

Review Article

Tumor Evasion from T Cell Surveillance

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An intact immune system is essential to prevent the development and progression of neoplastic cells in a process termed immune surveillance. During this process the innate and the adaptive immune systems closely cooperate and especially T cells play an important role to detect and eliminate tumor cells. Due to the mechanism of central tolerance the frequency of T cells displaying appropriate arranged tumor-peptide-specific-T-cell receptors is very low and their activation by professional antigen-presenting cells, such as dendritic cells, is frequently hampered by insufficient costimulation resulting in peripheral tolerance. In addition, inhibitory immune circuits can impair an efficient antitumoral response of reactive T cells. It also has been demonstrated that large tumor burden can promote a state of immunosuppression that in turn can facilitate neoplastic progression. Moreover, tumor cells, which mostly are genetically unstable, can gain rescue mechanisms which further impair immune surveillance by T cells. Herein, we summarize the data on how tumor cells evade T-cell immune surveillance with the focus on solid tumors and describe approaches to improve anticancer capacity of T cells.

1. Introduction

The theory of immune surveillance was introduced in the early 1900s by Ehrlich, who hypothesized that one critical function of the immune system was to detect and eliminate tumors from the host [1]. As a logical consequence, tumor development should more likely occur when the innate and/or adaptive immunity is impaired or repressed. This hypothesis could be tested in a variety of knock-out mice that were deficient in one or more components of the innate or adaptive immune system. And indeed, the elimination of perforin, interferon (IFN)- γ , or *STAT1* genes (thus lacking interferon-mediated pathways) in mice resulted in increased incidence and growth of spontaneous and chemically-induced tumors [2–5]. Further evidence that the adaptive immune system is involved in immune surveillance of tumors was provided by experiments using *RAG-2*-deficient mutant mice [6]. The *RAG* genes encode DNA repair enzymes which are essential for B-cell receptor (i.e., antibody) and T-cell receptor (TCR) rearrangement. Mice

with homozygous deletion of the *RAG-2* alleles completely lack NKT, T, and B cells and have an increased incidence and growth of spontaneous tumors and chemically induced cancer lesions [5]. In humans these findings are reflected by the fact that immunocompromised patients, in particular transplant recipients and patients suffering from acquired immunodeficiency syndrome (AIDS), are more susceptible to certain types of neoplasms [7, 8].

Although the theory of immune surveillance will remain a matter of debate, it is meanwhile accepted that T cells play a crucial role in controlling the development of neoplastic lesions *in vivo*. T cells are activated via their T-cell receptor, which binds to antigen peptides presented on major histocompatibility complex class molecules (MHCs). Following the recognition of peptides presented by MHC class I molecules, activated CD8⁺ cytotoxic T cells (CTLs) can efficiently destroy target cells using death cell ligands such as TRAIL (TNF-related apoptosis-inducing ligand) or by execution of the perforin/granzyme pathway [9, 10]. Another fraction of T cells, the CD4⁺ T cells, recognizing peptides

presented by MHC class II molecules, play also an important role in adaptive anticancer immunity [11]. CD4⁺ T cells can improve the capacity of dendritic cells (DCs) to induce CTLs by crosslinking the costimulatory molecule CD40 on DCs with the CD40 ligand on activated CD4⁺ T cells [12]. Furthermore, by secreting cytokines such as interleukin-2 (IL-2), activated CD4⁺ T cells support the clonal expansion of activated CTLs [13]. Besides this, activated CD4⁺ T cells can significantly boost cellular components of the innate immunity, such as macrophages and NK cells by enhanced IFN- γ secretion [14]. Concomitantly, increased IFN- γ levels improve the recognition capacity of T cells through induction of higher expression levels of MHC class I molecules on the target cells [14, 15].

Despite ongoing surveillance by T cells and other components of the immune system, tumors develop even in presence of an intact immune system and become eventually clinically detectable. Schreiber and colleagues have put forward the hypothesis of cancer immunoediting to explain this discrepancy [16]. According to their theory, cancer development can be divided in three phases. In the first phase, immune surveillance is intact and cells of the innate and adaptive immune system destroy neoplastic cells. During the second phase a long-winded ongoing campaign between the immune system and cancer cells establishes a dynamic equilibrium. The third phase is characterized by genetic and epigenetic instability of tumor cells which eventually give rise to variants escaping from immune surveillance (for reviewing see [16, 17]) and develop to clinical apparent tumors. Due to the constant selective pressure by the immune system, these variants display a multitude of evasion mechanisms from immune recognition and destruction. In the following paragraphs, we will focus in particular on evasion strategies which outmanoeuvre the immune recognition by T cells. Only a better understanding of the manifold interactions between tumors and T cells will help to improve current T-cell-based immunotherapy strategies.

2. Central Tolerance and Peripheral Tolerance Mechanisms Restrict Tumor-Specific T-Cell Responses

T cell surveillance of neoplastic development and growth primarily depends on recognition of processed so-called tumor-associated-antigen-(TAA-) derived peptides presented by MHC class I molecules on the surface of tumor cells. Conceptually, there are three different types of TAAs: the first group are “neoantigens” which originate from transforming viruses or are due to mutations or chromosomal aberrations in the tumor cells and to which the host is not tolerant, and secondly, “self-antigens” which are mainly proliferation and differentiation markers overexpressed in tumors or normal embryonic antigens aberrantly expressed in the course of epigenetic changes and cellular dedifferentiation of the tumor cells. Finally, the third group are “modified self-antigens” representing self-antigens having different tumor-specific posttranslational modifications due to metabolic

