Drug Resistance Updates 53 (2020) 100718

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Cancer immunotherapy resistance based on immune checkpoints inhibitors: Targets, biomarkers, and remedies

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ARTICLE INFO

Keywords:
Cancer
Biomarker
Immunotherapy
Checkpoint inhibitors
Drug resistance
Surmounting drug resistance

ABSTRACT

Cancer is one of the main public health problems in the world. Systemic therapies such as chemotherapy and more recently target therapies as well as immunotherapy have improved the prognosis of this large group of complex malignant diseases. However, the frequent emergence of multidrug resistance (MDR) mechanisms is one of the major impediments towards curative treatment of cancer. While several mechanisms of drug chemoresistance are well defined, resistance to immunotherapy is still insufficiently unclear due to the complexity of the immune response and its dependence on the host. Expression and regulation of immune checkpoint molecules (such as PD-1, CD279; PD-L1, CD274; and CTLA-4, CD152) play a key role in the response to immunotherapy. In this regard, immunotherapy based on immune checkpoints inhibitors (ICIs) is a common clinical approach for treatment of patients with poor prognosis when other first-line therapies have failed. Unfortunately, about 70 % of patients are classified as non-responders, or they progress after initial response to these ICIs. Multiple factors can be related to immunotherapy resistance: characteristics of the tumor microenvironment (TME); presence of tumor infiltrating lymphocytes (TILs), such as CD8 + T cells associated with treatment-response; presence of tumor associated macrophages (TAMs); activation of certain regulators (like PIK3γ or PAX4) found present in non-responders; a low percentage of PD-L1 expressing cells; tumor mutational burden (TMB); gain or loss of antigen-presenting molecules; genetic and epigenetic alterations correlated with resistance. This review provides an update on the current state of immunotherapy resistance presenting targets, biomarkers and remedies to overcome such resistance.

1. State of the art in cancer immunotherapy

Cancer incidence and mortality are rapidly growing worldwide. Freddie Bray and colleagues (Bray et al., 2018) reported more than 17.0 million new diagnosed cases and 9.6 million cancer deaths in 2018. Provided that both cancer incidence and mortality are highly associated with social and life style factors and related to the degree of economic development in each country (Allemani et al., 2018), there is a clear need to continue working in new strategies that improve these determinants. In this respect, intrinsic and acquired multidrug resistance (MDR) to various chemotherapeutic agents constitute a major impediment towards curative cancer treatment. These mechanisms of chemoresistance are often mediated: (i) via transmembrane efflux pumps of the ATP-binding cassette (ABC transporter) family that extrude a plethora of structurally and mechanistically distinct anticancer drugs; or (ii) via MDR efflux pump independent determinants. (Zhong and

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https://doi.org/10.1016/j.drup.2020.100718
Received 11 May 2020; Received in revised form 9 June 2020; Accepted 13 July 2020
Available online 15 July 2020

Virshup, 2020; Cui et al., 2018; Gacche and Assaraf, 2018; Wijdeven et al., 2016; Li et al., 2016; Zhitomirsky and Assaraf, 2016; Niewerth et al., 2015; Livney and Assaraf, 2013; Gonen and Assaraf, 2012; Shapira et al., 2011). Based on the multifactorial nature of MDR, targeting one mechanism is not sufficient to surmount the chemoresistance phenotype (Assaraf et al., 2019).

In recent years, technological developments in cancer research and increasing knowledge about cancer biology, cancer genomics, and personalized molecular cancer therapies have improved clinical outcomes in treating different types of tumors. In this scenario, two new distinctive hallmarks have recently been proposed for a deeper characterization of the tumors: inflammation associated with cancer and evasion from immune control. These new hallmarks show the important role of the immune system in cancer, that is essential to understand this complex multifactorial disease and to develop new therapeutic strategies (Fouad and Aanei, 2017; Hanahan and Weinberg, 2011).

T cell activation plays a crucial role in cancer immunity and these cells trigger several pathways leading to the formation of "immune checkpoints" (IC) controlled by immune checkpoint receptors and ligands. One of the best studied IC molecules is the *Programmed Cell-Death 1* protein (PD-1, also called CD279, official symbol PDCD1 and gene ID 5133), that contributes to cancer immune evasion. Another important immune checkpoint molecule is the *Cytotoxic T Lymphocyte-associated Antigen 4* (CTLA-4, also called CD152, official symbol CTLA4 and gene ID 1493) responsible for T cell responses modulation (Alkhazraji et al., 2019). This knowledge lead to the development of immunotherapies based on immune checkpoint inhibitors (ICIs) which mark the beginning of a new era in the treatment of cancer (Diesendruck and Benhar, 2017; Hays and Bonavida, 2019; Kon and Benhar, 2019; Leonetti et al., 2019; Dal Bo et al., 2020). In a 2013 cover story *Science* magazine featured cancer immunotherapy as the "Breakthrough of the Year", indicating that turning off those brakes (i.e. the immune checkpoint molecules) allows T cells to destroy cancer cells. Therefore, this strategy of "cutting the brakes" elicited strong anti-tumor immune responses and paved the way for a new type of cancer therapy. Since then, a full battery of new immune checkpoint blocking antibodies (Ab) has been developed to target the cytotoxic T-lymphocyte antigen 4 (CTLA-4, CD152), programmed cell-death protein 1 (PD-1, CD279) and PD-1 ligand 1 protein (PD-L1, CD274) (Table 1). These therapeutic antibodies have demonstrated acceptable toxicity, promising objective clinical responses, durable disease control, and improved survival in many type of tumors. Several examples include: ICI Ab *Durvalumab* in stage III lung cancer (i.e., stage III non-small-cell lung carcinoma, NSCLC) (Antonia et al., 2017); ICI Ab *Nivolumab* in advanced NSCLC (Borghaei et al., 2015); ICI Ab *Atezolizumab* in advanced and metastatic urothelial cancer (Balar et al., 2017); ICI Ab *Nivolumab* in advanced renal-cell carcinoma (Motzer et al., 2015); ICI Ab *Nivolumab* in recurrent or metastatic squamous-cell carcinoma of the head and neck (Ferris et al., 2016); ICI Ab *Avelumab* in refractory metastatic Merkel cell carcinoma (Kaufman et al., 2016); ICI Ab *Ipilimumab* in stage III melanoma (Eggermont et al., 2016); ICI Ab *Nivolumab* in metastatic melanoma without a BRAF mutation (Robert et al., 2015); combined ICI Abs *Nivolumab* and *Ipilimumab* in metastatic melanoma (Larkin et al., 2015); and ICI Ab *Pembrolizumab* in refractory melanoma (Ribas et al., 2015).

