Review

Immuno-oncology-101: overview of major concepts and translational perspectives

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ARTICLE INFO

ABSTRACT

Cancer immunotherapy is demonstrating impressive clinical benefit in different malignancies and clinical oncologists are increasingly turning their attention to immune-oncology. It is now well recognized that innate and adaptive immune cells infiltrating tumors are associated with clinical outcomes and responses to treatments, and can be harnessed to patients' benefit. Considerable advances have also been made in understanding how cancers escape from immune attack. Targeting of immunological escape processes regulated by the expression of immune checkpoint receptors and ligands and the down-modulation of tumor antigen presentation is the basis of immuno-oncology treatments. Despite recent achievements, there remain a number of unresolved issues in order to successfully implement cancer immunotherapy in many cancers. Importantly, clinical biomarkers are still needed for better optimization of emerging combination immunotherapies and better treatment tailoring. In this review, we summarize the function of innate and adaptive immune cells in anti-tumor immunity and the general mechanisms exploited by tumor cells to escape and inhibit immune responses as well as therapeutic strategies developed to overcome these mechanisms and discuss emerging biomarkers in immuno-oncology.

1. Introduction

Cancer pathogenesis has been traditionally viewed as a multistep process through which normal cells progressively acquire the capacity to transform. Acquisition of these essential traits, so-called "hallmarks of cancer" [1], are the result of genetic mutations and epigenetic alterations. The cell-centric (or cell-autonomous) view of cancer recently evolved to integrate the complex interactions between transforming cells and their surrounding environment, including immune cells. Accordingly, the ability of cancer cells to actively evade the immune system, along with the tumor-promoting effects associated with a chronic inflammatory state are each respectively recognized as a new hallmark and an enabling characteristic of cancer [2].

The recognition of the immune system's role in the anti-tumor response accommodates the concept of "cancer immunosurveillance", which postulates that nascent tumor cells are eliminated by the immune system until malignant cells escape detection or actively suppress immune responses [3]. Potent suppression of anti-tumor immunity is even now considered a critical mechanism by which primary tumors can arise, grow and eventually disseminate to distant organs. Paradoxically, in many cancers, malignant cells are detectable by the immune system [4]. Accumulation of mutations, chromosomal rearrangements and abnormal protein synthesis are common features of cancer cells that can generate "neoantigens" and thus favor tumor cell recognition by the immune system [5]. In addition, chronic cellular stress caused by DNA damage/instability, unfolded protein response and aberrant metabolism can induce the production of danger signals that activate innate immune cells and prime adaptive immune responses. Tumor cell death occurring in the tumor microenvironment (TME), for example following exposure to cytotoxic agents or irradiation, can further release tumor antigens and pro-inflammatory mediators creating an immunogenic milieu promoting the initiation of an anti-tumor immune response [6].

Tumor-immune infiltrates reflect this immune response and is referred to as the "immune contexture" which is defined as the density, composition, organization and functional state of tumor-infiltrating immune cells [7]. The "immune contexture" can either suppress or promote tumorigenesis and has been demonstrated to be relevant to predict outcome and response to treatment [7].

Tumors use multiple immune regulatory mechanisms to inhibit antitumor immune responses. These include overexpression of inhibitory receptors, also known as "immune checkpoints", recruitment of professional immunosuppressive cells such as T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSC) [8], production of immunosuppressive mediators by tumor cells and stromal cells [9], increased fibrogenesis [10], aberrant endothelium function [11], alterations in tumor antigen presentation and resistance to immune effector pathways [12]. Therapeutic manipulation of these regulatory mechanisms can significantly enhance anti-tumor immune responses and prolong survival of cancer patients. A striking example is the use of monoclonal antibodies (mAbs) targeting immune checkpoints, which represents one of the greatest advances in medical oncology in recent years [13].

In this review, we summarize the function of innate and adaptive immune cells in anti-tumor immunity as well as the general mechanisms exploited by tumor cells to escape and inhibit immune responses. We will present an overview of the major immune therapeutic strategies currently under clinical development, and discuss the roles of some biomarkers and environmental factors, such as the gut microbiome, on tumor immunity and clinical responses to immunotherapy.

2. Anti-tumor immunity

2.1. Innate immune response

The innate immune response is generally characterized by a rapid inflammatory response (within minutes), that is unspecific and will not lead to memory formation. As such, it precedes and prepares the activation of the adaptive immune system. Innate immune cells orchestrate inflammatory responses by sensing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) that are exposed following loss of tissue integrity, infection and cancer [14]. Innate immune cells include tissue resident and inflammatory macrophages, granulocytes, dendritic cells (DCs), myeloid derived suppressor cells (MDSC), natural killer (NK) cells and other innate lymphoid cells (ILC) (Fig. 1). Depending on the tumor type and organ they can be very abundant in the TME and are often correlated with patient outcomes [15–18]. Innate immune cells sustain or suppress anti-tumor immunity through multiple mechanisms (Fig. 1).

MDSC, for instance, are a heterogeneous group of immature cells that encompass both monocytic and polynuclear precursors [8]. They mediate immunosuppression via the production of arginase (ARG)-1, inducible nitric oxide synthase (iNOS), transforming-growth factor (TGF)-β, interleukin (IL)-10, cyclooxygenase 2 (COX2) and indoleamine 2,3-dioxygenase (IDO) [8,19]. Tumor associated macrophages (TAM) are attracted by the C-C Motif Chemokine Ligand 2 (CCL2), produced by tumor cells, into the TME. Interestingly, TAM exert a dual yin-yang influence on the anti-tumor response depending on their activation status [20,21]. M1-like macrophages are generally anti-tumoral TAM that can directly kill tumor cells and enhance T cell and NK cell killing via the production of IL-12 [22,23]. In contrast, M2-like macrophages are generally pro-tumoral TAM that induce angiogenesis, tumor invasion and decrease T cell activity through production of several mediators such as vascular endothelial growth factor (VEGF), IDO, TGF-β, and matrix metalloproteinases. Notably, it should be pointed that M1/M2 classification represents two extremes of a continuum of stimulus-dependent polarization states of macrophages [24].