disturbances (for reviewing see [18]). Most TAAs of solid tumors correspond to self-antigens and modified self-antigens which are re-expressed or overexpressed in tumors and are barely detected in normal tissues. However, T cells with high affinity receptors for MHC/self-peptides are eliminated during development in the thymus to establish central tolerance. Therefore, the repertoire of T cells specific for self-peptides in the periphery is restricted to those T cells displaying a low affinity T-cell receptor. Furthermore, under normal circumstances T cells reactive against self-peptides are in an ignorant state called peripheral tolerance and need to be activated by professional antigen-presenting cells (APCs), usually DCs, in a process termed cross-priming, before they can exert their effector functions [19]. Briefly, immunogenic responses of T cells require that DCs must encounter antigens that are associated with evolutionary conserved “pathogenic-associated molecular patterns” (PAMPs) or in other words “danger signals” derived from pathogenic microorganisms or viruses [20, 21]. After sensing such danger signals (i.e., LPS, CpG-rich DNA, and viral RNA) via toll-like receptors (TLRs) or other sensor molecules such as members of the *retinoid inducible gene 1* (*RIG-I*) family the DCs upregulate costimulatory molecules such as CD80 and CD86 and now can fully activate CTLs in concert with activated CD4⁺ T cells [12, 22–25] (Figure 1). Despite the control mechanism of central tolerance, self-reactive CD4⁺ T cells and CTLs exist in the periphery and under certain conditions DCs can provide sufficient costimulation to activate these cells as exemplified in human autoimmune diseases such as psoriasis and systemic lupus erythematoses [26]. In particular, it has been shown that the antimicrobial peptide LL37 from psoriasis patients activates TLRs 7 and 9 when associated with self-nucleic acids [27]. Meanwhile, lines of evidence indicate that under certain circumstances tumor cell death can also deliver danger signals required for DC priming via TLRs. In fact, it has been shown that release of several factors such as calreticulin and high-mobility group box1 protein (HMGB1) from dying cancer cells can codeliver so-called “damage-associated molecular pattern” (DAMP) signals to DCs which in turn can break peripheral tolerance of T cells [28, 29] (Figure 1). Especially HMGB1 which associates with DNA from necrotic cells has been shown to play a pivotal role during sepsis and induction of TLRs [30]. Furthermore, the effects of some anticancer drugs, in particular anthracyclines and platinum-based drugs and also radiotherapy, suggest an immunogenic cancer cell death via calreticulin exposure and HMGB1 release [31]. Anthracycline-based chemotherapy limits tumor growth in wild-type mice, whereas mice with homozygous deletion of TLR4 or its downstream effector molecule MYD88 (myeloid differentiation primary response protein 88) failed to efficiently respond to chemotherapy. In addition, it has been reported that colon cancer patients having a loss of function allele of TLR4 exhibited a reduced progression-free survival compared to patients carrying the normal TLR4 allele after treatment with oxaliplatin (OXP) [28]. DCs which have not been primed by PAMP or DAMP danger signals can also display self-antigens in association with MHC molecules, but unlike in the

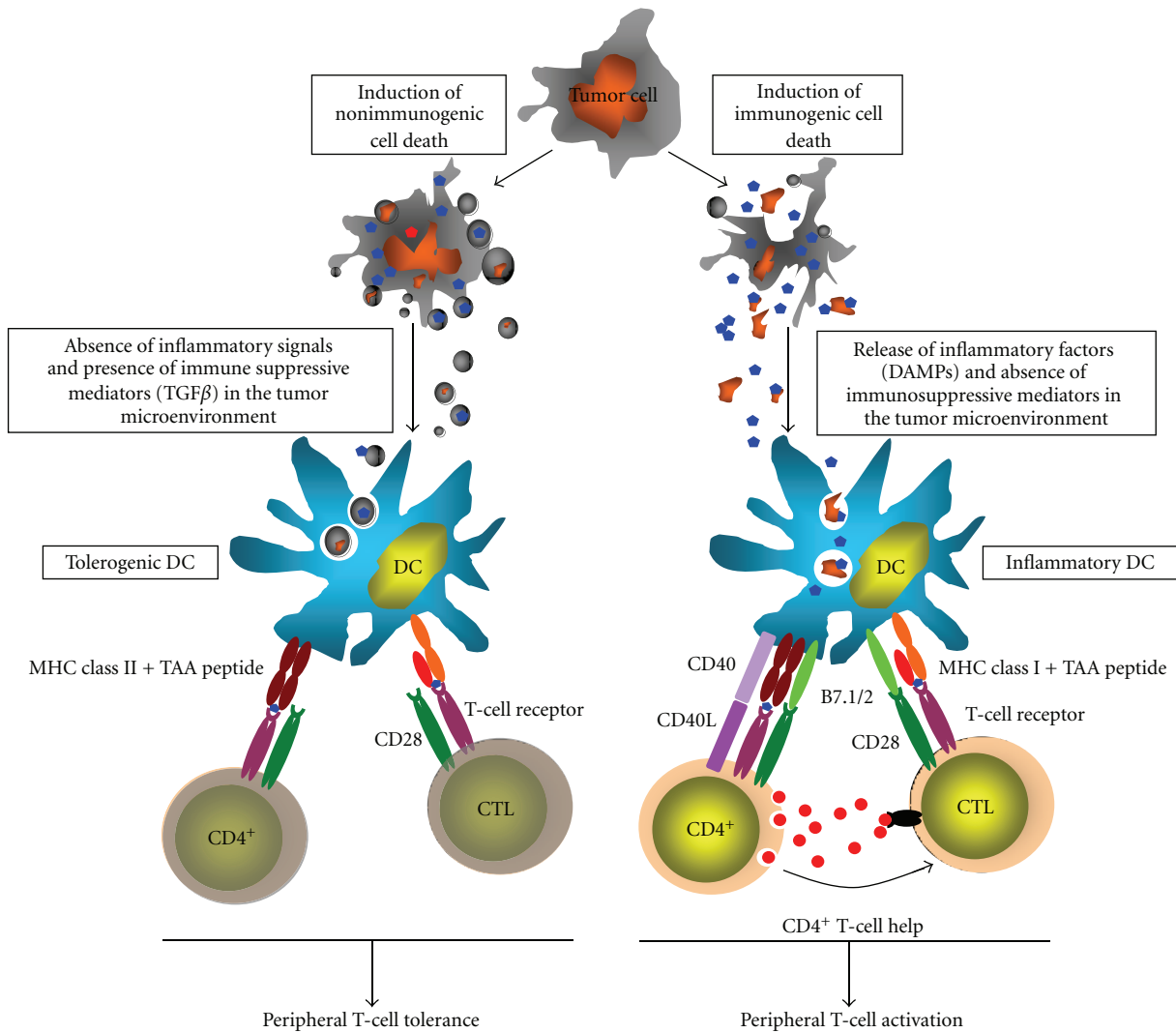


FIGURE 1: T-cell conversion from anergic to an activated status upon immunogenic cell death of tumor cells. The activation of tumor-specific T cells is dependent on DCs, which endocytose tumor cell debris and apoptotic vesicles. After intracellular processing the DCs present peptides derived from tumor-associated-antigens in complex with MHC class I molecules to T cells. Without the stimulation by danger-associated molecular patterns (DAMPs), DCs remain immature in a hostile immunosuppressive milieu and anergize $CD4^+$ T cells and cytotoxic T cells (CTLs) resulting in peripheral tolerance. The release of inflammatory factors and the appearance of DAMPs lead to activation of DCs (inflammatory DCs) which subsequently upregulate costimulatory molecules of the B7 family. Inflammatory DCs are able to activate naïve CTLs through MHC I tumor peptide/TCR and B7/CD28 crosslinking. Furthermore, inflammatory DCs can activate naïve $CD4^+$ T cells after MHC class II tumor peptide/TCR and B7/CD28 crosslinking. Activated $CD4^+$ T cells in turn support clonal expansion and activity of CTLs by CD40/CD40L interaction and release of inflammatory cytokines such as IL-2.

primed state, they cannot provide sufficient costimulation for T-cell activation. Consequently, T cells recognizing MHC/peptide complexes on the surface of nonactivated DCs become anergic and eventually undergo apoptosis in a process termed cross-tolerance [32] (Figure 1). Cross-tolerance is a major hurdle for the generation of potent CTL immune responses against self-antigens as seen in various tumors where immature DCs mostly lacking costimulatory receptors are not able to elicit T-cell responses [33–36]. In summary, evidence is accumulating that immunogenic cell death of tumor cells provides tumor antigens and concomitant danger signals to DCs which are now able to

activate tumor-specific T cells which can appear as so-called tumor-infiltrating lymphocytes (TILs) at the tumor site. So far, TILs, which were proven to specifically react against tumor cells or which were associated with a better clinical outcome, were reported for advanced ovarian cancer [37], breast cancer [38, 39], melanoma [40], and colorectal cancer [41]. Yet, the appearance of TILs in patients *per se* did not predict an efficient immune response or improved clinical outcome against the tumor since various further mechanisms, commonly defined as “tumor escape mechanisms,” can impair the effector function of tumor-reactive T cells.

