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Review

Immune evasion in cancer: Mechanistic basis and therapeutic strategies

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ABSTRACT

Cancer immune evasion is a major stumbling block in designing effective anticancer therapeutic strategies. Although considerable progress has been made in understanding how cancers evade destructive immunity, measures to counteract tumor escape have not kept pace. There are a number of factors that contribute to tumor persistence despite having a normal host immune system. Immune editing is one of the key aspects why tumors evade surveillance causing the tumors to lie dormant in patients for years through "equilibrium" and "senescence" before re-emerging. In addition, tumors exploit several immunological processes such as targeting the regulatory T cell function or their secretions, antigen

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presentation, modifying the production of immune suppressive mediators, tolerance and immune deviation. Besides these, tumor heterogeneity and metastasis also play a critical role in tumor growth. A number of potential targets like promoting Th1, NK cell, γδ T cell responses, inhibiting Treg functionality, induction of IL-12, use of drugs including phytochemicals have been designed to counter tumor progression with much success. Some natural agents and phytochemicals merit further study. For example, use of certain key polysaccharide components from mushrooms and plants have shown to possess therapeutic impact on tumor-imposed genetic instability, anti-growth signaling, replicative immortality, dysregulated metabolism etc. In this review, we will discuss the advances made toward understanding the basis of cancer immune evasion and summarize the efficacy of various therapeutic measures and targets that have been developed or are being investigated to enhance tumor rejection.

1. Introduction

Cancer remains one of the leading causes of death globally, with an estimated 12.7 million cases around the world affecting both sexes equally. This number is expected to increase to 21 million by 2030. The immune system interacts intimately with tumors over the entire process of disease development and progression to metastasis. This complex cross talk between immunity and cancer cells can both inhibit and enhance tumor growth and is now classified as a hallmark of cancer [1]. The balance of these actions between and across the hallmarks determines the eventual outcome, which in the case of clinically overt cancer results from evasion of the destructive elements of the immune response by the tumor. Mechanisms resulting in evasion of immune attack include the selection of tumor variants resistant to immune effectors (sometimes designated "immunoediting") and progressive formation of an immune suppressive environment within the tumor. Although considerable knowledge has been accumulated on how tumors avoid immune destruction, discovering effective cancer therapies still remains a daunting task for the researcher and clinician. In this report, we will briefly present an overview of how tumors evade immune surveillance by focusing on how the immune system reacts to the development of tumors, how certain cancers evade immunity, and what measures can be taken to eradicate cancer. We will address important aspects of tumor and host immune interactions as set out below.

2. Tumors and immunity

The involvement of the host immune system in cancer progression is well established, although greater emphasis has been placed on tumor eradication by immunity than tumor immune potentiation, which may be equally important. These interactions between the immune system and the tumor occur through complex events that usually eventually climax either in successful tumor eradication or immune evasion by the tumor [2].

2.1. Relationship between tumor formation and immune responses

Tumor development and survival is a chaotically governed process involving the interplay between cancer cells, normal stromal cells and host defense mechanisms. Several other factors such as cellular changes due to infection or disease-induced stress may also contribute to tumor growth or tumor suppression. Generally, $CD8^+$ cytotoxic T cells (CTL) and $CD4^+$ helper T (Th)1 cells curb cancer development via mechanisms commonly involving their production of interferon (IFN)-γ and cytotoxins [3] but other factors such as chronic inflammation may override these effects to promote cancer development [4,5]. For example, the risk of overt hepatocellular carcinoma (HCC) appears to be closely linked to the duration of the Hepatitis B and C viral-induced inflammatory state [6–9]. Compelling evidence has also documented, both in animal tumor models and in human cancers, that chronic inflammation plays a critical role in the development of colon and pancreatic cancers [6]. Therefore, when beneficial acute responses fail to resolve tumors/cancer, lingering chronic inflammation can lead to promotion of tumor cell growth and angiogenesis [6,10]. In addition, ongoing activity due to autoimmune disease has also been shown to support development of many cancers including lymphoma [6,10–12].