The main function of DCs is antigen presentation, typically in the context of major histocompatibility complex (MHC)-I or II molecules.

However, in the TME, accumulation of immature DCs with poor antigen presentation and co-stimulatory capacities can induce tolerance and anergy of T cells. Maturation of DCs occurs through activation via DAMPs or PAMPs that are recognized by pattern recognition receptors (PRRs), leading to upregulation of CD80/86 and other receptors that can deliver costimulatory signals for T cells [25]. NK cells have direct cytolytic activity towards cancer cells and additionally secrete Th1 cytokines such as IL-12 and IFN-γ [26]. Interestingly activation of NK cells occurs upon recognition of stress signals by activating receptors such as NKG2D and typically in the absence of MHC-I expression, thereby emphasizing that the innate immune response is not antigen specific, in contrast to the adaptive immune response. NK cells play a major role in murine tumor models, however their role in human malignancies is less clear.

The role of mature granulocytes in tumor immunity is less well-defined. Similarly to macrophages, anti- or pro-tumoral effects of granulocytes have been reported and are likely dependent on activation status shaped by the local microenvironment. Neutrophils are the most abundant granulocytes and are found in many solid tumors. Tumor-associated neutrophils (TANs) are highly heterogeneous, similar to TAMs. Based on their anti- or pro-tumorigenic properties, they are also classified as N1 or N2, respectively. N1 neutrophils secrete the cytokines IL-1β, IL-6, IL-12 and tumor necrosis factor (TNF)-α, as well as reactive oxygen species to control tumor growth. Upon tumor progression, neutrophils acquire a more tumor supportive N2 phenotype [27], characterized by production of immunosuppressive ARG-1 [28]. Eosinophils are another type of granulocyte that can either secrete anti-tumor mediators such as cationic proteins, TNF-α and chemokines, or pro-tumorigenic factors such as IL-10 and prostaglandins [29]. Granulocytic mast cells have also been shown to be associated with cancer outcomes [15]. Notably, the presence of activated mast cells has been shown to be significantly associated with poor prognosis [15]. This likely reflects the immunomodulatory and pro-angiogenic effects of mast cells mediated by production of vascular endothelial growth factors (VEGF) and matrix metalloproteinases (MMPs) [30]. The pro-tumorigenic functions of mast cells have been documented in genetically-engineered mouse models of cancer nearly two decades ago [31].

2.2. Adaptive immune response

2.2.1. Cellular immune response

Adaptive immune cells are composed of T and B lymphocytes that become activated in response to specific antigens. In the case of T cells, antigens must first be presented by professional antigen presenting cells (APC) on MHC class I (for CD8+ T cells) or class II (for CD4+ T cells) molecules, together with co-stimulatory signals, in order to generate effector cells. Lymphocytes observed in tumor lesions are called "tumor-infiltrating lymphocytes" (TIL) and are generally associated with a better prognosis in solid tumors [7]. Integration of TIL scoring as a prognostic factor has been proposed in several solid malignancies including breast [32] and colon cancers [33,34]. In the TME, distinct subpopulations of TILs that differ in their functions and mechanisms of action have been identified. CD8+ T cells are generally *cytotoxic T cells* able to directly kill tumor cells and their presence in tumors has been associated with improved cancer survival for various cancers. CD4+ T cells are generally *helper T* cells whose functions are mediated by the production of cytokines. In response to different cytokines, naïve CD4+ T cells differentiate through transcriptional activation and epigenetic modification of cytokine genes into different subsets including Th1, Th2, Th17 and follicular helper T cells (Tfh) etc [35]. Each subset has specialized functions that can be classified as anti- or pro-tumoral according to the cytokine secretion profile (Fig. 1). A specialized subset of CD4+ T cells, called Tregs, are critical to inhibit immune response and to maintain self-tolerance. Tregs in tumors can be associated with a good or bad prognosis, as their presence reflects either active or suppressed anti-tumor immunity [36] (Fig. 1).