3. Defective Recognition of Tumors by Activated T Cells

One of the best studied evasion mechanisms of tumor cells to escape recognition by CTLs are abnormalities in the antigen presentation machinery (APM). This includes downregulation or complete loss of MHC class I molecules as observed in head and neck squamous carcinoma [42], human esophageal squamous carcinoma [43], lung cancer [44], and prostate carcinoma [45]. Downregulation of MHC class I molecules can be caused by point mutations or by large deletions correlating with loss of heterozygosity (LOH) on chromosome 6p21 [46, 47]. Another reason for defective MHC class I surface expression as detected in colorectal tumors and melanoma is due to mutated β 2-microglobulin (β 2m) which severely impairs the transport of MHC class I molecules to the cell surface [48, 49]. Moreover, disturbed transcriptional regulation, such as decreased levels or loss of locus-specific transcription factors as well as epigenetic alterations like DNA hypermethylation can contribute to the decrease of MHC class I expression [43, 50, 51].

Assembly and transport of HLA class I molecules to the cell membrane crucially depends on the APM. The APM includes the proteasome subunits of low-molecular mass polypeptides 2 and 7 (LMP2 and LMP7), transporter associated with antigen processing 1 and 2 (TAP1 and TAP2), and several chaperons such as tpsin (for reviewing see [52]). In melanoma and renal cancer, cell lines promoter methylation has been demonstrated as a mechanism to inhibit or impair expression of tpsin, TAP2, and TAP1 that finally leads to a decrease or loss of MHC class I surface expression [53, 54].

IFN- γ plays a major role in the regulation of the APM. Particularly, TAP1 and LMP2 genes are controlled by a shared bidirectional IFN- γ -dependent promoter. In the presence of IFN- γ , the transcription factor interferon regulatory factor-1 (IRF-1) binds the interferon regulatory element (IRF-E) within the TAP1/LMP2 promoter and enhances the expression of TAP1 and LMP2 [55]. Epigenetic silencing of IRF-1 transactivation results in IFN- γ unresponsiveness and subsequently in lower expression levels of MHC class I molecules [56]. Further defects within the IFN- γ signaling pathway such as deletion or mutations in Janus kinases 1 and 2 (Jak1 and JAK2) genes, downstream of IFN- γ receptor and upstream of STAT1 have been described in several IFN- γ -resistant melanoma cell-lines and uterine leiomyosarcoma [57, 58]. Therefore, in certain tumors lack of IFN- γ sensitivity supports immune evasion from CTL recognition.

Besides the impaired MHC-class-I-dependent recognition, tumor cells can avoid confrontation with T cells by inhibiting extravasation of lymphocytes to the tumor site. Defects in adhesion of molecule expression on blood vessels have been described in human breast cancer [59], melanoma [60], and human squamous cell carcinoma [61]. Noteworthy, it was shown that decreased expression levels of addressins E-Selectin, P-Selectin, and intercellular adhesion molecule-1 (ICAM-1) in blood vessels of melanoma resulted in impaired T-cell extravasation at the tumor site when compared to accumulation of T cells in adjacent healthy tissue [62].

4. Resistance to T-Cell-Mediated Killing Mechanism

In the last years evidence accumulated that altered or defective apoptotic pathways might contribute to immune evasion of tumors. There are two distinct effector mechanisms, how T cells can eliminate target cells such as virus-infected cells or malignant cells. Generally, they induce apoptosis by the calcium-dependent “perforin/granzyme pathway” or by the calcium-independent “death receptor pathway”. During the last years, *in vivo* and *in vitro* studies have demonstrated that tumor cells can resist killing by CTLs through interference with the perforin/granzyme pathway, caused by the expression of the granzyme B inhibiting serine protease inhibitor PI-9/SPI-6. In particular melanoma, cervical carcinoma, and breast carcinoma were demonstrated to express PI9/SPI-6 [63]. A recent study revealed a poorer clinical outcome of vaccinated melanoma patients when the tumors expressed PI9/SPI-6 [64].

Death receptors are members of the tumor necrosis factor (TNF) receptor superfamily and are characterized by an intracellular death domain (DD). The crosslinking of death receptors such as CD95 (Fas; Apo-1) and TRAIL receptor 1 and 2 on tumor cells with their natural ligands CD95L and TRAIL induce formation of the death-inducing signaling complex (DISC). Within the DISC, procaspase-8 is recruited by the DD-associated adaptor protein Fas-associated death domain protein (FADD/MORT-1) and activated by autocatalytic cleavage. This event initiates downstream apoptotic processes causing mitochondrial cytochrome C efflux and subsequent activation of effector caspases-3, -6, and -7 [65]. The induction of apoptosis through death receptor signaling can be blocked in tumor cells at several steps. For example, in melanoma cells high levels of antiapoptotic regulator FLICE inhibitory protein (c-FLIP) have been shown to correlate with increased resistance to TRAIL-mediated apoptosis [66]. Due to its structural homology to procaspase-8, but lacking a catalytic site, c-FLIP binds to DISC and inhibits cleavage of procaspase-8 [67]. C-FLIP has been detected in different types of cancer and cancer cell lines [68–71]. In particular its increased expression in colorectal cancer predicts a poorer clinical outcome [72]. Moreover, tumor cells can obtain further apoptotic resistance by downregulation or inactivation of death receptors. Loss of CD95/FAS can occur at the transcriptional level which seems to be affected by oncogenic *ras* [73] or loss of functional p53 [74]. A decreased expression of CD95/FAS also has been found in colon cancer [75]. Noteworthy, expression levels of CD95/FAS in colon cancer cell lines can be improved by TNF- α and IFN- γ [75]. Besides transcriptional downregulation, a variety of tumor-associated mutations and deletions can lead to a loss of function of CD95/FAS and TRAIL receptors. For example, lack of cytoplasmic signaling domains of CD95/FAS, TRAIL-R1, and -R2 was detected in multiple myeloma [76], adult T-cell leukemia [77], gastric cancer [78], and breast cancer [79].