2.2. Tumor progression and immunity

Vital fundamental discoveries made over the last few decades have unequivocally shown that the immune system plays a critical role in maintaining an equilibrium between immune recognition and tumor development with a dual capacity to both promote and suppress tumor growth. These discoveries collectively support the concept of "immunoediting" and help to explain why tumors can sometimes lie dormant in patients for years before re-emerging, and why tumors grow despite the host having a fully functional immune system [13]. During cancer immune editing, the immune system is able to recognize and destroy the most immunologically vulnerable cancer cells because they present tumor antigens, resulting in their elimination [14]. Nonetheless, due to genetic instability, constant tumor cell division can generate with reduced immunogenicity that can evade immune elimination. This state of production of new tumor cell variants balanced by the elimination has been dubbed "equilibrium", during which the cancer cells continue to divide, accumulating mutational changes by chance or in response to immune-induced inflammation. Thus, a balance between immune control and tumor growth is maintained, giving the appearance of tumor dormancy [15]. However, these processes eventually enable tumors to impair the capacity of the immune system to eradicate them by immune suppressive effects or by loss of target antigen expression. It is at this stage that tumor escape occurs, resulting in overt clinical cancer. Nonetheless, there may also be conditions under which tumor cells are truly dormant, for example by induction of "senescence". In this case, they would be likely to remain dormant permanently, as replicative senescence is generally believed to be irreversible [16].

2.3. Factors that tumors exploit to avoid immune responses

2.3.1. Regulatory cells

Immune suppression in the tumor microenvironment, mediated by $CD4^+CD25^+$ $FoxP3^+$ regulatory T cells (Tregs), or other types of suppressive cells, seems to be a major mechanism of tumor immune escape and can be a crucial hurdle for tumor immunotherapy [17]. A number of studies have shown that tumor-derived Tregs have comparatively higher suppressive activity than naturally occurring Tregs [18,19]. Tregs are drawn into the tumor microenvironment via tumor cell-mediated chemokine production [20,21]. Evidence

also suggests that transforming growth factor (TGF)-β, produced by tumor cells among other cells, aids conversion of $CD4^+$ T cells into suppressive Tregs in situ [22]. Thus, elimination of Tregs by anti-CD25 monoclonal antibodies (mAbs) or by other means may promote tumor rejection. Myeloid cells, especially "myeloid-derived suppressor cells" (MDSCs), modulated dendritic cells (DCs) and alternatively-activated M1 and M2 macrophages create an inflammatory microenvironment and can also act as mediators of tumor initiation, angiogenesis, and metastasis [23,24]. Moreover, a vicious cycle may be instigated in that higher levels of inflammatory mediators confer resistance to apoptosis in MDSCs which would otherwise be subject to downregulation by T cells in complex interaction networks [25]. Thus, $CD11b^+Gr1^+$ MDSCs suppress $CD8^+$ T cell-mediated antitumor immunity [26], one mechanism for which may be TCR ζ-chain downregulation. MDSCs with this phenotype accumulate in, for example, melanoma lesions in a manner intimately linked to the inflammatory milieu, implying that the tumor inflammatory microenvironment supports MDSC recruitment and immunosuppressive activity. Reduction of chronic inflammatory mediators by pharmacological means can reduce the amounts of MDSC and decrease immunosuppression [27]. $CD11b^+F4/80^+$ macrophages having an M2 phenotype produce high levels of TGF-β, IL-10, and vascular endothelial growth factor (VEGF) and promote tumor growth [28–30]. In addition, a number of tumor-derived factors and gangliosides have been reported to alter DC phenotype. These immature, functionally-impaired DCs have lower levels of CD80, CD86, CD40, and high indoleamine 2,3-dioxygenase (IDO) expression that also contributes to suppression of T cell immunity [31].

2.3.2. Defective antigen presentation

It is well established that another fundamental mechanism by which tumors evade immune surveillance is by down-modulating antigen processing machinery affecting the major histocompatibility complex (MHC) I pathway, proteosome subunits latent membrane protein (LMP)2 and LMP7, transporter associated with antigen processing (TAP) protein, and tapasin [32–37]. Thus, expression of tumor antigen is downregulated, which can lead to enhanced tumor incidence and metastasis because cytotoxic T lymphocyte (CTL) can no longer recognize target antigens on the tumor cells [38].