Innate Immune System

Adaptive Immune System

anti-tumoral   pro-tumoral   anti-tumoral   pro-tumoral
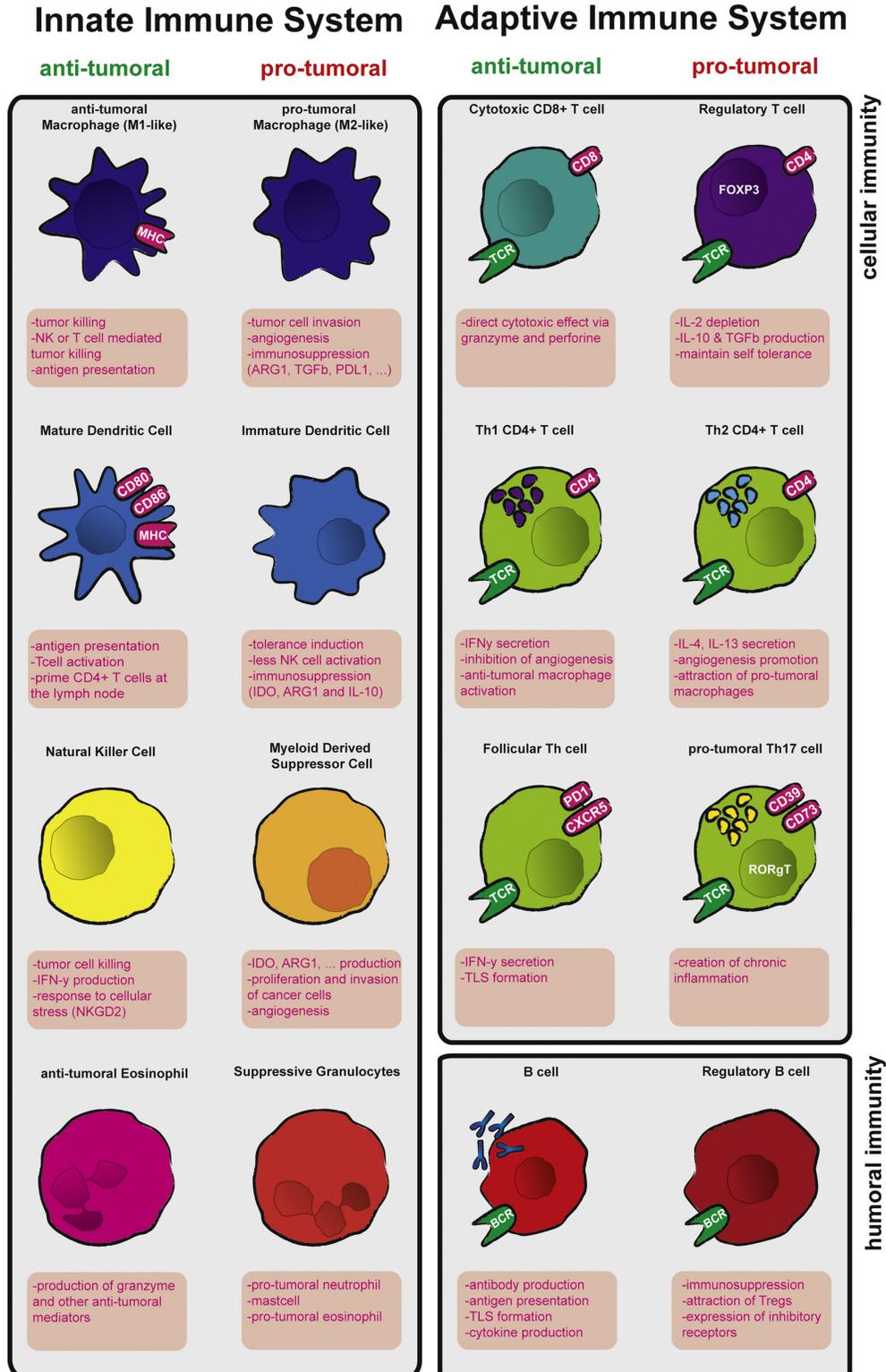
Fig. 1. Overview of different immune cell subsets from both innate and adaptive immune system with their pro- or anti-tumoral contribution to the tumor immune response. Abbreviations: ARG: arginase; IDO: indoleamine 2,3-dioxygenase; IL-2: interleukin-2; IL-4: interleukin-4; IL-10: interleukin-10; IL-13: interleukin-13; IFN-: interferon-gamma; NK: natural killer; PDL1: programmed death ligand 1; TGFb: tumor growth factor beta; TLS: tertiary lymphoid structure; Treg: regulatory T cell

In tumors, TILs recognize and are activated by specific antigens expressed by tumors. These antigens are either highly specific to tumors (such as mutated neoantigens or viral antigens), or unspecific to tumors (such as overexpressed or differentiation antigens)[5]. Several studies have recently provided evidence for the immunogenicity of mutation-derived neoantigens. The quantity and quality of these neoantigens were demonstrated to influence patient anti-tumor immune response and survival [37–40] Tumor-reactive T cells can also recognize non-mutated antigens, including from non-intronic (i.e. non-protein coding) regions [41] or non-mutated proteins (self-antigens) that are shared between cancers to which T cell tolerance is incomplete [42].

Activation of T cells requires engagement of the TCR (T cell receptor) and CD28 (a co-stimulatory receptor) on MHC and B7 molecules, respectively, expressed by antigen-presenting cells. If there is no co-stimulation or if there is a co-inhibitory signal (instead of the co-stimulatory one), immune cells become anergic or die by apoptosis [14]. Receptors delivering co-inhibitory signals function as an "immune checkpoint" and their role is to maintain peripheral tolerance and to prevent auto-immunity [43]. In cancers, co-inhibitory signals impede the anti-tumor immune response both at the level of activation of immune effectors by antigen presenting cells and in the phase of immune recognition of tumor cells by immune effectors (explained in the next paragraph).In the TME, co-inhibitory receptors are upregulated on "exhausted" T cells due to chronic antigen stimulation and sustained exposure to pro-inflammatory cytokines [44]. The function of T cells in tumors can also be impaired by a continuous competition for nutrients between immune cells and tumor cells. This metabolic competition is mainly caused by limited availability of amino acids, glucose, fatty acids and oxygen in the TME which alters the function of intratumoral T lymphocytes [45].

2.2.2. Humoral immune response

Humoral anti-tumor immune responses are characterized by the presence of specific serum antibodies directed against overexpressed or mutated antigens, tumor reactive lymph node B cells and tumor-infiltrating B cells [46]. Several studies have reported associations between tumor-specific autoantibody responses against tumor associated antigen (TAA) and prognosis. Anti-MUC1 antibodies, for instance, have been associated with favorable prognosis in ovarian, gastric, lung, pancreatic, and breast cancers, while anti-p53 and anti-NY-ESO-1 antibodies have been associated with poor disease outcome in prostate, ovarian, breast, colorectal, and lung cancers, respectively [47]. These antibodies are produced by antibody-secreting plasma cells arising from specific B cell activation after the recognition of antigens. Tumor-infiltrating B cells (TIL-B) have been observed in many different solid tumors and were mainly associated with improved survival in human cancer [48]. TIL-B are mainly located in the peripheral stroma of the invasive tumor and are found in dense conglomerates of immune cells named tertiary lymphoid structures (TLS) [49]. Notably, the presence of B cells within TLS correlates with CD8$^+$ TIL infiltration [50]. These observations suggest that the role of B cells in anti-tumor immunity extends beyond antibody production and includes T cell help (cytokine production, antigen presentation, co-stimulation) and participation in TLS formation. Interestingly, B cells are also APC and interact with T cells by presenting internalized antigens, through MHC-II molecules. This APC function has been outlined in high-grade serous ovarian tumors where TIL-B expressing antigen-presenting cell markers were co-localized with CD8$^+$ T cells [51] and was recently demonstrated in non-small cell lung cancer (NSCLC) patients using an in-vitro antigen-presentation assay [52].

Despite these favorable roles associated with effective immune responses, some B cell subpopulations have been involved in the attenuation/blunting of the immune response. Regulatory B cells (Bregs) suppress cellular immune response and have been observed in several solid cancers [53–57]. Exhausted B cells are characterized by low expression of cell surface markers such as CD21 and CD27 and high expression of inhibitory receptors. Similarly to T cells, they are generated by chronic antigen exposure and inflammation and were recently described in NSCLC [52].