Another mechanism by which tumors gain resistance to apoptosis is the expression of transmembrane and soluble decoy receptors with a truncated nonfunctional or a missing

death domain, respectively. Interactions of ligands with their respective decoy receptors have been shown to competitively inhibit death receptor signaling. So far, different decoy receptors for CTL's death ligands CD95L and TRAIL have been characterized: soluble CD95/FAS (sCD95) in various malignancies [80–82], decoy receptor 3 (DcR3) in lung cancer [83], colon cancer [83], as well as glioblastoma [84], and TRAIL-R3 (DcR-1) in primary gastrointestinal tract (GIT) cancers [85], TRAIL-R4 (DcR-2) in colon cancer [86], and TRAIL-R5 (Osteoprotegerin; OPG) in breast [87] and prostate cancer [88].

5. Induction of Anergy in Activated T Cells

Inhibitory coreceptors, including “cytotoxic T lymphocyte antigen-4” (CTLA-4) and “programmed death-1” (PD1), play a major role in maintaining peripheral T-cell tolerance. These inhibitory coreceptors are upregulated during T-cell activation and interact with molecules of the B7 family that are found on DCs but are also expressed in many tumor tissues [89]. CTLA-4 competes with the costimulatory receptor CD28 in binding to CD80 (B7.1) and CD86 (B7.2) molecules and activates protein phosphatase 2A (PP2A) [90]. PP2A dephosphorylates Akt kinase and therefore antagonizes the TCR/CD28 signaling pathway resulting in decreased IL-2 production, impaired TCR signalling, and cell cycle arrest [91, 92]. The inhibitory T-cell receptor PD1 which is upregulated by IFN- γ [93] interacts with the B7 family member B7-homolog 1 (B7-H1) which is found in many tumor types [94–98]. Increased B7-H1 levels correlate with a poor outcome in ovarian cancer, esophageal cancer, and urothelial cancer [94–96]. Mechanistically PD1/B7-H1 interaction leads to recruitment of SH2-containing protein tyrosine phosphatases-1 and -2 (SHP-1, -2) at the immunoreceptor tyrosine-based switch motif of PD1 which ultimately results in downstream signals inhibiting phosphoinositide 3 kinase (PI3K) activity and disruption of TCR/CD28 signaling [99]. Furthermore, an induction of IL-10 was observed which might influence suppressive activity of Tregs (discussed in Section 7) [89]. A soluble form of B7-H1 was detected in aggressive renal cell carcinoma which could further promote immunosuppression [100].

Furthermore, anergy in T cells can be induced by high levels of intratumoral TGF- β and of the arachidonic acid derivative prostaglandin E2 (PGE2). TGF- β controls T-cell homeostasis by inhibiting T-cell activation, proliferation, and differentiation [101, 102]. Numerous *in vivo* and *in vitro* studies demonstrated that expression of TGF- β at the tumor site correlates with poor prognosis in many human cancer types such as colorectal cancer, esophageal adenocarcinoma, glioblastoma, breast cancer, and lung cancer [103–107]. However, the molecular mechanisms which eventually lead to TGF- β -mediated T-cell inhibition are still not well characterized. It is hypothesized that the TGF- β -induced mRNA downregulation of TCR components and signaling molecules like IL2-inducible T-cell kinase (ITK), ZAP70, and CD3-zeta chain results in an insufficient T-cell signal transduction [108]. Furthermore, TGF- β is also known for blocking the cytotoxic reaction of CTLs by transcriptional

repression of genes encoding the cytotoxic mediators perforin, granzyme A and B, FasL, and INF- γ [109]. More recently, accumulating data suggests that under certain circumstances TGF- β also impairs the function of tumor-reactive CD4⁺ T cells by inducing them to become FoxP3-positive regulatory T cells (“Tregs”, discussed in Section 7) [110].

The inducible isoform of the cyclooxygenase enzyme COX2 is overexpressed in several tumor types and produces PGE2 which affects various processes relevant to tumorigenesis such as apoptosis, angiogenesis, and migration [111]. It is proposed that PGE2 shifts the immune system to a Th2-type response. Supporting evidence came from the observation that breast cancer patients showing increased intratumoral COX2/PGE2 expression had impaired DC and T-cell function, reduced Th1-type, and increased Th2-type cytokine levels in the serum [112]. In addition, it has also been proposed that PGE2 augments the induction of FoxP3 in CD4⁺ T cells [113]. In particular, mice with homozygous deletion of the PGE2 receptor *P4* gene showed significantly reduced intratumoral levels of FoxP3⁺ Tregs, increased serum level of Th1-type cytokines, and an increase in IFN- γ -dependent antitumor reactivity of T cells [114].

Another immune evasion mechanism of tumors is based on protein-glycan interactions involving galectins. Galectins, defined as glycan-recognizing proteins with an affinity for β -galactosides, affect many cellular functions including adhesion, migration, chemotaxis, proliferation, apoptosis, and differentiation [115–117]. During the last years, galectins have been recognized as natural immunosuppressive proteins which also inhibit antitumor immune responses. Their overexpression in tumors such as melanoma [118], glioblastoma [119], prostate cancer [120], bladder cancer [121], ovarian cancer [122], and breast cancer [123] often correlates with tumor aggressiveness. Especially galectin-1 might play an important role in immune evasion by inducing T-cell apoptosis [124, 125]. So far little is known about how galectins impair T-cell functions. Yet, some evidence suggests that galectin-1 interferes with the correct assembly of the T-cell receptor complex in lipid rafts [126].

6. Tumor Cell “Counter Attack”

In an immunocompetent organism, T-cell activation by pathogens leads to a clonal expansion of antigen-specific T cells. Once they have accomplished their mission, T-cell expansion bearing the inherent danger of autodestruction is terminated by T-cell activation-induced cell death (AICD) resulting in clonal contraction of antigen-specific T cells [127]. The CD95/FAS death receptor, which is upregulated in activated T cells, is playing a key role in AICD. It is well known that upon TCR engagement in the absence of costimulation, T cells express high amounts of Fas ligand (FasL), which is assumed to induce apoptosis of these T cells (“suicide”) and between T cells (“fratricide”). Yet, some tumors such as melanoma [128], lung cancer [129], pancreatic cancer [130], and breast cancer [131] express Fas ligand (FasL), which might accelerate AICD and therefore

could contribute to tumor immune evasion. First evidence that FasL can confer resistance to T-cell-mediated tumor rejection was demonstrated by delayed growth of FasL-positive melanoma cells in *lpr*-positive mice (*lpr*, lymphoproliferation gene, encoding mutated CD95/FAS with loss of function) when compared to congenic controls, supporting the concept that tumor cells can eliminate effector T cells by FasL counter attack [128]. However, despite accumulating data in support of FasL counter attack, many conflicting studies have reported that FasL can also induce proinflammatory and antitumoral effects *in vivo*. In particular, tumor xenografts genetically modified to express membrane-bound FasL showed an accelerated rejection which was accompanied by neutrophil infiltration [132–134]. In contrast, a more recent study revealed that antisense-mediated downregulation of FasL in colon cancer cells reduced tumor growth in syngeneic and immune competent mice [135]. It remained to be clarified whether other factors such as cytokines, tumor microenvironment, or technical peculiarities account for the different outcomes. The situation becomes far more complex by a recent report describing the appearance of so called microvesicles containing FasL which were found to be released by melanoma cells [136]. These microvesicles are endosome-derived small particles of 50 to 100 nm in size and are secreted through exocytosis pathways [137]. These microvesicles were able to induce cell death in lymphoid cells and furthermore might cause systemic immunosuppressive effects in patients [136]. In particular, it is assumed that besides the effects of death receptor ligands the microvesicles can carry various immunomodulatory factors that exert immunosuppressive effects on lymphocytes in draining lymph nodes but also modulate myeloid-derived cells to become myeloid-derived suppressor cells (MDSC) [137] (which are further discussed in Section 7).