Unfortunately, only 30–40 % of patients benefit from these agents, and yet fewer achieve a durable response (Ma et al., 2016). The cancer-immunity cycle, as described by Chen and Mellman (Chen and Mellman, 2013), requires: (i) the release of tumor antigens; (ii) presentation of these antigens, leading to effector cell activation; (iii) successful trafficking and infiltration of such cells into the tumor microenvironment (TME); and (iv) overcoming an often immunosuppressive microenvironment to recognize and ultimately kill tumor cells. These progressive steps of the immune reaction are linked to the complexity of the host (i.e. the variability of the response that depends on age, sex, comorbidities, etc). Such a complexity needs an important multidisciplinary effort to elucidate the mechanisms of response and resistance to immunotherapy, in order to predict and improve the clinical benefits. The objective of the current review is to provide an update on the mechanisms of resistance to ICI treatment and the approaches to surmount this resistance. Furthermore, we consider that this investigation will help to improve the identification of biomarkers of response and anticancer drug resistance.

2. Tumor resistance to immunotherapy based on immune checkpoint inhibitors (ICIs)

Contrary to conventional cytotoxic chemotherapy and radiotherapy, which affect both healthy and tumor cells, immunotherapy treatments are designed to target the immune system itself by triggering an effective immune attack against tumor cells. In the case of immune checkpoint inhibitors (ICIs), these targets are the co-inhibitory signals that block effective cytotoxic T lymphocyte activation. Although in normal tissues the autoimmunity is prevented, the tumor microenvironment (TME) represents a route for immune escape, which is considered one of the hallmarks of cancer (Hanahan and Weinberg, 2011). Indeed, studies on TME show that interactions between the immune system and cancer cells are continuous, dynamic and evolving from the initiation of tumorigenesis to the development of the metastatic disease, in each case, the ability of tumor cells to evade the host's immune response plays a significant role. Despite the unprecedented durable response rates observed with cancer immunotherapies, the majority of patients do not benefit from the treatment (i.e., they present intrinsic resistance), and some responders relapse after a period of response (i.e., they present acquired resistance). Considering these differences, immuno resistance was originally classified by Sharma, Wargo and Ribas (Sharma et al., 2017) into three main categories: "primary", "adaptive" and "acquired". In essence, from a pragmatic clinical point of

Table 1
Main immune checkpoint targets for cancer immunotherapy.

IMMUNE CHECKPOINT TARGET	OVERVIEW
CTLA-4 (**CD152**) (Gene ID: 1493 ; CTLA4) (ENSG00000163599)	CTLA4 signalling inhibits T cell activation. This co-inhibitory receptor is constitutively expressed on the surface of regulatory T cells and frequently upregulated in activated $CD4^+$ cells and exhausted T cells. The encoded protein contains an immunoglobulin V-like domain, a trans-membrane domain, and a cytoplasmic tail. CTLA4 blockade prevents interaction with CD80/86 avoiding T cell inactivation and energy.
PD-1 (**CD279**) (Gene ID: 5133 ; PDCD1) (ENSG00000188389)	PD-1 pathway regulates activated T cell activity at the later stages of an immune response. The expression of this co-inhibitory receptor is constitutive in exhausted T cells and can be temporary activated in CD8+ T cells, natural killer T cells or myeloid cells after T cell receptor activation by cytokines and interleukin. PD-1 blockade improves T cell-mediated immune response by preventing interaction with the inactivating ligands, PD-L1 and PD-L2, which decrease T cell proliferation, cytokine production and other effector functions.
PD-L1 (**CD274**) (Gene ID: 29126 ; PDCD1L1) (ENSG00000120217)	This immune inhibitory receptor ligand inhibits different pathways related to T cell activity and survival. PD-L1 is expressed by both hematopoietic and non-hematopoietic cells as well as by different tumor cells. The encoded protein is a type I transmembrane protein that has immunoglobulin V-like and C-like domains. PD-L1 inhibition can preserve antitumor T cell activity.