2.3. Immune response to metastases – the metastatic immune-oncological microenvironment

The immune contexture has been less widely studied in metastases compared to primary solid tumors. However, recent data showed that immune infiltration within metastases is also correlated with clinical outcome and response to therapy in several malignancies including melanoma, breast and colorectal cancers [58–62]. Of interest, distinct immune tumor microenvironments between primary tumor and metastases, have recently been associated with heterogeneous clinical behaviors within the same patient [63]. Several studies have specifically evaluated the pattern of TILs within metastases and revealed lower immune infiltration levels compared to primary tumors as well as heterogeneity in TIL density and composition across different organ metastatic sites [59,64] and according to the tumor origin [65]. For example, in a report from Turcotte et al., a lower TIL density was observed in visceral metastases from gastrointestinal cancers compared to melanoma [65]. Another group reported highest TIL levels in brain metastases from melanoma, followed by renal cell and lung cancers [66]. The primary tumor is an important determinant of the immunogenicity of metastatic disease and thus of TIL levels in secondary lesions. TIL isolated from melanoma metastases were demonstrated able to recognize and kill tumor cells [67]. Even if in lower abundance tumor-reactive TIL were also found in metastases from other solid tumors [68].

Innate immune cells have also been detected in metastatic lesions and have been demonstrated to have a pivotal role in the metastatic process. In lung metastases, phagocytic CD11b+ myeloid cells accumulated in the lung interstitium close to metastatic cells, with a pro-tumor effect in mouse models. In contrast, resident conventional DCs conferred an anti-metastatic protection, acting in competition with pro-tumor macrophages [69]. Brain metastases from renal cell carcinoma (RCC) seem to express more CCL2, which plays a major role in attracting TAM in the tumor microenvironment [70] and additionally it was shown that microglia, brain tissue resident macrophages, helps tumor cells to invade the brain [71].

3. Tumor immune escape mechanisms and overcoming therapeutic strategies

3.1. Immune evasion and induction of immune suppression in the TME

Despite both innate and adaptive immunity being able to induce anti-tumor responses in cancers, most progressing tumors successfully manage to escape cancer immunosurveillance and destruction by the immune system [3]. This immune escape results from tumors co-opting and exacerbating a variety of physiological feedback mechanisms that control self-tolerance, resolve inflammation and promote wound-healing and tissue repair. Interestingly, many of these subversion mechanisms are induced upon tumor cells being attacked by the immune system and evolve over time, shaped by the selective pressure of anti-tumor immunity. Moreover, many of these mechanisms are non-redundant and operate specifically or simultaneously at multiple levels of the anti-tumor immune response. In the following section, we review the different immunosuppressive mechanisms implemented by tumors to dampen anti-tumor immunity and classify them according to which step of the anti-tumor immunity cycle they interfere with (Fig. 2).

3.1.1. Tumor-cell-intrinsic inhibition of tumor antigenicity and immunogenicity

The ability of the immune system to discriminate healthy cells from malignant ones relies, at least in part, on tumor cell antigenicity; in
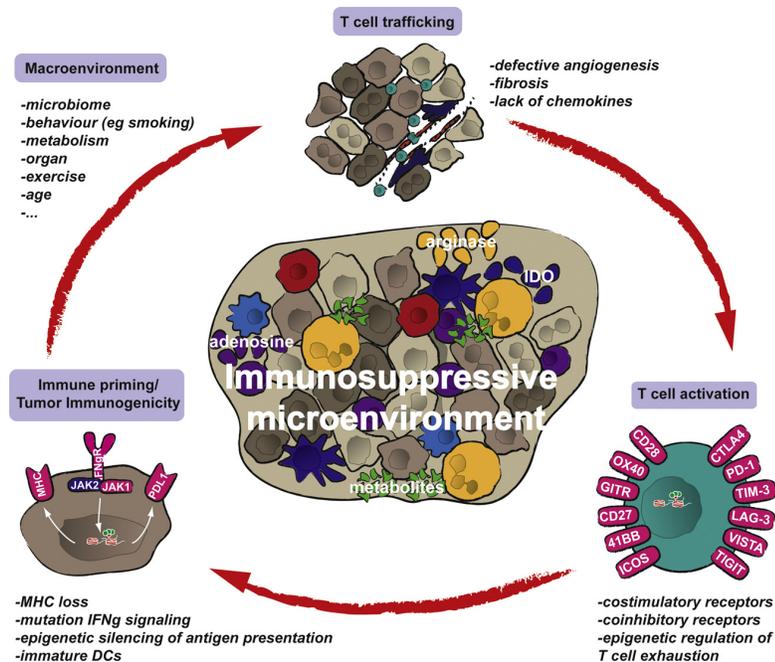
Fig. 2. Schematic overview of different steps required for cancer cell immune recognition.

Cancer cells present their (neo)antigens on class I MHC molecules whose expression is influenced by intracellular IFN-signaling (JAK1 and 2 dependent). Cancer (neo)antigens can also be presented by professional antigen presenting cells such as dendritic cells. Upon antigen recognition (via the TCR) T cells are activated and incited to traffic intra-tumorally to exert their activity against tumor cells. Many mechanisms as defective angiogenesis and lack of chemokine attraction prevent immune cells to enter the tumor microenvironment (TME). T cell activation is regulated by inhibitory (PD1, CTLA4, …) and stimulatory (CD28, OX40, …) immune checkpoints receptors. Several mediators in TME produced by tumor, stromal cells and immune cells exhibit regulatory and immunosuppressive functions.