In addition to FasL-mediated apoptosis induction in antitumor effector cells, a recent report also described expression of TRAIL in hepatocellular carcinoma which induced cell death of Jurkat leukemia T cells [138].

Another mechanism that may contribute to tumor evasion from tumor-specific T cells is based on the expression of the enzyme indoleamine 2,3-dioxygenase (IDO). This heme-containing enzyme degrades the essential amino acid tryptophan and catalyzes the initial and rate-limiting step of the kynurenine pathway leading to nicotinamide dinucleotide (NAD) biosynthesis. Initially, IDO was thought to represent a defence mechanism against bacteria, but it soon became evident that IDO plays a physiological role in the establishment of an immune privilege at the fetoplacental border. IDO expression at this site is proposed to block T-cell attack and therefore protects the embryo [139]. This effect was confirmed by *in vitro* studies showing that tryptophan depletion led to cell cycle arrest in T cells [140]. So far IDO expression was found in several primary tumors such as gastric cancer, colon cancer, and renal cell carcinoma as well as in derived cell lines [141]. Interestingly, some of the tumor cell lines expressed IDO only after IFN- γ treatment and the activity of IDO could be blocked by administration of the specific inhibitor levo-1-methyl-tryptophan [141]. Thus,

in certain tumors pharmacological blockade of IDO may impair the development of an immune privileged tumor site and may improve immunotherapy.

7. Immunosuppressive Roles of FoxP3⁺ Regulatory T Cells and of Myeloid-Derived Suppressor Cells (MDSCs)

The existence of peripheral T cells exerting a suppressor function has been a matter of debate for many years. Nowadays it is widely accepted that a distinct population of CD4⁺ cells constitutively expressing the surface markers CD25 (the alpha-chain of the IL-2 receptor) and accounting for approximately 5–10% of all peripheral T cells can suppress responses of tumor-specific CD4⁺ T cells and CTLs [142]. Moreover, these cells, designated Tregs, are characterized by the expression of the transcription factor forkhead box P3 (FoxP3), CTLA-4, glucocorticoid-induced TNF receptor (GITR), and by their ability to suppress the activation of other T-cell subpopulations [110, 143, 144].

In humans, high numbers of CD4⁺ CD25⁺ Tregs were found in head and neck cancer [145], lung cancer [146, 147], pancreatic cancer [148], breast cancer [149], liver cancer [150], ovary cancer [151], and gastrointestinal cancer [152] either in the circulation or in the tumor itself. The appearance of Tregs at the tumor sites often correlates with poor prognosis of cancer patients [148, 151, 153, 154]. So far, it is not clarified why and how Tregs accumulate at the tumor site. As a mechanism of Treg recruitment, it has been proposed that tumor cells or tumor-infiltrating macrophages secrete the chemokine CCL22 which chemoattracts CD4⁺CD25⁺ Tregs [151, 155]. On the other hand, it is also likely that the immunosuppressive milieu of the tumor, that is, high concentrations of TGF- β , induces tumor infiltrating CD4⁺ T cells to become FoxP3⁺ Tregs [110]. Tregs, either regular Tregs or induced Tregs prevent antitumoral immune responses by inhibiting tumor-specific CD4⁺ cells and CTLs.

Another recently described immunosuppressive cell population in tumors are the MDSCs [156, 157]. These cells are generated in response to a variety of tumor-derived cytokines and appear as heterogenous populations representing myeloid cells at different stages of differentiation. In advanced cancer stages peripheral blood MDSCs were found to inhibit IFN- γ production by autologous CD8⁺ T cells stimulated with peptide-pulsed DCs [156, 158]. It is hypothesized that the appearance of MDSCs in tumors and in peripheral blood might be due to increased granulocyte macrophage colony-stimulating factor (GM-CSF) levels produced by human tumor cells [159–162] and that the immunosuppressive phenotype is induced by tumor-derived microvesicles [137]. Meanwhile, some evidence is accumulating that MDSCs might inhibit T cells by the production of amino acid metabolizing enzymes such as arginase, nitric oxide synthetase and the production of reactive oxygen species (ROS) [157, 158, 163]. Especially, the chemical modification of T-cell receptors by reactive nitrogenous species was demonstrated to impair binding to the cognate MHC/peptide complex [163].

8. Immunotherapeutic Approaches to Induce Antitumor T-Cell Responses

A number of different immunotherapeutic approaches focus on the generation of an effective T-cell-mediated antitumor response in patients (Table 1). Exploiting T cells as a target tool for cancer treatment seems to be advantageous as T cells have an exact specificity for their target, can home into antigen-expressing tumor sites and can generate a long-lasting immune response against reoccurrence of the disease. However, so far none of the various T-cell-dependent approaches has been established as a routine clinical treatment strategy for cancer as, for example, monoclonal antibody-based pharmaceuticals have been in the last years. The failure of various T-cell-based immunotherapeutic approaches in clinical studies is related in many aspects to escape mechanisms of tumors from T cell surveillance and the immunosuppressive effects mediated by tumors described in the preceding chapters (summarized in Figure 2). While in this section we will describe immunotherapeutic approaches using DCs and TILs, in the following sections we will give an overview on new strategies to enhance T-cell-mediated anti-tumor response.

Strategies based on vaccination with tumor cell lysates, TAAs, or tumor peptides can elicit antitumoral responses through priming of DCs and subsequent activation of tumor-specific T cells [164]. However, many clinical trials were disappointing in terms of tumor regression or increased survival rates [164]. Potential reason for failure of this vaccination strategy can be alterations in number as well as functional defects in DCs which has been observed in a number of patients [33, 35]. In addition, lack of immunological response seemed to be more severe in patients bearing a large tumor burden and is likely caused by immunosuppressive factors released by the tumor, Tregs [101] and MDSCs [165]. It is assumed that induction of T-cell tolerance by immature or dysfunctional DCs is mostly responsible for the observed unresponsiveness of T cells [164]. Therefore, new vaccine strategies concentrate on the targeting of certain DC subsets and codelivery of PAMP or DAMP signals to DCs to improve the T-cell priming capacities. In particular, activators of TLRs, for instance the cytosine-phosphate-guanosine (CpG) dinucleotide CpG 7909, which induces TLR9 activation, came into the focus of tumor immunotherapy. Intradermally injected CpG 7909 near the tumor site obviously provided sufficient danger signals to plasmacytoid DCs which in turn were able to elicit melanoma responsive CTLs in sentinel lymph nodes of patients, whereas in patients treated with saline no melanoma-reactive CTLs were detected [166]. The chemical compound imiquimod, a potent TLR7 agonist, has been approved for treatment of basal cell carcinoma [167] and was shown to improve survival of glioblastoma patients bearing tumors with mesenchymal gene expression profile and vaccinated with *ex vivo* tumor cell lysate pulsed DCs [168].