2.3.3. Immune suppressive mediators

As alluded to above, tumors can evade immune surveillance by crippling CTL functionality via production of several immune suppressive cytokines, either by the cancer cells or by the non-cancerous cells present in the tumor microenvironment, especially including immune cells and epithelial cells. TGF-β is a chief mediator of this activity [39]. In addition, tumor necrosis factor (TNF)-α, IL-1, IL-6, colony stimulating factor (CSF)-1, IL-8, IL-10, and type I IFNs can also significantly contribute to cancer growth [40–44]. In addition to immune suppressive cytokines, other factors such as VEGF produced by tumors, inhibit the differentiation of progenitors into DCs [45], thus affecting efficient uptake and antigen presentation. VEGF and IL-10 and TGF-β are also known inhibit maturation of DCs. DCs retaining the immature phenotype are tolerogenic as they do not present antigen in the proper context with appropriate costimulation to T cells [46]. Other factors such as tumor gangliosides and receptor-binding cancer-associated surface antigen (RCAS1) also contribute to tumor progression [47,48]. Additional studies revealed that expression of RCAS1 is associated with apotosis of tumor infiltrating lymphocytes (TILs) [49,50]. Similarly, ganglioside antigens, on cell surface or shed from cells surface, are known to suppress CTL and DC function [51]. Immunosuppressive enzymes such as IDO, arginase, and inhibitor of nuclear factor kappa-B kinase (IKK)2 may also contribute significantly to tumor progression [52–55] via direct actions on tumor cell proliferation or through induction of T cell tolerance/suppression [56–58].

2.3.4. Tolerance and immune deviation

Most tumor cells fail to express costimulatory molecules and can thereby induce anergy or tolerance in T cells by engaging the T cell receptor in the absence of costimulation [59]. Tumors are also known to evade immune attack by shifting the balance from Th1 to Th2 (immune deviation) in a TGF-β- and IL-10-dependent manner [60]. In addition, tumor expression of inhibitory molecules like programmed cell death (PD)-L1/B7H1 has been shown to cause deletion or anergy on tumor reactive cells [61,62]. There is also evidence that down regulation of death receptors prevents death ligand-mediated killing of tumor cells by both CTLs and natural killer (NK) cells [63]. Slavin-Chiorini et al. [64] have demonstrated that CTL studies in conjunction with antibody blocking studies enhanced antitumor effector activity mainly through CD54. There are reports to show that p53 tumor suppressive gene is implicated in the regulation of tumor cell death by CTLs [65]. Thus, factors promoting tolerance and immune deviation are significant contributors to cancer immune evasion.

2.3.5. Apoptosis

A number of studies have shown that cancer cells delete tumor-specific CTLs through apoptosis [66,67]. The different influences governing tumor growth and immune evasion strategies are briefly outlined in Fig. 1.

3. Tumor heterogeneity and immune responses

Cells of the immune system can inhibit tumor growth and progression through the recognition and rejection of malignant cells containing initiation mutations. Though tumors originate from a single transformed cell, due to genetic instability, they commonly become genetically heterogeneous, exhibiting multiple phenotypes both in terms of morphology and physiology. They also display striking heterogeneity in cell surface molecule expression, proliferative and angiogenic potential [68], which is believed to stem from morphological and epigenetic plasticity. Thus, the tumor cells express a wide variety of antigens including some which may be tumor-specific or tumor-associated, differentiation antigens, and lectin-binding sites. These antigens are unevenly distributed on tumor subpopulations and induce different immune responses to the same determinant [69]. This tumor antigenic heterogeneity has a significant effect on genotype, gene expression, cellular morphology, metabolic activity, motility, and behavior such as proliferation rate, antigen expression, drug response and metabolic potential [70–74]. Such heterogeneity has important implications for diagnosis, treatment efficacy, and the identification of potential targets [70,75]. The key aspects of tumor heterogeneity and its subsequent effects on tumor growth are briefly outlined in Fig. 2.

4. Immune system and cancer metastasis

It is fascinating how cancer cells migrate throughout the body from their original location to establish themselves at a new location [76]. How this exodus of tumor cells occurs is only now beginning to be understood. In general, cancer cells detach from the primary tumor and travel through the surrounding tissues and basement membranes, avoid immune destruction and metastasize to distant organs [77,78]. This metastatic process is what is responsible for most cancer deaths [79–82]. Although there are several underlying mechanisms of tumor dissemination and colonization [83], the "progression model" which suggests that a series of mutational events occur either in a subpopulation of primary