Abbreviations: CTLA-4: cytotoxic T lymphocytes associated protein 4; DCs: dendritic cell; GITR: glucocorticoid induced tumor necrosis factor receptor; ICOS: inducible T cell costimulatory; IDO: indoleamine 2,3-dioxygenase; IFNR: interferon gamma receptor; JAK: Janus kinase; LAG-3: lymphocyte-activation gene 3; PD-1: programmed death −1; TIM-3: T cell immunoglobulin mucin-3; TME: tumor microenvironment.

other words, the capacity of the tumor cells to express and present antigens at their cell surface in the form of MHC-peptide complexes that are recognized by specific T cells. However, many tumors evolve towards reduced antigenicity, thus avoiding recognition and destruction by the immune system [72]. One of the main mechanism used to decrease tumor antigenicity involves the reduction of antigen presentation at the cell surface by MHC class I. Downregulated expression of MHC-I has been observed in 20–60% of patients bearing melanoma, lung, breast and prostate cancers [72]. MHC-I expression has also been found to be an independent prognostic marker in several types of cancers [61,73,74]. High expression of MHC-I is generally associated with a better response to immunotherapy and chemotherapy [75]. Importantly, loss of tumor antigen presentation on MHC-I has been reported as a resistance mechanism of immune checkpoint blockade immunotherapy [12]. Alterations of other components of the antigen presentation machinery, including beta-2 microglobulin or transporter for antigen presentation (TAP) deletion, have also been documented as means to reduce tumor antigenicity [76].

Reduced tumor immunogenicity is often a dynamic and inducible process occurring in response to tumor cell attack by the immune system. This process can interfere with multiple steps of the anti-tumor immune response and is shaped by the phenotype of the surrounding microenvironment [76,77]. One of the main cytokines regulating tumor cell immunogenicity is IFN-γ. While IFN-γ secretion by activated effector T cells favors anti-tumor immunity by (i) enhancing antigen presentation on tumor cells, (ii) increasing recruitment of other immune cells and (iii) inducing tumor cell-growth arrest and apoptosis, chronic exposure to this cytokine can lead to immune escape and resistance to immunotherapy [78,79]. Recent reports investigating resistance mechanisms to immune-checkpoint blockade have identified mutations in several components of the IFN-γ signaling pathway, including IFN-γ receptor as well as janus kinases (JAK1/2) and IFN regulatory factor-1 (IRF-1) proteins, as a major mechanism of primary, adaptive and acquired resistance to cancer immunotherapy [12,80–82]. Interestingly, multiple other tumor-intrinsic mechanisms which reduce tumor immunogenicity have been recently discovered [76]. This includes oncogenic signaling through the mitogen MAPK pathway [83,84], PI3 K pathway (due to PTEN loss) [85] and the WNT pathway

(due to β catenin stabilization) [86].

3.1.2. Suppression of innate immunity and DC activation

Activation of innate immune cells as well as professional APC is a critical step in the induction of an adaptive immune response. In the TME, specific immunosuppressive mechanisms are implemented to interfere with these pivotal initiation steps of the anti-tumor immune response. For instance, increased β catenin expression in melanoma has been associated with a reduced infiltration of CD103⁺ DCs in a CCL4-dependent manner eventually leading to poor response to cancer immunotherapy [86]. Furthermore, secretion of immunosuppressive mediators by tumors cells such as TGF-β, PGE2, VEGF or CD73-derived adenosine can skew DCs or other APCs like macrophages to a tolerogenic phenotype, which is characterized by a poor capacity to cross-present tumor antigens to T cells and by the expression of tolerogenic molecules like PD-1, T cell immunoglobulin mucin-3 (TIM-3), IDO, ARG-1 and IL-10. Defective DC activation in the TME also impairs IL-12 and IL-15-mediated NK cells cytotoxicity.

3.1.3. Suppression of T cell priming in draining lymph nodes

Activated DCs that captured tumor-derived antigens can then migrate to the closest tumor-draining lymph node (TdLN) to prime helper CD4⁺ T cells and initiate an adaptive anti-tumor immune response. However, emerging evidence demonstrates that TdLN undergo profound alterations due to the presence of the upstream tumor ultimately leading to defective local T cell priming and reduced systemic anti-tumor immunity [87]. In fact, tumor secreted factors such as TGF-β, COX-2-derived metabolites or even tumor-derived exosomes have been shown to drive the accumulation of immunosuppressive cells in TdLN including Bregs, Tregs and tolerogenic DCs. Moreover, TdLN are also subjected to a structural remodeling orchestrated by the primary tumor that involves lymphatic endothelial cells (LECs) and follicular reticular cells (FRCs) reprogramming towards an immunosuppressive phenotype [88]. For instance, in TdLN, LECs have been shown to overexpress PD-L1 and to acquire the ability to cross-present tumor-derived antigens via MHC-II thereby impairing tumor-specific T cell activation [89,90]. In parallel to this process, FRCs in TdLN display reduced expression of key chemokines like IL-7 and CCL21 which perturbs immune cell

composition and localization ultimately leading to impaired anti-tumor immunity [91].

3.1.4. Interference with T cell homing and trafficking into tumors

Recent reports investigating the localization of TILs in various human tumors, have demonstrated different patterns of CD8$^+$ T cell infiltration in cancers. Indeed, in some tumors, CD8$^+$ T cells can be evenly distributed in the tumor tissue while in some others, T cells are selectively excluded from certain areas, restrained to the tumor margins or simply absent [92,93]. Interestingly, those different localization patterns have also been associated with specific gene expression signatures indicating that, in some types of cancers, mechanisms to restrain or prevent T homing or trafficking into tumors are used as a strategy to dampen anti-tumor immunity [86,94]. Moreover, further supporting the critical role of CD8$^+$ T cell distribution in tumors for anti-tumor immunity, T cell localization patterns have been associated with patient's outcome and clinical response to immunotherapy in several types of cancers [86,94]. Several molecular mechanisms involving modifications of the tumor associated vasculature to prevent T cells homing to tumors have been described. These include upregulation of RGS-5 by tumor cells [95] or endothelin-B receptors [96] and Fas-ligand by vascular endothelial cells [97]. Interestingly, a more global crosstalk between T cells and tumor-associated vasculature has recently been established showing a mutual positive regulation of tumor vessel normalization with Th1 T cell infiltration and activation [98]. Another important pathway limiting T cell motility and trafficking into tumors involve the activation of a desmoplastic response by cancer associated fibroblasts (CAFs). This reaction, characterized by CAF proliferation, dense collagen deposition and extracellular matrix stiffness, severely limits T cell motility by confining them to the tumor stroma or to the tumor periphery thereby protecting tumor cells from immune-mediated destruction [99,100].