Another strategy to enhance vaccination-induced T-cell activation is the *ex vivo* modulation of autologous or allogeneic DCs. This is often accomplished by incubation with factors like type-1 and type-2 interferons, TLR ligands

or GM-CSF, which all enhance the antigen-presenting and T-cell activating capacities of DCs [164]. As an encouraging result of these efforts, Sipuleucel-T, a dendritic-cell-based vaccine recently approved by the FDA and based on peripheral blood cells *ex vivo* stimulated with a fusion protein of prostatic acid phosphatase and GM-CSF was shown to improve survival of prostate carcinoma patients in a phase III trial [169]. Furthermore, depletion of Tregs prior to vaccination of *ex vivo*-modulated DCs can be used to improve immune responses. In particular, Denileukin diftitox, an IL-2 peptide fused to diphtheria toxin which is approved for treatment of cutaneous T-cell lymphoma [170] enhanced T-cell activation of patients when applied before vaccination with DCs *ex vivo* transduced with a fowlpox vector encoding the TAA carcinoembryonic antigen [171].

Furthermore, the direct transfer of tumor-specific either allogeneic or *ex vivo* expanded patient-derived autologous T cells emerged as a promising approach for cancer immunotherapy (adoptive cell therapy, ACT). The rationale behind this strategy is to circumvent or break tolerance against the tumor by the transferred T cells. Direct clinical evidence has accumulated that adoptively transferred T cells can delay or even prevent tumor relapse after initial standard treatment [172]. Yet, in this first clinical trial the response rate was only transient, and transferred tumor-specific T cells vanished rapidly [173]. Recently, improvements of *ex vivo* cultivation conditions and more important lymphodepletion prior to infusion of T cells led to remarkable cancer regression [174–176]. One probable explanation for the efficiency of ACT after lymphodepletion might be the removal of immunosuppressive Tregs.

9. Improving Antitumoral Responses by Blocking Self-Restricting Inhibitory Circuits of T Cells

To further improve the outcome of immunotherapy immune-restrictive signals to T cells can be either blocked or eliminated. In particular, blocking antibodies can be utilized for switching off self-restricting inhibitory circuits of T cells directly at the site of the tumor, resulting in enhanced antitumor immune responses. Promising candidates are antibodies inhibiting CTLA-4 [177] which blocks the intrinsic T-cell regulatory pathway or anti-B7-H1 antibodies which block extrinsic T-cell inhibitory pathways driven by ligands on DCs and tumor cells, respectively [98, 178]. In preclinical studies, blockade of B7-H1 has resulted in enhanced antitumoral immune responses [98, 178]. Recently, a blocking anti-PD1 antibody (MDX-1106), the receptor for B7-H1 on T cells, has been evaluated in a clinical phase I study. So far, MDX-1106 was well tolerated in most patients bearing different solid tumor types. A small proportion of patients showed complete and partial responses to treatment whereas one case was associated with development of inflammatory colitis [179]. So far no clinical studies using PD-1 blockade during immunotherapeutic approaches have been reported. In preclinical mouse models CTLA-4 blockade-based immunotherapy enhances the T-cell-mediated killing

TABLE 1: Selected approaches to tumor immunotherapy.

Approach	Target	Agent	Immune modulation of host	Phase of experimentation	Main findings
Vaccination	Glioma	Tumor-cell lysate pulsed DCs	—	Phase I clinical trial completed (NCT00576537)	T-cell responses, detection of infiltrating T cells in recurrent glioma associated with prolonged survival [210]
Vaccination	Adenocarcinoma of the prostate expressing “prostatic acid phosphatase” (PAP)	DCs <i>ex vivo</i> primed with PAP-GM-CSF fusion protein (Sipuleucel T, FDA-approved for treatment of hormone-refractory prostate cancer)	—	Phase III clinical trial completed (NCT00065442)	Increased overall survival, but no increase in progression-free survival of patients [169]
Vaccination and chemotherapy (Doxetacel)	Breast cancer with expression of MUC-1, CEA	Recombinant Vaccinia and Fowlpox virus (PANVAC) encoding MUC-1 and CEA	GM-CSF treatment during vaccinations	Phase II clinical trial ongoing (NCT00179309)	Induction of T-cell specific immune responses [211]
Vaccination	Adenocarcinoma of the prostate expressing “TCR γ Alternative Reading frame Protein”	Vaccination with TARP peptides	Use of Montanide ISA-51 VG as adjuvant and concomitant GM-CSF treatment	Preclinical study and phase-I clinical trial ongoing (NCT00908258)	Preclinical study demonstrated induction of T-cell-specific immune responses [212]
Vaccination	Melanoma	MART-1-, gp100-, tyrosinase-peptides	Subcutaneous injection of IFN- α 2b and/or GM-CSF	Phase II clinical trial completed (ECOG E1696)	Neither IFN- α 2b nor GM-CSF improved immune responses, 35% of patients developed T-cell responses associated with prolonged median overall survival [213]
Vaccination	Melanoma	MAGE-3.A1 peptide and/or NA17.A2 peptide	peritumoral injection of IL-2, IFN- α and GM-CSF, and topical application of imiquimod	Phase I/II clinical trial ongoing (NCT01191034)	—
Vaccination	CEA expressing cancers	<i>Ex vivo</i> activation of DCs using recombinant Fowlpox virus encoding CEA	Denileukin diftitox-mediated depletion of Tregs	Phase I clinical trial ongoing (NCT00128622)	Increased T-cell responses to CEA-positive target cells [171]
Vaccination	Melanoma	Tyrosinase/gp100/MART-1 Peptides	Use of Montanide ISA-51 VG as adjuvant, treatment with anti-CTLA4 antibody (MDX-010)	Phase I/II clinical trial ongoing (NCT00028431)	T-cell reactivity against gp100 and MART-1. CTLA-4 antibody dose-related adverse autoimmune effects in skin and gastrointestinal tract [214]
	Melanoma	gp100 peptides	Vaccination using incomplete Freund’s adjuvant, treatment with anti-CTLA4 antibody (Ipilimumab)	Phase II clinical trial completed (NCT00094653)	Improved overall survival when applying Ipilimumab irrespective of gp100 vaccination, adverse immunological site effects [185]

TABLE 1: Continued.