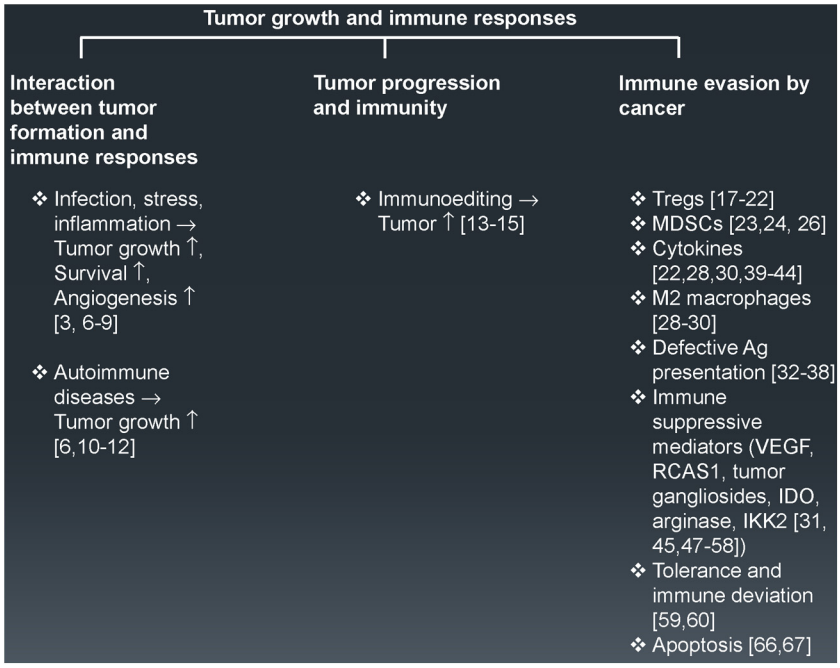

Fig. 1. Tumor growth and immune response. An overview of the different key factors governing tumor formation, progression, and immune evasion. The numbers in parentheses represent the relevant references in support of the statements made.

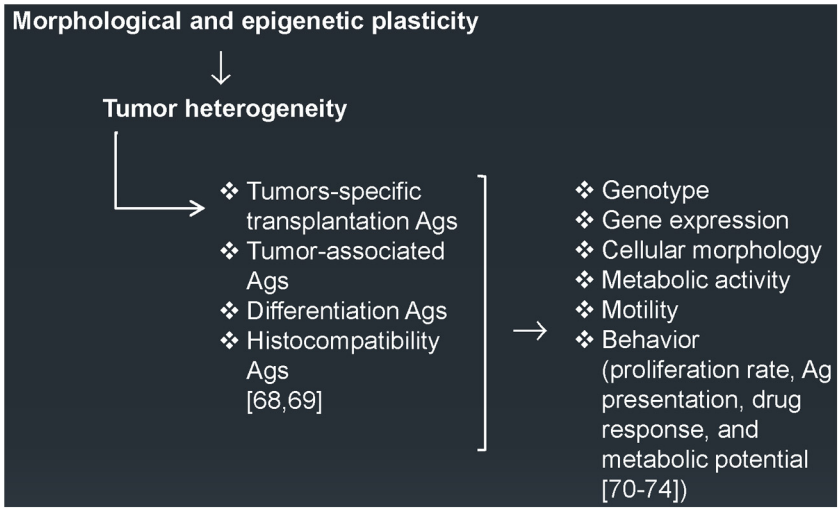

Fig. 2. Tumor heterogeneity and immune response. Shown here are important sequential events leading to tumor heterogeneity and its consequences for the various aspects of the immune response. The numbers in parentheses are the relevant literature cited.

tumor or in disseminated cells, resulting in a small fraction of the cells that acquire full metastatic potential is a well-accepted theory [84]. This view has been corroborated by a number of investigations [85–88]. Among other factors, once again, it is the TGF-β secreted by the cancer cells that makes a major contribution to tumor metastasis [89]. In addition, the vasculature also plays an important role in metastatic seeding at different sites. It has been shown that tumor vasculature hyperstimulated by VEGF often has reduced pericyte coverage and that looser association of such pericytes with the endothelium facilitates metastatic dissemination [90]. In addition, hypoxia in and around tumor vessels also contributes to metastatic dissemination of cancer cells in an hypoxia inducible factor (HIF)-, VEGF-, and inducible nitric oxide synthase (iNOS)-dependent manner [91,92]. Notably, hypoxia promotes the formation of pre-metastatic niches through the production of lysyl oxidase [93]. Hypoxia further conditions pre-metastatic niches by recruiting MDSCs and suppressing NK cell functions [94]. In support of a role for immunosurveillance in controlling tumor metastasis, a recent study revealed that high expression of Irf7-regulated genes in primary human breast tumors is associated with prolonged bone metastasis-free survival [95]. A brief overview of the events promoting tumor metastasis and the involvement of immune responses is provided in Fig. 3.