3.1.5. Suppression of effector T cell activation

Once localized in the tumor microenvironment, in close vicinity to tumor cells, effector T cells can receive their final activation signal and mediate their tumoricidal functions. However, a large variety of soluble or membrane-bound immunosuppressive factors present in the TME can impair this last step and protect tumor cells from destruction. Upregulation of immune checkpoint molecules on various cell types present in the TME is now recognized as major mechanism to suppress anti-tumor immunity [101]. Upon activation, T cells upregulate co-inhibitory checkpoint receptors like CTLA-4 or PD-1 as a natural physiological feedback mechanism, originally designed to prevent autoimmunity. In the TME, the tumor exploits this physiological feedback loop to suppress T cell activation. Similarly, effector T cell responses such as IFN-γ production, can induce potent physiological counter-regulatory mechanisms to block T cell activation, including PD-L1 or IDO upregulation in tumor cells, DCs or macrophages [76,77]. Furthermore, chronic T cell stimulation by tumor-derived antigens further amplifies these feedback immunosuppressive mechanisms to finally induce T cell exhaustion, a phenotype characterized by reduced anti-tumor functions and by the expression of multiple other checkpoint molecules such as TIM-3, LAG-3, TIGIT, BTLA or VISTA [101].

Apart from checkpoint-mediated T cell inhibition, various soluble factors enriched in the TME also have the ability to potently suppress T cell anti-tumor functions. The most important factors include TGF-β, IL-10, CD73-derived adenosine, VEGF and prostaglandins [76,77,102]. These soluble factors usually mediate multiple immunosuppressive functions, acting on various immune and non-immune cell subsets to coordinately prevent T cell activation at different levels. These soluble factors, together with several other chemokines, can also recruit immunosuppressive cell subsets to the TME or even convert naïve or anti-tumor infiltrating cells into tolerizing ones. For instance, TGF-β and CD73-derived adenosine have been shown to promote the conversion of naïve CD4$^+$ T cells into Tregs and to favor the differentiation of TAMs

into anti-inflammatory M2-like macrophages [103,104]. Chemokines such as CCL2, CCL5 or CXCL12 have been implicated in MDSC and Tregs recruitment into tumors [105].

Aberrant cellular metabolism constitutes one of the hallmarks of cancer. In the TME, energy demand is high and competition for energetic resources between the different cell subtypes is fierce. In a recent report, it was shown that tumor-imposed glucose restriction is a potent mechanism that dampens effector T cell anti-tumor functions [106]. Moreover, byproducts of intensive glucose consumption by tumor cells such as lactic acid can damage effector T cells and block their activation. Likewise, competition for other metabolites essential for T cell functions has been described in the TME. This is the case for tryptophan, an amino acid essential for effector T cell proliferation. In the TME, tryptophan degrading enzymes like IDO or TDO can be upregulated upon IFN-γ secretion and deplete extracellular tryptophan [107]. This process has been shown to severely inhibit T cell activation and to generate toxic byproducts triggering T cell apoptosis and promoting Tregs generation.

3.2. Therapeutic strategies to overcome tumor immune escape

The improved understanding of cancer cells' ability to exploit immune mechanisms and to evade immune surveillance has led to the development of therapeutic strategies to induce or enhance anti-tumor immunity. Treatments targeting various steps of the anti-tumor immune response are under development in ongoing clinical trials (Fig. 2) [108]. Given the large number of new immunomodulatory agents under development [109], this review is not exhaustive but discusses the main therapeutic strategies currently being developed to overcome immune evasion and potential biomarkers of response.

3.2.1. Immune checkpoint blockade

The use of mAbs targeting immune checkpoints to enhance the functions of effector T cells has been shown to be one of the most promising approaches to date. The goal of these treatments is to harness and enhance the immune system by disrupting negative immune regulation. Immune checkpoint blockade (ICB) with anti-PD-1 and anti-CTLA-4 mAbs represents one of the most encouraging advances in oncology in recent years and has demonstrated impressive antitumor activity and durable clinical benefit in diverse advanced malignancies [13,110–112]. Based on these encouraging results, multiple PD-1 or PD-L1 inhibitors have entered into clinical development, and some have been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for several indications such as melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma (UC), head and neck cancer, Hodgkin's lymphoma and are under investigation in other tumor types [113,114]. Melanoma was the first cancer indicated for ICB with ipilimumab (anti-CTLA-4), approved in 2011 [112]. Later both pembrolizumab and nivolumab, two antibodies targeting PD-1, were also demonstrated to improve survival in metastatic melanoma [115,116]. PD-1 blockade was even demonstrated to be more effective than ipilimumab in advanced and resected melanoma [117,118]. PD-1 blockade also demonstrated remarkable benefit in NSCLC. Two anti-PD-1 antibodies (pembrolizumab and nivolumab) and more recently two anti-PD-L1 antibody (atezolizumab and durvalumab) have been approved for therapeutic use in NSCLC [119–124]. ICB mAbs are well tolerated and associated with fewer side-effects when compared to chemotherapy; however, they are associated with substantial inflammatory effects that can resemble autoimmune diseases [125].

3.2.2. Synergistic combinations with immune checkpoint blockade

Targeting multiple immune checkpoints could enhance immune response [126]. Several combinations of mAbs targeting multiple non-redundant inhibitory receptors such as PD-1, CTLA-4 and LAG-3 or with co-stimulatory receptors as OX40, 4-1BB and GITR, are under clinical evaluation. In human melanoma, the combination of nivolumab and

ipilumumab has already shown a higher response rate for patients with untreated advanced melanoma; however, side-effects were substantially increased compared to monotherapies [127]. This combination was approved by the FDA in 2015.