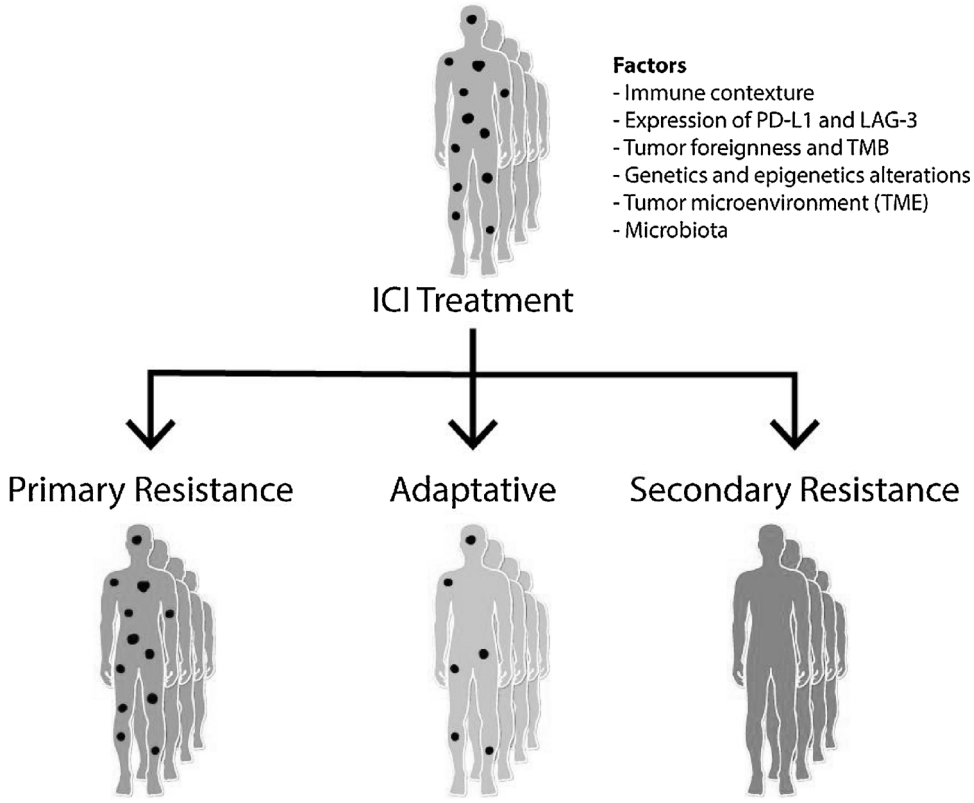

Fig. 1. Types of immuno resistance emerging upon treatment ICIs: primary resistance, adaptive resistance and secondary or acquired resistance. Resistance to immunotherapy depends on different factors: PD-L1 (Protein Death-Ligand 1), LAG3 (Lymphocyte Activation Gene 3), TMB (Tumor Mutational Burden), etc.

view, "primary" means pre-existing to immunotherapy exposure and usually applies to patients who do not respond at all to immunotherapy; "adaptive" means appearance of resistance mechanisms as a Darwinian mechanism of adaptation; and "acquired" (also called "secondary") refers to appearance after immunotherapy instigation following a transient period of disease control (Fig. 1).

Several factors contribute to resistance to immunotherapy: The most likely mechanisms involve reduction in the quantity and/or quality of anti-tumor T lymphocytes, which are ultimately driven by multiple and heterogeneous molecular changes: tumor mutations and adaptations (such as epigenetic or genetic loss of antigen presentation capabilities or diminished responsiveness to interferons, IFNs); down-regulation or loss of neoantigen expression; indoleamine 2,3-dioxygenase (IDO) overexpression; loss of phosphatase and tensin homologue (PTEN) expression; overexpression or gain of function mutations in the WNT and beta-catenin pathway or microbiota modifications (Kelderman et al., 2014; Pitt et al., 2016; Rieth and Subramanian, 2018).

The identification and validation of biomarkers that can predict the appropriate response or resistance of cancer patients to immunotherapy is of utmost importance, because the use of such molecular markers would be associated with relevant reductions in the clinical costs and toxicity of the treatments. Some of these biomarkers are described in the following sections and are listed in Table 2.

3. Factors and/or biomarkers relevant to resistance to ICIs therapy

3.1. Immune contexture and tumor microenvironment (TME)

The tumor and the surrounding microenvironment that includes blood vessels, immune cells, signalling molecules, fibroblasts and the extracellular matrix constitute a heterogeneous and complex system known as "tumor microenvironment" (TME) with an important influence on tumor development and progression. TME has been classified into three main categories in order to better understand all the interacting factors involved in TME and their role in the success to immunotherapies (Binnewies et al., 2018):

- **Infiltrated-excluded TME**: They are poorly immunogenic or "cold" tumors may be representative of immunological ignorance. Infiltrated-excluded TME presents localized cytotoxic T lymphocytes along the border of the tumor mass in the invasive margin or within fibrotic nests. These type of tumors are often associated to epithelial cancers such as colorectal carcinoma, melanoma or pancreatic ductal adenocarcinoma in which tumor-associated macrophages (TAMs) along the tumor margins may prevent cytotoxic T cell infiltration into the tumor core.
- **Infiltrated-inflamed TME**: These tumors are considered immunologically "hot" tumors with high infiltrated cytotoxic T cells expressing PD-1 and PD-L1, and also presenting tumor cells accompanied by high microsatellite instability, related to a better response to ICIs.
- **Tertiary Lymphoid Structure TME**: Appears as a class of infiltrated inflamed TME presenting tertiary lymphoid structure with aggregates of immune cells and a similar composition to that in lymph nodes, including B cells, dendritic cells and regulatory T cells ("Treg" cells).

Despite this classification, the evidence shows that the intricate interplay among the different cellular and non-cellular components of TME result in different TME subclasses not only among patients or tumor types but also within a patient's tumor. In this way, multiple studies started to consider the differences in the spatial localization, density and functional orientation of immune cell populations in the TME, defining the "immune contexture" (Fig. 2). These differences in samples from different individuals with the same type of malignancy

Table 2
Mechanisms of resistance and contributing factors.

		Primary resistance	Acquired resistance	Secondary resistance
IMMUNE CONTEXTURE AND TUMOR MICROENVIRONMENT	**TILs**	Absence		Absence
	CD8_G			Presence
	CD8_B	Presence		
	TIM3 / LAG3 / TIGIT		Presence	
	Myeloid-derived suppressor cells (MDSCs)	Presence	Presence	Presence
	Tumor-associated macrophages (TAMs)	Presence	Presence	Presence
	T regulatory cell (Treg)	Presence	Presence	Presence
GENETIC AND EPIGENETIC ALTERATIONS	**Loss of antigenicity**	Presence		Presence
	Specific HLA		Transcriptional suppression of HLA	
	INF gamma pathway	JAK mutation		JAK mutation
	WNT / β-catenin signalling		Presence	Presence
	PTEN loss	Mutations or deletion		
	IPRES signature	Presence		Absence
	Epigenetic signature	Presence		Absence
	STK11 / LKB1 in KRAS mutant lung cancer	Presence		
MICROBIOTA		Presence	Presence	Presence