Approach	Target	Agent	Immune modulation of host	Phase of experimentation	Main findings
Vaccination	Glioma	Tumor cell lysate pulsed dendritic cells	TLR agonist Imiquimod	Phase II clinical trial ongoing (NCT01204684)	Improved survival of a subset of glioma patients [168]
Vaccination	Leukemia	Autologous leukemia cells	Autologous skin fibroblasts transduced with recombinant adenoviral vectors encoding CD40L and IL-2	Phase I/II clinical trial ongoing (NCT00058799)	Observed immune responses including antibodies against leukemic blasts, prolonged survival time of patients [215]
TLR agonist monotherapy	TLR 9 in Melanoma	CpG 7909	—	Phase II clinical trial completed (NCT00070642)	Increased frequencies of T cells reactive against target cells expressing melanoma-associated-antigens in sentinel lymph nodes [166]
TLR agonist monotherapy	TLR7 in basal cell carcinoma	Imiquimod	—	Phase II clinical trial completed (NCT00189241)	FDA approved for treatment of superficial basal cell carcinoma [167]
Immunotoxin monotherapy	Renal cell carcinoma	Denileukin diftitox (IL-2-diphtheria toxin fusion protein)	Complementary IL-2 treatment	Phase I clinical trial completed (NCT00278369)	Partial depletion of Tregs, no increase in antitumor response rates when compared to controls [216]
TGF β antisense (AS) oligonucleotide monotherapy	TGF β expression in patients with recurrent high grade glioma	TGF β AS (AP-12009, Trabedersen)	Local depletion of TGF β	Phase IIb clinical trial completed (NCT00431561)	Well tolerated, increased median survival time of patients [195]
Anti-TGF β antibody monotherapy	TGF β expression in patients with renal cell carcinoma, melanoma	Blocking anti-TGF β antibody (GC-1008)	Systemic depletion of TGF β	Phase I clinical trial safety and efficacy study (NCT00356460)	—
Anti-PD-1 antibody monotherapy	Refractory or relapsed malignancies (solid tumors)	Anti-PD-1 antibody (MDX-1106)	Blocking extrinsic self-regulatory pathways of T cells	Phase I clinical trial (NCT00441337)	Complete and partial responses, induction of inflammatory colitis [179]
Anti-CD137/4-1BB monotherapy	Melanoma	Anti-CD137/4-1BB antibody (BMS-663513)	Systemic co-stimulation of T cells	Phase II clinical trial completed (NCT00612664) [188]	—
Adoptive cell therapy	Melanoma	<i>Ex vivo</i> expanded TILs	Chemotherapy-mediated lymphodepletion prior infusion of TILs, high dose IL-2 treatment	Phase II clinical trial ongoing (NCT00513604)	Objective clinical responses, in some cases durable complete responses, toxic side effects after chemotherapy and high IL-2 doses [174, 176]
Adoptive cell therapy	Melanoma	<i>Ex vivo</i> expanded TILs enriched for CD8 ⁺ T cells genetically engineered to express IL-12	Chemotherapy-mediated lymphodepletion prior infusion of TILs	Phase I/II clinical trial ongoing (NCT01236573)	—

TABLE 1: Continued.

Approach	Target	Agent	Immune modulation of host	Phase of experimentation	Main findings
Genetic manipulation of T cells for immune therapy	Neuroblastoma cells expressing L1-CAM (CD171)	<i>Ex vivo</i> generated anti-CD171-CAR engineered T cells	—	Phase I/II clinical trial completed (BB-IND#9149, FDA)	Weak tumor responses and limited persistence of CD171-CAR [201]
Genetic manipulation of T cells for immunotherapy	Non-Hodgkin lymphoma and mantle cell lymphoma	<i>Ex vivo</i> generated anti-CD20-CAR engineered T cells	Low dose IL-2 treatment	Phase I/II clinical trial completed (NCT00012207)	No side effects, regression of tumors, persistence of modified T cells for 9 weeks [202]
Genetic manipulation of T cells for immunotherapy	Metastatic cancers that express NY-ESO-1	<i>Ex vivo</i> generated anti-NY ESO-1 TCR-gene engineered T cells	Chemotherapy-mediated lymphodepletion prior infusion of modified T cells. Modified T cells are further stimulated using ALVAC-ESO-1 vaccine, G-CSF and high dose IL-2 treatment	Phase II clinical trial ongoing (NCT00670748)	—
Genetic manipulation of T cells for immunotherapy	B-cell malignancies with expression of CD19	<i>Ex vivo</i> generated anti-CD19-CAR engineered T cells	Chemotherapy-mediated lymphodepletion prior infusion of TILs, high dose IL-2 treatment	Phase I/II clinical trial ongoing (NCT00924326)	Regression of B-cell lymphoma and elimination of B-cell precursors in patients [203]
Genetic manipulation of T cells for immunotherapy	Metastatic cancers expressing Her2	<i>Ex vivo</i> generated anti-Her2-CAR engineered T cells	Chemotherapy-mediated lymphodepletion prior infusion of modified T cells, IL-2 treatment	Phase I/II clinical trial completed (NCT00924287)	—

ClinicalTrials.gov identifier, Eastern Cooperative Oncology Group (ECOG) identifier, and FDA-authorized pilot clinical study identifier are given in brackets.

of tumor cells such as prostate [180] and colon cancer [181]. Also anti-CTLA-4 antibodies have entered the clinic and have been used as monotherapy or in combination with vaccination strategies targeting melanoma [182]. Although clinical responses were observed in some patients with metastatic melanoma or renal cell cancer in a phase I clinical trial with humanized anti-CTLA-4 antibody (ipilimumab), caution is advised since CTLA-4 blockade in some patients caused immune-mediated site effects such as hypophysitis, enterocolitis, and nephritis [183–185]. Alternatively, agonistic antibodies specific for costimulatory receptors can be applied to improve T-cell responses to tumors. An example is CD137 (4-1BB) antibodies which trigger via their receptor the upregulation of antiapoptotic BclXL, Bfl-1, and c-FLIP through the PI3K/Akt and NFκB pathways and therefore rendered reactive T cells more resistant to AICD [186, 187]. Notably, a humanized monoclonal anti-CD137/4-1BB antibody (BMS-663513) has entered a clinical phase II trial as a second line monotherapy for previously treated unresectable melanoma, but so far no combinations

with immunotherapeutic approaches have been reported [188]. Other attempts focus on OX40 (CD134), a co-receptor playing a central role in generating CD4⁺ and CD8⁺ memory cells [189]. A preclinical study using OX40L or an agonistic antibody during vaccination was shown to augment protection against melanoma, breast and colon carcinoma, and sarcoma in mice [190]. Currently, the role of OX40-OX40L interaction in the induction, maintenance, and function of Tregs came into focus of interest. Some lines of evidence support the view that OX40-OX40L interaction inhibit the induction of Tregs in the tumor, which might further enhance immunotherapy of cancer [189].