Another conceptually promising strategy is to combine ICB immunotherapy with conventional cancer treatments such as chemotherapy and radiotherapy. Although it is often argued that chemotherapy has immunosuppressive effects, several chemotherapeutic agents have been demonstrated to promote immune responses by releasing tumor antigens, inducing the so-called immunogenic cell death (ICD) and also by decreasing the number of immunosuppressive cells [128,129]. ICD relies on three components: i) translocation of calreticulin to the cell-surface, ii) release of the Toll-like receptor (TLR) agonist HMGB1, and iii) release of ATP into the extracellular milieu. Consequently, ICD promotes DC activation, presentation of tumor-associated antigens and production of inflammatory cytokines [130]. This process increases the immunogenicity of cancers and primes the immune system by stimulating innate immune effectors and inducing cytotoxic T cell responses [131]. Radiation therapy has also been demonstrated to enhance immune responses by promoting ICD, DC activation, antigen cross presentation, activation and proliferation of cytotoxic $CD8^+$ T cells [132]. Numerous clinical trials in different malignancies are currently evaluating the combination of chemotherapy and/or radiotherapy with ICB agents.

3.2.3. Targeting the tumor microenvironment

Targeting the immunosuppressive TME is another strategy to potentiate the immunostimulatory activity of ICB. Multiple therapeutic strategies to eliminate or reprogram immunosuppressive cells are under active pre-clinical and clinical development. One of these strategies is to target the CD73 pathway to relieve adenosine-mediated immunosuppression. In pre-clinical models, the potential of these agents was enhanced when combined with other immunomodulatory treatments [133–135]. Phase I trials with anti-CD73 compounds or antagonists of the adenosine A2A receptor ($+/-$ ICB) in advanced solid tumors are ongoing (NCT02503774; NCT02403193; NCT02655822).

Another immunometabolic pathway that can be disrupted to counteract the immunosuppressive phenotype of immune cells is the production of tryptophan by IDO. Multiple IDO inhibitors are emerging and have already demonstrated promising activity in melanoma, squamous cell carcinoma of the head and neck in combination with PD-1 checkpoint inhibitors and also in other solid tumors [136]. Other strategies under development to counteract immunosuppression in the TME are to inhibit chemoattractive signals (IL-8, CCR2, CCR5, CSF-1) to decrease the number of immunosuppressive cells or to reverse their immunosuppressive phenotype by targeting keys signaling pathways (PI3Kγ) [137]. Ipilimumab, the CTLA-4 inhibitor is also known to act by depleting Tregs that constitutively expressed CTLA-4 [138].

As specified, defective tumor vessels impair the trafficking of immune cells into the tumor compartment. Interestingly, anti-VEGF and anti-angiopoietin antibodies can facilitate cytotoxic T cell infiltration in the TME by normalizing tumor vasculature and as such synergize with ICB [139,140]. The combination of anti-angiogenics with ICB is currently ongoing in different clinical trials (NCT02921269, NCT02856425). Encouraging results from this approach have been observed in RCC where bevacizumab was demonstrated effective to increase intratumoral $CD8^+$ T cell infiltration [141,142].

3.2.4. Immune cell priming and targeting innate cells

Before entering the TME, immune cells are activated by antigen presented by APC in draining lymph nodes. Modulating the innate response to enhance the antigen presentation of APC was one of the first strategies developed after the discovery of tumor associated antigens. Several vaccines against well-known tumor antigens have been developed. Vaccines have demonstrated limited success, largely attributed to the immunosuppressive TME. The combination of vaccines with

therapies targeting checkpoint molecules and the development of vaccines against specific tumor antigens, for instance neoantigens, to selectively enhance T cell reactivity could improve vaccination efficacy and clinical benefit [143]. Tumor-specific mutated proteins, aberrantly expressed normal proteins, cell lineage proteins, viral antigens as well as non-coding sequences can all serve to prime immune cells for better tumor control [5]. Other ways to activate endogenous APC are using modalities that promote ICD such as chemotherapy or radiotherapy.

3.2.5. Epigenetic modulation of the immune response

Multiple mechanisms of tumor immune escape including silencing of the MHC genes [144], production of immunosuppressive cytokines [145] and immune checkpoint receptor expression such as PD-L1 [146] are regulated by epigenetic processes. Pre-clinical studies have demonstrated that inhibitors of histone deacetylases (HDACi) or DNA methyltransferases (DNMTi) reversed these epigenetic modifications and could enhance anti-tumor immune responses in different cancer models [146,147]. It has also been demonstrated that DNA-demethylating agents upregulate immune signaling in cancer by inducing an IFN response through activation of endogenous retroviruses [147,148]. Moreover, epigenetic alterations were implicated as mechanisms involved in resistance to immunotherapy [146,149]. Combination of epigenetic therapy (HDACi or DNMTi) with ICB might therefore be synergistic [150,151] and this approach is under evaluation in several clinical trials. A randomized phase II study currently assesses the effect of the combination of azacitidine, a DNA-demethylating agent and nivolumab in subjects with recurrent metastatic NSCLC (NCT01928576). Another phase II study investigates the impact of azacitidine in combination with durvalumab in patients with microsatellite stable (MSS) colorectal carcinoma, platinum resistant epithelial ovarian cancer, and estrogen receptor positive and HER2-negative breast cancer NCT02811497).

3.2.6. Biomarkers of I-O responses and the emerging role for the gut microbiome

The immunity of a cancer patient is influenced by a complex set of tumor, host and environmental factors that govern the threshold, the strength and timing of anticancer immune responses [152,153]. Patient response to ICB has been highly variable with some patients experiencing exceptionally long-lasting responses and others having only short, partial responses, or disease stabilization, with a large proportion of non-responding patients.

PD-L1 expression in tumors, or in the TME, evaluated by immunohistochemistry has shown some predictive value in PD-1 blockade trials but its use as a biomarker is still controversial, as responses have also been observed in 5–20% of PD-L1 negative cases [154]. Additionally, PD-L1 negative patients were excluded from many trials making it difficult to properly define the predictive significance of the biomarker. Moreover, different antibodies, staining platforms, thresholds of positivity on different type of cells have been used across different clinical trials to assess PD-L1 expression [155]. TIL levels evaluated within metastases were recently demonstrated to correlate with response to pembrolizumab in breast cancer [58]. A model combining PD-L1 expression with TIL levels has been proposed to classify the TME and to identify tumors that are most likely to respond to a PD-1 blockade [156,157].