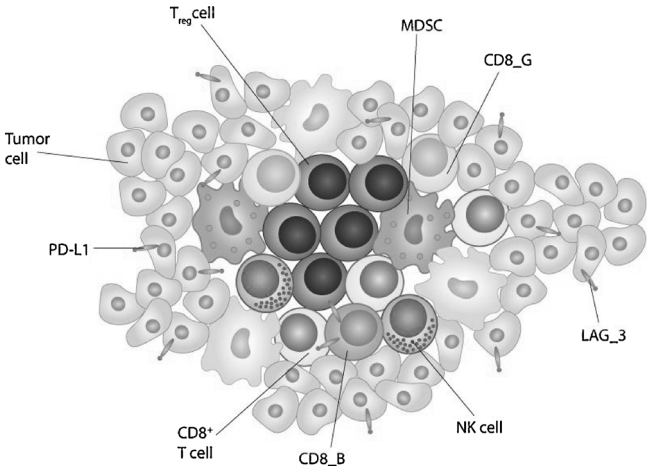

Fig. 2. Tumor microenvironment (TME) including immune contexture shows a diversity of tumor cells (blue), stromal cells (brown) and several types of immune cells (purple, green and red). The immune contexture refers to spatial localization, density and functional orientation of immune cell populations in TME. Abbreviations: PD-L1 (Protein Death-Ligand 1); LAG3 (Lymphocyte Activation Gene 3); CD8 + T cell (T lymphocytes CD8+); CD8_B (lymphocytes CD8+ that overexpress TIM3 and CD39); CD8_G (lymphocytes CD8+ that express TCF1); NK cell (Natural Killer cell); MDSC (Myeloid-Derived Suppressor cells); Treg (Regulatory T cells). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

have paved the way to investigations considering whether this immune stat might affect patient clinical outcome (Bindea et al., 2013). In this regard, recent studies have shown that tumor associated B cells are vital to melanoma-associated inflammation (which also includes a concomitant increase in the number of CD8 + T cells), and, in this context, tumor-associated inflammation predicts response to immune checkpoint blockade (Griss et al., 2019). Although the presence of tumor infiltrating lymphocytes (TILs) in biopsies is also related to a better prognosis in different neoplasms (Fridman et al., 2012), the validity of abundance and pre-treatment presence of TILs as response predictor to immunotherapy is still considered a controversial issue. Thus, even though TIL analysis among patients with metastatic melanoma who participated in a phase II trial with *Ipilimumab* showed that the pre-treatment abundance of TILs was not a predictor of clinical response, the increase in the density of the TILs after the second cycle of *Ipilimumab* was associated with better clinical response (Hamid et al., 2011). Likewise, Tumeh et al., showed that the increase in lymphocytes CD8+, PD-1+ and PD-L1+ cells both at the margins and in the tumor centre were observed in on-treatment biopsies from those patients who experienced a response to anti-PD-1 therapy (Tumeh et al., 2014).

On the other hand, published data also indicate that although infiltrated regulatory T cells (Treg) in different human tumors predict a worse prognosis in general, the presence of these immune cells in head and neck carcinomas is associated with a good outcome (Chaudhary and Elkord, 2016; Ormandy et al., 2005). Interestingly, Quezada et al., reported that Tregs control both CD4+ and CD8 + T cells activity within the tumor mass, highlighting the importance of the intra-tumoral ratio between effectors and regulators, since an inverse ratio correlates with tumor rejection during GVAX / anti-CTLA-4 immunotherapy (Quezada et al., 2006). In this line, a study published by Hacohen and colleagues (Sade-Feldman et al., 2018) profiled transcriptomes and identified two T cell states associated with clinical outcomes: (a) The "CD8_G" are T cells that express the TCF1 transcription factor (TF) and display memory and self-renewal features (these were enriched in treatment-responsive tumors); (b) the "CD8_B" are T cells overexpressing exhaustion markers such as TIM3 and CD39 (that were clustered in anti-PD-1 non-responsive tumors).

Provided that quantitative analysis of TILs is not a valid marker on its own, there is a current need to determine if, as a compensatory inhibitory mechanism, the blockade of one immune checkpoint would interfere with the immune response by increasing the expression and activating another immune checkpoint on immune cells (Saleh and Elkord, 2019). This idea is under investigation given the correlation between upregulated TIM3 (gene T cell immunoglobulin and mucin domain-containing protein 3, CD366), LAG3 (gene lymphocyte activating 3, CD223) and TIGIT (gene T cell immunoreceptor with Ig and ITIM domains) expression on immune cells with the exhausted T cell phenotypes and poor clinical therapeutic outcome (Koyama et al., 2016; Limagne et al., 2019) (Zhang et al., 2018).

The composition of TME is very heterogeneous (Fig. 2) with cell and non-cell factors perfectly orchestrated and communicating with tumor cells. Moreover, the TME is complex and the relationship between all factors is not completely elucidated. Among stromal cells, myeloid-derived suppressor cells (MDSCs) are a very important type of cells in the TME, which correlate with decreased efficacy of immunotherapies, including ICIs (Zhu et al., 2014), adoptive T cell therapy (Kodumudi et al., 2012) and dendritic cells (DC) vaccination (Laborde et al., 2014).

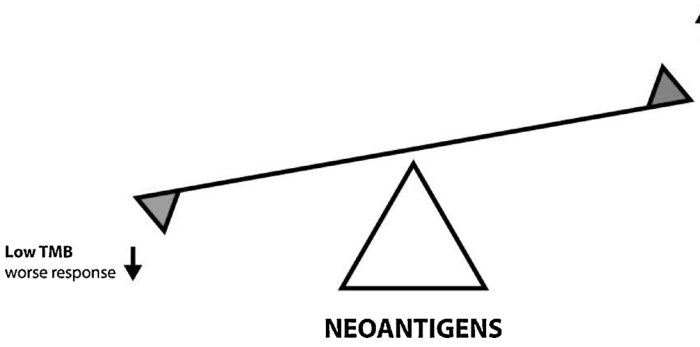

Fig. 3. Response to neoantigens produced by the cancer cells. The production of more or less neoantigens by tumors (i.e., neoantigen burden) is directly related to the tumor mutational burden (TMB), and also to the good or bad response to immunotherapy. These burdens are emerging biomarkers that correlates with patient response to ICIs.