5. Conventional cancer therapy and the immune system

Although a variety of agents have been screened for their antitumor effects and some have been approved for the treatment of cancer patients, chemotherapy, radiation therapy, and surgery remain the mainstays of standard cancer therapeutic strategies. A downside to these therapies is their ability to cause a transient immune suppression which in turn increases the risk of infection

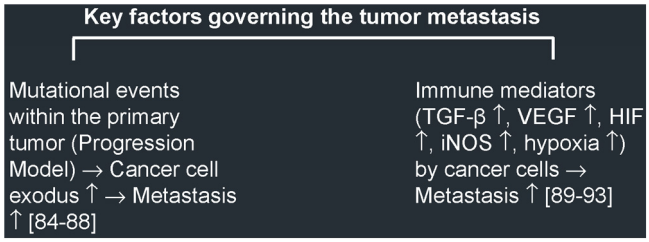

Fig. 3. Immune system and tumor metastasis. Depicted here are the key sequential events based on the "Progression Model" leading to cancer cells exodus from the primary location and subsequent establishment at a distant location and the possible role of various immune modulators that aid this process. The numbers in parentheses are the relevant literature cited.

and is also likely to decrease the immune system's ability to inhibit further development of cancer. For example, standard chemotherapy decreases the host's native immune competent cells including T cell populations. However, this transient loss of immune activity has been shown to return 2–3 weeks after chemotherapy [96]. In addition, patients are at risk for viral, fungal, and parasitic infections, and when chemotherapy continues long-term, these patients may permanently lose their cell-mediated immune function [97]. Nevertheless, recent evidence suggests that some chemotherapeutic drugs rely on the induction of anticancer immune responses for therapeutic activity by inducing a type of tumor cell death that is "immunogenic" [98]. The immune-stimulating property of some chemotherapeutic drugs, such as anthracyclines and oxaliplatin, requires preapoptotic translocation of calreticulin (CRT) on the tumor cell surface, post-apoptotic release of the chromatin-binding protein high mobility group B1 (HMGB1), and extracellular release of ATP. Interestingly, phosphohydrolysis of extracellular ATP by ecto-nucleotidases (i.e. CD39 and CD73) acts as a counterbalancing process to chemotherapy-induced immunogenic cell death [99]. Other chemotherapies appear to alter the phenotype of surviving tumor cells making them better targets for immune cells [100,101]. Radiation therapy has also been shown to impact cell-mediated immunity. On the one hand, radiotherapy can suppress antitumor immunity, presumably due to the high radiosensitivity of lymphocytes [102]. There are also reports to suggest that high doses of total lymphocyte irradiation increase T suppressor cell activity and loss of the ability to recognize autoantigens [103]. On the other hand, low doses of radiation result in the generation of reactive oxygen species (ROS) leading to the activation of intracellular signaling pathways that induce T cell proliferation and differentiation [104,105]. Radiation has been shown to alter the phenotype of cells resulting in increased expression of death receptors [106], chemokines [107], adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and MHC-I [108], and costimulatory molecules [109,110] on tumor cells. Moreover, tumor cells surviving radiation have also been shown to be more sensitive to cytolysis by T cells [108,111]. Radiation has also been shown to result in the increased expression of proinflammatory cytokines such as TNF-α and IL-1β that activate antigen presenting cells (APCs) [112,113]. Radiotherapy can thus trigger significant antitumor immune responses, related to the well-known abscopal effect, that is, the regression of metastases upon irradiation of the primary tumor, despite the metastasis being outside of the radiation field [114,115]. It is indeed generally accepted that radiotherapy depends to some degree on the activation of antitumor immune responses for its efficacy [116].