Mutational load (as a marker for tumor foreignness) is another parameter that has been associated with ICB response [39,158]. NSCLC and melanoma, two cancers caused by chronic exposure to exogenous mutagens (ultraviolet light [159] and cigarette smoke [160] respectively) are tumors with a high mutational burden and have been associated with increased response rates and clinical benefit from ICB. DNA mismatch repair (MMR) deficiency results in increased rates of mutation and MMR status has also been correlated with ICB benefit [161]. The higher mutational load of these tumors results in a higher immunogenicity due to the expression of neoantigens [162]. These

observations suggest that the immune system's ability to recognize neoantigens is important for ICB activity. However, there is still a lack of valid assays to predict tumor immunogenicity or to monitor relevant antigen specific immune responses.

We are now faced with a paradigm shift in immune-oncology, whereby the gut microbiota is in part responsible for the immune response elicited by immunotherapy agents. Intestinal microbiota represents a highly diverse ecosystem remodeled over time by the host and environmental factors such as diet, medications (antibiotics, ATB), alcohol and tobacco [163]. This ecosystem composed of bacteria, archaea, viruses and fungi contributes to gut homeostasis maintenance and host protection against pathogenic invasions. The gastrointestinal tract harbors the largest number of immune cells of any tissue in the body and is constantly exposed to a large range of antigens and potential immune stimuli [164]. The interactions between the host and micro-organisms have been recently identified as a crossroad where the host immune pressure, environmental factors and food intake influence the quality of the microbiota and in turn certain microbes tailor the local and systemic immune system [165]. Experimental models and clinical evidence in various tumors underscore that the immune anti-cancer efficacy of chemotherapy [166], allogeneic stem cell transplantation [167,168] and ICB [169,170] are influenced by the gut microbiota composition.

Experiments in germ-free animals or mice treated with broad spectrum ATB unveiled the importance of an intact microbiota and allowed the identification of immunogenic commensal bacteria capable of influencing local and systemic anti-cancer responses. In this setting, *Enterococcus hirae* [166], *Bacteroides. Fragilis* [169] *and Bifidobacterium* [170] amplify the anti-tumor immune response and dictate the outcome in murine tumor models treated with cyclophosphamide, anti-CTLA-4 and anti-PD-L1 mAbs respectively. Following these seminal observations, several groups confirmed the clinical relevance of gut microbiota in cancer patients treated with ICB.

Firstly, in NSCLC, RCC and UC, patients who received ATB before or after the first injection of anti-PD(L)-1 had a worst clinical outcome when compared with patients untreated with ATB [171].

Secondly, a metagenomic shotgun sequencing technique exploring the microbiota composition identified the commensal bacteria *Akkermansia muciniphila* to be associated with favorable clinical outcomes in NSCLC and RCC treated with anti-PD1 antibodies. To demonstrate the immune-potentiating impact of the gut microbiota and *A. muciniphila* towards PD-1 ICB, fecal microbiota transplantation (FMT) was performed using NSCLC patient feces to recolonize germ-free or antibiotic-treated mice intestines. In these human microbiota-colonized mice, anti-PD-1 responses were paralleled with the clinical response of corresponding patients whose feces were transplanted.

Two other groups from the MD Anderson and University of Chicago sequenced feces from patients with metastatic melanoma and demonstrated that a microbiota enriched with *Ruminococcaceae*, *Faecalibacterium*, *Bifidobacterium longum* and *Collinsella aerofaciens* translated into an improved overall response rate to anti-PD-1 therapy at 6 months and enrichment in intratumoral lymphocytes [172,173].

Additional studies corroborated the importance of the microbiota composition for patients with metastatic melanoma receiving ICB [174,175].

The clinical relevance of the microbiota composition and its implication for ICB anti-cancer response is rapidly emerging. Prospective clinical trials are needed to validate the importance of the microbiota in order to develop new predictive markers of response/resistance and to further describe immune mechanisms. Furthermore, modulating microbiota composition with diet modifications, ATB, fecal microbiota transplantation or administration of live or attenuated bacteria represents a new therapeutic intervention. Researchers will need an unprecedented collaboration between microbiologists, oncologists and epidemiologists to build a future where both prognostication and treatment of cancer can be improved by the gut microbiota.

4. Discussion-Perspectives

The involvement of innate and adaptive anti-tumor immune responses in tumor development has long been recognized, and immunotherapies have been used in cancer for a hundred years with limited success. It is only recently that advances in our understanding of the interactions between the immune system and tumor cells have led to the development of novel therapies, including ICB agents that are changing treatment paradigms in a variety of neoplastic diseases [13]. However, only few patients benefit from the "breakthrough" cancer immunotherapy and several challenges remain to be addressed to improve the use of this treatment modality.

Recent research advances using relevant pre-clinical tumor models and more sophisticated approaches to depict and reveal the "immune contexture" are allowing to elucidate the mechanisms of resistance and the development of new therapeutic strategies in immuno-oncology [7,176]. As outlined in this review multiple different mechanisms are used by tumors to shut down the anti-tumor response or to exacerbate a pro-tumor inflammatory response, identification of which has led to the development of several therapeutic approaches to overcome tumor immune escape. Biomarkers to appropriately select the pertinent treatment are still lacking even if some biomarkers such as PD-L1 expression or TIL levels have already been recognized as determinants of response to immunotherapy [177].

Therefore, it is warranted to develop well-designed clinical trials with comprehensive translational research and adequate bio-banking of peripheral blood, stool and tissue samples to help to identify biomarkers to better select patients for cancer immunotherapy [177]. In several malignancies, bio-sampling could delay and discourage recruitment in clinical trials but it is the only way to do appropriate basic and translational scientific research.

The clinical landscape of immunotherapy development is currently moving towards "add on design" where each new effective immunomodulatory compound is added to the last combination of ICB and standard therapy to strengthen anti-tumor immunity and attempt to improve response rate without rationale patient selection [109]. Escalations in the combination of drugs will lead to increased toxicity and financial burden. On the other hand, extreme stratification of patients will make it impossible to perform large randomized statistically powerful clinical trials. The new challenge is to design more rational and appropriate synergistic combinations based on recent results from pre-clinical research with parsimonious and smart clinical designs.

Conflict of interest statement

The authors declare that there are no conflicts of interest. JS is a consultant and member of the Scientific Advisory Board for Surface Oncology Inc.

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