In this regard, an interesting work published by De Henau et al., has already showed that targeting Phosphoinositide 3-Kinase gamma (PI3K-γ, gene PIK3CG), a master regulator of cell cycle and apoptosis, in myeloid cells could prevent resistance to ICI therapy (De Henau et al., 2016).

On the other hand, tumor-associated macrophages (TAMs) are another subset of hematopoietic cells that have been correlated with poor prognosis (Guo et al., 2016). TAMs seem to affect responses to immunotherapy because of their immunosuppressive action based on release of anti-inflammatory cytokines such as interleukin 10 (IL-10) or transforming growth factor beta (TGF-β) (Saleh and Elkord, 2019). In this respect, a number of preclinical studies have also reported the potential value of targeting kinase receptors pathways, such as TGF-β (Ungefroren, 2019) and vascular endothelial growth factor (VEGF) (Fukumura et al., 2018) to enhance the response to immunotherapies, diminishing the risk of immune-related adverse effects and improve patient outcomes.

Recently, Ribas and collaborators have published interesting data about a new potential strategy to overcome resistance due to poorly infiltrated tumors. In their work, they show that p21-activated kinase 4 (PAX4) is overexpressed in tumor cells from non-responder patients and associated with low T and dendritic tumor infiltrated cells, demonstrating that the inhibition of this kinase on KO^{PAX4} mice models improves the efficacy of anti-PD1 therapy (Abril-Rodriguez et al., 2020). These results are one of the multiple preclinical and clinical studies carried out in recent years in which the use of kinase inhibitors emerges as a promising strategy to enhance the response and to overcome resistance to PD1/PD-L1 blocking therapies in human cancers, a field that deserves further investigation (García-Aranda and Redondo, 2019).

3.2. Expression of PD-L1 (CD274) and LAG3 (CD223) in tumors

Although different biomarkers have been proposed as tools to predict patient response to PD-1/PD-L1 inhibitors, PD-L1 (CD274) expression remains the most widely considered. For example PD-L1 expression has been established as a *sine qua non* condition in the case of disseminated NSCLC patients candidates for immunotherapy (Gandhi et al., 2018).

The percentage of PD-L1 expressing cells is an immunohistochemistry parameter referred to total nucleated cells versus malignant cells. Although different cut-off points have shown that patients with higher PD-L1 expression usually benefit more from anti-PD-1 treatment; it has been reported that patients with negative expression for this ligand can also benefit from this treatment (Zou et al., 2016). Importantly, the immunohistochemistry technique does not measure the intensity of expression on the positive cells but the percentage of cells with positive expression, which limits the potential of this technique given the frequent heterogeneity with regard to expression of PD-L1 even within a single tumor lesion (Patel and Kurzrock, 2015).

A recent meta-analysis published by Saleh and collaborators reported that a high expression of LAG3 (CD223) is associated with a better overall survival in different types of tumors (Saleh et al., 2019). Expression of PD-L1 or LAG3 can induce immunosuppressive responses and in this situation facilitate tumor escape. However, the upregulation of these molecules may initiate a negative feedback mechanism that creates an active immune environment in an inflamed tumor, which leads to an improved prognosis (Saleh et al., 2019).

In the last few years, new techniques such as spatially-resolved and multiparametric single-cell analysis showed that the expression of different markers as PD-1, LAG3 and TIM3 have distinct tissue/cell distribution and functional implications in NSCLC and it even seems that expression of LAG3 is associated with no response to anti-PD1 therapies (Datar et al., 2019). For these reasons, although PD-L1 immunostaining can be a predictive factor of treatment response, it is still necessary the use of additional biomarkers, present in the TME, including also the nature and quantitative value of TILs in the immune system (Festino et al., 2016).

3.3. Tumor mutational burden (TMB)

Immune recognition of cancer cells relies on altered HLA-presented peptides as a result of mutations, abnormal ectopic expression, expression of placental/fetal proteins (not present in adult tissues), or the expression of external foreign proteins such as viral oncogenes. Neoantigens resulting from genetic alterations and mutations are probably the most relevant, and the probability of having an immunogenic peptide produced by the array of HLA antigen presenting molecules of the tumor-bearing subject increases with the amount of mutations in the genome. Studies on tumor mutational burden (TMB) (Alexandrov et al., 2013) showed that tumors such as metastatic melanoma (MM) or NSCLC usually present a better response to ICI, since abundant mutations are likely to generate more neoantigens triggering effector immune response activation (Fig. 3).

Snyder and collaborators were the first to demonstrate that patients with melanoma displaying higher TMB, had better clinical benefit from *Ipilimumab* treatment. Furthermore, it was strikingly correlated with the predicted antigenic peptides (neoepitopes) according to the class I HLA alleles of the patients (Snyder et al., 2014). Similar conclusions were reached in a cohort of patients with NSCLC treated with *Pembrolizumab* (Rizvi et al., 2015).

Whole exome sequencing (WES) studies are the gold standard for the assessment of TMB in tumor biopsies. Apart from the complexity derived from the analysis and comparison of WES data from germinal and tumor DNA, the limited availability of WES data from diagnostic biopsies represent one of the main limiting factors for the widespread use of these techniques. With respect to other new technologies, the development of liquid biopsy (LB) has revolutionized tumor evaluation, allowing the detection and identification of circulating tumoral DNA. In this way, the use of LB has allowed estimation of TMB (Gandara et al., 2018). Gandara et al., presented the data on TMB determined in LB of patients with NSCLC treated with *Atezolizumab*, evidencing that patients with higher TMB responded better to the treatment with this ICI (Gandara et al., 2018).

