promote long-lasting disease control for the majority, rather than a select few.

Compliance with ethical standards

Conflict of interest Marco Donia has received honoraria for lectures from Bristol-Myers Squibb, Merck, Astra Zeneca, and Genzyme, as well as financial support for attending symposia from Bristol-Myers Squibb, Merck, Novartis, Pfizer, and Roche. The other authors declare that they have no conflict of interest.

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