Finally, trauma due to surgical resection of tumors has profound effects on the immune system because of increased production of proinflammatory cytokines and other immune modulators like IL-6, C-reactive protein (CRP), TNF-α, IL-1β etc. [117,118]. Also, decreased delayed-type hypersensitivity (DTH) reactions, due to surgery, pose a risk for infection [119]. To overcome surgery-mediated transient immune suppression, the introduction of laparoscopic methods may reduce such suppression and thus decrease tumor growth [120]. Conversely, surgery has also been shown to induce danger/damage that enhances antitumor efficacy and reduces metastasis [121]. There is evidence that tumor growth control can actually potentiate rather than curb metastasis, again illustrating the general finding that very similar pathways can have either inhibitory or facilitatory activity on tumor growth. A case in point is that chemotherapy, radiotherapy, and biological/targeted therapies can promote tumor metastasis via the so-called tumor bed effect [122,123]. Currently, both primary and metastatic cancers are treated by similar approaches where radiation is often the mainstay choice of therapy [124]. Surgery is rarely performed on metastatic lesions. Thus, these standard anticancer therapies, although they can be effective alone, will have enhanced therapeutic efficacy when combined with agents that boost the weakened immune system, if we are able to learn how to avoid potential tumor growth stimulatory effects.

6. Strategies for cancer immunotherapy

Tumor cells have developed multiple mechanisms for evading immune surveillance. Current treatments for cancer include chemotherapy, radiation therapy, immunotherapy, targeted therapy, and surgery which all have limitations and detrimental side effects [125]. Recent investigations have identified several classes of anticancer agents that are targeted, efficient, and have less adverse side effects. An increasing number of clinical trials are currently underway to stimulate the immune system to combat cancer. Important among these include vaccination with peptides [126], vaccination with DCs [127], vaccination with viral-based vectors [128,129] and immunotherapy with autoreactive effector cells [130]. Interestingly, there are also studies to show that administration of bacteria can increase tumor immunogenicity [131]. For example, treatment with *Clostridium novyi-NT* is shown to attract many inflammatory cells such as neutrophils, monocytes, and lymphocytes that can kill tumor cells [132]. Especially important will be the extended use of immunomodulatory antibodies which have recently yielded such dramatic effects in highly refractory tumors (see below). Many clinical trials of all these approaches, and especially combinations thereof, are currently ongoing and hold great promise.

6.1. Cellular targets

In addition to the obvious targets, the tumor cells themselves, some of the several regulatory cells including regulatory B cells or their products implicated in tumor escape are currently being targeted to promote tumor rejection. For example, IDO is an immunoregulatory enzyme which suppresses T-cell immunity but can be targeted in the tumor microenvironment by IDO-reactive $CD8^+$ T cells. It was shown that IDO-specific T cells could enhance tumor immunity by eliminating IDO^+ suppressive cells and changing the regulatory microenvironment [133].

As mentioned above, important among suppressive cells are Tregs, which are powerful inhibitors of antitumor immunity and an impediment to successful immunotherapy [22]. In support of this, inhibition of Tregs by monoclonal antibodies has been shown to decrease tumor development [134,135]. In addition, other regulatory cell populations such as MDSCs which accumulate in spleen, blood, tumors, and bone marrow of tumor-bearing mice and cancer patients [136,137] have been considered as important targets for therapeutic intervention [138]. MDSCs secrete IL-10 and TGF-β and enhance angiogenesis and metastasis by inducing Treg production

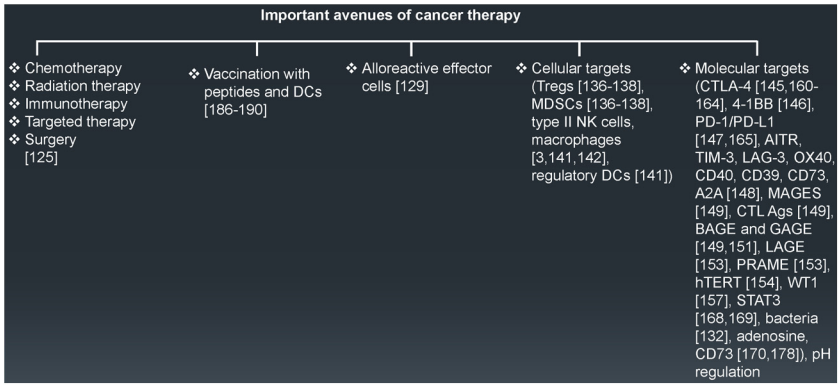

Fig. 4. Cancer therapy. A brief overview of the various available therapeutic options for cancer. A few of these have entered clinical trials some of which have been approved for treatment of specific types of cancers. The numbers in parentheses are the literature cited.