Consistently, those tumors with deficiency in DNA repair enzymes

(mismatch repair system, MMS) generate multiple neoantigens, and it has been observed in different studies that those tumors which had defects in MMS, responded better to PD-1 inhibitors (Chang et al., 2018). In fact, this triggered the accelerated approval by the FDA of the ICI *Pembrolizumab* for children or adults with any tumor that presents MMS deficiency (Le et al., 2015). More recently, the Chan´s group (Mandal et al., 2019) has demonstrated that tumor-bearing mice treated with antibodies against PD-1, displayed a variable response to therapy, depending on their genomic tumor MSI (Microsatellite Instability) burden. They also suggested immunoediting as the possible cause of the variable response to anti-PD-1 therapy, because the loss or the reduction in frequency of tumor missense and indel mutations in anti–PD-1 MSI-high tumors treated with anti-PD-1 antibodies (when compared to their preimplantation baseline). Accordingly, studies in NSCLC reported the loss of immunogenic neoantigens or their antigen presenting molecules (McGranahan et al., 2017), which supports the fact that those tumors with increased neoantigen expression at the beginning of the malignant cell clonal evolution would be better responders to ICI (Jamal-Hanjani et al., 2017), and therefore a strong neoantigen expression could be considered a predictive marker of such response. Finally, loss-of-function BRCA2 mutations, leading to defects in homologous recombination and double-stranded DNA break repair, have also been associated with a favorable response to anti-PD-1 (Hugo et al., 2016).

3.4. Key genetic and epigenetic alterations

There are a number of key genetic alterations and epigenetic changes that correlate with resistance to ICI. The genetic alterations include modification or modulation of a series of genes that are directly involved in the activation and regulation of the immune system. Such genes are the major histocompatibility complex (MHC), that includes a set of closely linked polymorphic genes that encode for cell surface proteins essential for the adaptive immune system; the genes involved in the interferon gamma pathway, that include as key players IFNγ (interferon gamma), the receptors IFNGR1/2 and JAK2; the genes of the WNT and β-catenin signalling pathways; the genes of the PTEN pathway; and a series of genes regulating epigenetic changes.

3.4.1. Antigen-presenting molecules (MHC, HLA) facilitate immune response

The main mechanisms of tumor evasion from immunotherapy aim to reduce the recognition of the tumor by the immune system. That is probably the reason why there is an association between the heterozygosity in antigen-presenting molecules of MHC and the response to ICIs (Bach et al., 1997). Loss of antigenicity can be observed either as primary or acquired resistance to ICIs (Ribas and Wolchok, 2018). Paulson and collaborators (Paulson et al., 2018) showed that two patients with metastatic Merkel cell carcinoma (treated with autologous Merkel cell polyomavirus specific CD8 + T cells and immune checkpoint inhibitors), whose initially responded, had late relapses at 18 and 22 months. These patients had a transcriptional suppression of the specific HLA genes presenting the targeted viral epitope in the resistant tumor as a consequence of intense CD8-mediated immunologic pressure. This suppression was distinguished from genetic HLA-loss by its reversibility with drugs. Another very demonstrative case was reported by Rosenberg and colleagues who upon adoptive transfer with TILs recognizing a RAS mutation presented by HLA-C, there was loss of the antigen-presenting allele as an escape in eventually progressing tumor lesions that were resected (Tran et al., 2016).

3.4.2. Interferon-gamma (IFNγ) pathway benefits the activity of ICIs

It is known that after recognition of the tumor antigen, T cells produce interferon gamma (IFNγ, official symbol IFNG, gene ID 3458), which is a soluble cytokine able to act on the receptors (IFNGR1 and IFNGR2) expressed by most tumor cells and, in turn, activating the JAK1 and JAK2 kinases, and the transducers of transcription (STAT) forming STAT1 dimers. This staggered activation resulted in the transcription of a large number of genes beneficial for antitumor effects and increased antigen presentation. Intensely-increased antigen presentation is achieved through inducible proteasomal subunits and also by the major histocompatibility complex class I (MHC-I) molecules themselves. Furthermore, IFNγ triggers chemokines that drive more cytotoxic effector T cells into the malignant tissue microenvironment. In this cascade of interferon-driven reactions, JAK mutations have been correlated with a worse response to immunotherapy (Shin et al., 2017). In fact, other authors reported that these mutations resulted in secondary (acquired) immuno resistance (Zaretsky et al., 2016). Antigenic invisibility as an acquired resistance mechanism to anti-PD1 immunotherapy has also been demonstrated in a case with a new and homozygous truncating mutation in B2M gene (β-2-microglobulin), leading to lack of surface expression of HLA class I (Zaretsky et al., 2016).

As outlined above, the interferon-γ pathway is emerging as a key player to impede or prevent primary, adaptive and acquired resistance to immune checkpoint blockade therapy. A recent study carried out in a Spanish population of patients with lung and melanoma tumors treated with anti-PD1, suggested that those patients with an enhanced expression of IFNγ-related genes present an improved overall survival (Karachaliou et al., 2018). Likewise, genetic analysis of tumors in patients who did not respond to therapy with the anti-CTLA-4 antibody *Ipilimumab* revealed an enriched frequency of mutations in the interferon-γ pathway genes such as IFNγ receptor 1 and 2 (IFNGR1/2), JAK2 and interferon regulatory factor 1 (IRF1) (Gao et al., 2016). IFNγ may additionally promote the expression of immunosuppressive molecules such as indoleamine-2,3-deoxygenase (IDO1). This protein is a tryptophan-metabolizing enzyme that can contribute to peripheral tolerance and can have a direct negative action on effector T cell function as well as PD-L1 itself (Spranger et al., 2013).