10. Targeting Tregs and the Tumor Micromilieu in order to Improve Antitumoral T-Cell Responses

To date, it became very clear that the tumor microenvironment, consisting of immunosuppressive cells, especially

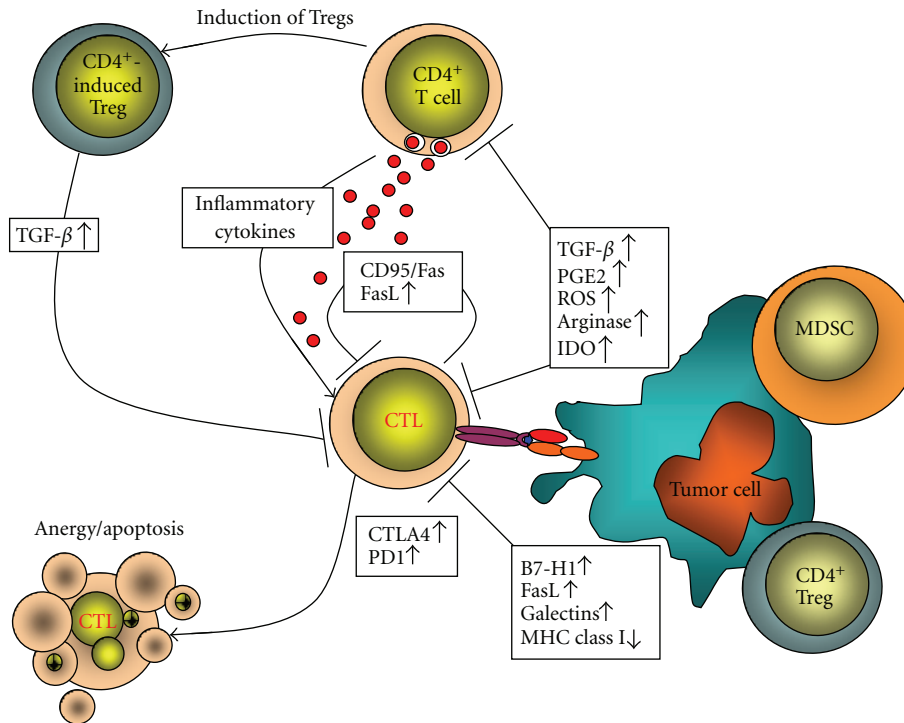


FIGURE 2: Overview of immunosuppressive evasion mechanisms. Tumor cells and tumor-infiltrating Tregs and MDSC can employ a plethora of immunosuppressive factors and molecules that impair T-cell function or lead to T-cell anergy and/or apoptosis. Depicted are immunosuppressive self-inhibitory circuits of activated CTLs and also immunosuppressive mechanisms of tumors.

Tregs, tumor metabolites, and tumor-derived cytokines critically affects T-cell-mediated immunotherapy. In particular, immunosuppressive effects of Tregs can nowadays be minimized by antibody-mediated (i.e., anti-CD25 [191], anti-GITR [192]) Treg depletion or chemotherapeutic lymphodepletion protocols prior to adoptive cell transfer of T lymphocytes and vaccination approaches. In addition, blocking antibodies or soluble receptors can be exploited for the blockade of cytokines that either suppress effector T cells directly or act via macrophages and MDSCs. Candidates include for instance TGF-β [102, 109] and IL-10 [193]. A further promising avenue to increase the effectiveness of antitumoral T cells might be the antisense oligodeoxynucleotide or siRNA-mediated silencing of TGF-βRI and RII receptor expression in the tumor-reactive T cells themselves or the knock down of TGF-β expression at the tumor site, in particular in Tregs [194]. Indeed a first clinical study targeting TGFβ using the antisense oligonucleotide trabedersen as single agent showed promising results when locally given in recurrent glioma patients [195]. A clinical phase I study for systemic antibody-mediated blockade of TGFβ is ongoing (see Table 1). It is foreseen that immunosuppressive enzymes such as COX2, IDO, arginase, and nitric oxide synthetase will be targeted by small chemical compounds and used in combination with immunotherapy. In particular, small molecule inhibitors targeting COX2 and decreasing intratumoral PGE2 levels showed promising results in preclinical studies [196].

11. Genetic Manipulation of T Cells for Immunotherapy of Tumors

Finally, T cells can be genetically manipulated to engraft polyclonal T cells with an additional antitumor specificity and/or improved antitumor response. Additional specificity can be provided by the engraftment of T cells with a second TCR recognizing a specific tumor-associated antigen. In first clinical trials, TCR gene transfer into peripheral blood T cells has been shown to be feasible and to reprogram polyclonal T cells towards tumor antigens [197, 198]. Another approach uses chimeric antigen receptors (CARs), which are fusion proteins of an antigen-binding moiety, usually an antibody-derived single chain fragment variable (scFv) specific to a surface tumor antigen, linked to an ITAM-bearing signaling receptor like the CD3 zeta chain [199, 200]. In general, the use of CARs is advantageous when treating tumors with IFN-γ unresponsiveness or defects in APM as the recognition of the tumor cell by the engrafted T cell is independent of MHC presentation. However, for a CAR approach, the targeted surface antigen should only be expressed on tumor cells in order to avoid off-target effects. And indeed, clinical trials have proven that CARs were safe and off-target effects were not apparent when a strong target antigen expression was restricted to tumor cells [201–203] (Table 1). Further signals can be provided upon antigen-binding by the incorporation of additional signaling subunits from costimulatory receptors like CD28 [204], OX40 (CD134) [205], or 4-1BB

(CD137) [206]. The combined signaling can induce the expression of anti-apoptotic proteins, sustained proliferation, inflammatory cytokine secretion, and resistance to immunosuppression by soluble or cellular components. The genetic manipulation of T cells can be further extended by including expression cassettes for homeostatic T-cell cytokines [207], anti-apoptotic molecules [208], shRNAs against T-cell inhibitory molecules, and chemokine receptors [209] to guide T-cell migration to tumor sides.

12. Conclusions

The considerable progress made in understanding the interaction between tumor cells and T cells opens avenues for the development of improved clinical protocols for T-cell-based immunotherapy. In particular, the development of therapeutic tools for efficient cross-priming such as TLR agonists and sustaining antitumoral functions of T cells as for example modifying self-restricting circuits should enable rejection of the tumor and should guarantee engraftment of long-lived memory T cells. To further improve outcomes, immunotherapy approaches need to be combined with other therapies that might target various components of tumor development such as tumor cell metabolism, apoptosis, angiogenesis, tumor stroma, and inflammation to reduce the immunosuppressive environment shaped by the tumor. Last but not least recent studies suggest that the immune system might contribute mechanistically to the clinical efficiency of chemotherapeutic protocols [28, 31] which should be further pursued in future clinical trials. We envisage that in future advanced protocols for adjuvant immunotherapy will complement conventional therapies for the benefit of cancer patients.

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