3.4.3. Activation of the WNT and β-catenin signalling axis facilitates immune-exclusion

Studies carried out in murine models have revealed that high β-catenin expression is associated with a lower presence of CD103 positive (CD103+) dendritic cells (DCs), decreased expression of the macrophage inflammatory protein 1β (MIP-1β, also called CCL4, MIP1B and LAG1) attracting chemokine and hence causing a worse response to ICIs (Spranger and Gajewski, 2015). Non-T-cell-inflamed human melanoma tumors, which lacked T cells and CD103+ DCs in the TME, had significantly higher expression of tumor intrinsic β-catenin signalling genes. Also, the Gajewski group analyzed activated WNT β-catenin signaling by somatic mutations, copy number alterations, gene expression, and reverse phase protein array showing a pan-cancer association of this signaling pathway with immune-exclusion (Trujillo et al., 2019). Hence, it is described that activation of tumor-intrinsic WNT β-catenin signaling is enriched in non-T-cell-inflamed tumors.

3.4.4. Loss of PTEN prompts immuno-resistance

During the last years different studies have evidenced loss of PTEN (Phosphatase and Tensin homolog gene, that encodes a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase) as one of the most frequently disrupted tumor suppressors in human cancer (Khan et al., 2013). One study in tumors of the Cancer Genome Atlas (TCGA) melanoma dataset correlated loss of PTEN with significantly decreased gene expression of IFNγ, granzyme B, and CD8 + T cell infiltration. Importantly, the frequency of PTEN deletions and mutations was higher in non-T-cell-inflamed tumors as compared to T-cell-inflamed tumors. In a murine model, PTEN-knockout tumors were less susceptible to adoptive cell therapy than PTEN-expressing tumors (Peng et al., 2016). Preclinical studies in melanoma have shown that PTEN loss in tumor cells inhibits T cell trafficking within the tumor, as well as T cell-mediated tumor cell death. Thus, PTEN loss in cancer patients increased

the expression of immunosuppressive cytokines, which resulted in decreased T cell tumor infiltration, and inhibited autophagy, which decreased T cell mediated cell death leading to a reduced efficacy of anti-PD-1 therapy (Peng et al., 2016). Since PTEN loss and PI3K-AKT pathway activation are frequently found in different types of cancer, with a relationship to resistance to T cell-mediated immunotherapy, combinational strategies targeting the PI3K-AKT pathway have proven their promising effects in preclinical models, and may emerge as a rational strategy to increase the efficacy of these treatments (Trujillo et al., 2019).

3.4.5. Other gene signatures associated with resistance

Cancer cell-intrinsic mechanism of primary resistance to immunotherapy was outlined by the expression of a certain set of genes that were found to be enriched in tumors from patients who did not respond to anti-PD-1 therapy (Hugo et al., 2016). This set of genes was termed IPRES, innate anti-PD-1 resistance signature (Hugo et al., 2016). A melanoma study employing single cell RNA sequencing (scRNA-seq) identified a gene activation program of primary resistance to immunotherapy expressed by malignant cells. This gene program was associated with the exclusion of T cells (cold niches *in situ*) and immune evasion, and it has prognostic and predictive value. Inhibition of CDK4 / CDK6 was found to suppress this program in malignant cells, causing senescence, and reducing melanoma tumor growth in mouse models *in vivo* when administered in combination with immunotherapy (Jerby-Arnon et al., 2018). It is also possible that the epistatic result of more than one gene alteration can cause primary resistance. In this regard, primary resistance has been proposed associated with KRAS and STK11 (LKB1) mutations in lung adenocarcinoma (Skoulidis et al., 2018).

3.4.6. Epigenetic changes

Epigenetic programs, which consist of stable changes in DNA methylation and histone modifications, regulate the ability of the transcriptional machinery to access promoter and enhancer regions of the genome and determine many of the properties acquired among memory T cells (Dogra et al., 2016). For this reason, alterations such as those affecting one of the major chromatin regulators, the nucleosome remodelling complex SWI/SNF (Switch/Sucrose Non-Fermentable) (Miao et al., 2018; Pan et al., 2018), represent promising biomarkers of the immune activity that can modulate the response to antiPD-1/PD-L1/CTLA-4 therapies (Topalian et al., 2016). Accordingly, different studies have recently suggested that the epigenetic signature of PD-1+, T cell transcription factor 1 (TCF1)+ and CD8 + T cells in human malignancies is critical for the effectiveness of PD-1 therapy and is associated with the clinical outcome of checkpoint immunotherapy (Jadhav et al., 2019).

Additional studies in this field have shown that alterations affecting NFATC (nuclear factor of activated T cells, NFATC1/2) can induce secondary transcription factors of the NR4A and TOX families (Seo et al., 2019) and prevent PD-1 degradation (Wang et al., 2019), leading to a persistent PD-1 expression in the tumor cell (Khan et al., 2019). Since such alterations would cause the permanent transcriptional and epigenetic induction of antitumor CD8 + T exhausted and dysfunctional phenotype (Khan et al., 2019), targeting these transcriptional factors may appear as a potential strategy to enhance effector function in cancer immunotherapy (Seo et al., 2019). Also related to epigenetics, in human ovarian cancers, the tumor production of T helper 1-type chemokines CXCL9 and CXCL10 is epigenetically repressed. This leads to a reduction in T cell trafficking to the TME. Such repression arises from enhancer of zeste homologue 2 (EZH2)-mediated histone H3 lysine 27 trimethylation (H3K27me3) and DNA methyltransferase 1 (DNMT1)-mediated DNA methylation (Disis, 2011). Other epigenetic alterations discovered in multiple cancers are aberrant DNA methylation (5mC) and hydroxymethylation (5hmC). These dynamic changes of the epigenomic landscape can serve as prognostic and predictive biomarkers of immune checkpoint blockade-sensitive cancers (Xiao et al., 2020).

Finally, epigenetic variations are also markers of the activity of Treg, which also mediate immune tolerance. Interestingly, EZH2 is also key in this process, since it determines the binding of FOXP3 (Forkhead Box P3) in activated Treg, and the consequent FOXP3-driven gene expression program that produces immune tolerance (Peng et al., 2015). Another example is the inhibition of methylation of gasdermin E (GSDME), a protein that can act as tumor suppressor by activating pyroptosis as well as enhances the number and functions of tumor-infiltrating natural-killer and CD8 + T cells in tumor that express it (Zhang et al., 2020). Using genome-wide screening of chromatin methylation, the group of Esteller has reported epigenetic signatures related to overall poor clinical outcomes in response to anti-PD-1 immunotherapy (Duruisseaux et al., 2018).

3.5. Microbiota affecting response to ICIs

The relationship between cancer and microbiota is complex and far from being completely elucidated. In recent years, the study of the intestinal microbiota has revealed a relationship between itself and the response to drugs used in cancer treatment such as chemotherapy with cyclophosphamide (Viaud et al., 2013), treatment with CTLA-4 inhibitors (Vétizou et al., 2015) or PD-L1 inhibitors (Sivan et al., 2015). Thus, studies developed by different researchers, such as the French group of Zitvogel, have recently demonstrated that the presence of the commensal bacterium *Akkermansia muciniphila* in the mouse or patient faeces is associated with the response to drugs that inhibit the PD-1 / PD-L1 axis (Routy et al., 2018). Other studies have shown how there is a specific T cell response against *Bacteroides thetaiotaomicron* or *B. fragilis* that is associated with the efficacy of CTLA-4 inhibitors (Vétizou et al., 2015). Thus, the tumors treated with antibiotic therapy or "free of germs" do not respond to the ICI although this defect is corrected with the transplant of *B. fragilis* or with T-specific adoptive cell therapy for *B. fragilis*. The mechanism of this effect remains unclear, although has been associated to the metabolites produced by different taxa that act on different subsets of non-conventional T cells probably setting an inflammatory tone in the organism (Zitvogel et al., 2016). Two pragmatic consequences of these observations are transplantations of stools (faecal implants) from responding patients in clinical trials to avoid immunotherapy resistance (Bunney et al., 2017), and the correlations that strongly suggest worse immunotherapy outcomes in patients receiving broad spectrum antibiotics for infectious comorbidities prior to immunotherapy onset.

4. How to overcome resistance to immunotherapy, conclusions and future perspectives

Resistance to immunotherapy represents one of the main challenges in medical oncology and is the subject of many preclinical studies and clinical trials focused in patients with primary or acquired resistance to ICI. Provided the limited efficacy of available immunotherapies as "single treatments", most studies recommend the implementation of "combined treatments" targeting several immune and non-immune targets before or once resistance is documented. Combinations appear to attain better signs of activity when given together from the initial treatment, as it is the case with antiangiogenic drugs for renal cell carcinoma (Rini et al., 2019), anti-CTLA-4 for melanoma (Larkin et al., 2015) and chemotherapy for NSCLC (Antonia et al., 2018; Leonetti et al., 2019). Besides, given the complex nature of immunotherapy resistance, with many causative factors, the implementation of one simple approach is not yet possible. Another essential factor in achieving better therapeutic strategies against immunotherapy resistance is the correct identification of all the drug-target associations of ICIs, because it has been shown that many cancer drugs have multiple side targets (Arroyo et al., 2020).

Since the publication of the first studies reporting on the utility of

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas-9 as genome-scale screening tools, multiple preclinical studies have identified a number of genes involved in resistance to immunotherapy and their blockade using CRISPR as promising strategies to enhance the response to these treatments (Manguso et al., 2017; Pan et al., 2018; Patel et al., 2017). Along these lines, we discussed multiple publications that use next-generation technologies as promising tools to expand our current understanding of immunotherapy and also how the complexity of the microenvironment (TME) affects the success of ICI therapies (Binnewies et al., 2018). Importantly, accurate predictive identification of non-responding patients would alleviate untoward toxicity, immense costs, and identify the patients in whom new clinical trials should be focused. Our progress in predicting primary lack of response is yet very limited and almost none in anticipating acquired resistance. In this regard, we are taking a partially new approach by looking into parameters that behave as negative predictors of response rather than positive predictors of response. In any case as elegantly described by Blank et al., prediction of immunotherapy response is a multiparametric task (Blank et al., 2016).

How to clinically address resistance is even more challenging. Identifying the missing link in subgroups of patients might offer opportunity to provide what is missing, but this might be unattainable at the individual patient level. For the time being, a myriad of combination clinical trials are precisely addressing the population of patients whose malignancies progress despite having received checkpoint inhibitors (Chen and Mellman, 2017). Ambitious associated biomarker studies to those trials need to narrow down which combination is adequate for each subset of patients. Besides the role of "cancer immunogram" in predicting responses to ICI (measuring the density and distribution of CD8 T lymphocytes, PD-L1 expression and T cell clonality), a significant progress is expected and certainly urgently needed to better understand and tackle immunotherapy resistance.

In conclusion, immune checkpoint inhibition has proven efficient in melanoma, non-small-cell lung cancer and renal cancer, but in the future, following the results of numerous ongoing clinical trials, a wider range of malignancies could benefit from new immunotherapy protocols and algorithms that consider resistance as a key factor. In this context, following the description of many studies that individually address the analysis of a single biomarker of response to immunotherapy, the future of immunotherapy personalization lies in a multiple biomarkers strategy that will contribute to the advancement of personalized cancer treatment. Along this line, some clinical trials are already being developed that stratify the patients by the penetrance of specific markers (such as PD-L1) and by the individual assessment of the tumor mutational burden (TMB). This individual custom approach will be more sensible to predict potential resistance events. Finally, cheaper gene sequencing and new molecular tools, such as CRISPR, should be incorporated into the identification of biomarkers of response and/or resistance to ICIs within clinical trials, allowing their combination with prognostic clinical factors to achieve a more comprehensive evaluation of each patient.

Compliance with ethical standards

Not applicable.

Acknowledgements

This article is based on the collaborative work of several members of COST Action 17104 STRATAGEM, supported by specific funding from COST (European Cooperation in Science and Technology). The authors wish to thank José Luis Vilar for his help in the design and production of several figures of this manuscript. JDLR also wishes to thank the financial support provided by the Spanish Government through the ISCiii with grant PI18/00591. EPR thanks the support provided by the Consejeria de Salud de Andalucia with grant PI-0135-2018.

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