[23,139]. Increasing evidence suggests that the M2 macrophages promote tumor growth and metastasis, and strategies to target these cells are also being developed [140]. Type II NK cells are also known to contribute to tumor development via their secretion of characteristic cytokines. About 60% of murine NK cells express Ly49 and CD94/NKGA inhibitory receptors, the blockade of which augments antitumor activity [3,141,142]. In addition, regulatory DCs (expressing CD25, PD-1, PD-L1, IL-10, TGF-β, kynurenine, IDO, cyclooxygenase (Cox)-2, and arginase (Arg)-1) play a significant role in tumor development [143] and therapies directed against these cells have also been investigated [144].

6.2. Molecular targets

In addition to cellular targets, several molecular targets including cytotoxic T-lymphocyte-associated protein 4 (CTLA)-4 [145], 4-1BB [146], PD1/PD-L1 [147], and activation-inducible TNFR (AITR), T cell immunoglobulin mucin (TIM)-3, Lymphocyte-activation gene (LAG)-3, OX40, CD40, CD39, CD73, A2A [148] and cancer antigens of different types, such as melanoma-associated antigen (MAGE) family members and NY-ESO-1, human telomerase reverse transcriptase (hTERT) and Wilm's tumor (WT)1 have been considered as important antitumor targets [149]. In melanoma, MAGE, B melanoma antigen (BAGE), and G antigen (GAGE) family antigens have been targeted for therapeutic vaccination [150,151]. The L antigen family member (LAGE)-1 gene closely related to NY-ESO-1 may also be an appropriate target [152]. The preferentially expressed antigen in melanoma (PRAME) is also a melanoma-associated antigen recognized by CTL [153]. Human telomerase activity and hTERT expression are detected in a majority (>90%) of human cancer cells [154]. To increase potential efficacy, hTERT promoters have been utilized for cancer gene therapy [155,156]. Wilms' tumor gene WT1 is expressed in several different cancers and illustrates the general principle that tumor escape from immunity as a result of downregulation of target antigen expression is unlikely to occur when the gene product has an essential role in tumorigenesis [157]. A number of studies suggest that the WT1 protein is a promising target for cancer immunotherapy [158,159].

Targeting cell surface molecules other than tumor antigen targets for antibody-based therapeutic intervention of cancer is becoming an important available option for the clinician. Of these, so far only anti-CTLA-4 (ipilimumab) has been approved for clinical use in the USA, Canada, United Kingdom, and European Union [160,161], but PD1 and PD-L1-specific antibodies will surely be licensed very soon. Ipilimumab is currently in phase III clinical trials for the treatment of prostate cancer [162] and for cancers of the lung [163] and kidney [164] as well as melanoma. In one recent trial, administration of the anti-PD-1 antibody nivolumab showed unprecedented therapeutic objective responses in 18–28% of patients with advanced non-small-cell lung carcinoma, melanoma, and renal cell carcinoma [165]. While CTLA-4 and PD-1/PD-L1 blocking Abs have shown efficacy by blocking inhibitory signals to responding T cells, agonist Ab to OX40 and 4-1BB propel T-cell immunity by sending stimulatory signals. Several clinical trials are underway investigating their therapeutic properties [166]. Targeting Tregs by anti-CD25 antibodies showed inhibition of neuroblastoma tumors in mice [167]. There are also data demonstrating that activation of the signal transducer and activator of transcription (STAT)3 signaling pathway supports tumor development by inducing accumulations of MDSCs and inhibition of DC differentiation [168]; hence its inactivation leads to inhibition of cancer development by a DC- and Treg-dependent mechanism [169].

Targeting immunosuppression by soluble mediators is another attractive approach for cancer immunotherapy. A plethora of immunosuppressive factors has been associated with tumorigenesis, including TGF-β, IDO, arginase, prostaglandin-E2 (PGE2) and extracellular adenosine. Recent studies have shown that extracellular adenosine, essentially produced by the ecto-nucleotidase CD73, plays an important role in tumor development and metastasis [170,171,99,172–174]. These findings are corroborated by studies using mice deficient in CD73 or the high affinity A2A adenosine receptor [173–176]. These animals exhibit increased CTL-mediated antitumor immunity [177]. Inhibition of pH regulatory molecules and certain heat shock proteins limit cancer cell-mediated immune suppression. Targeting these molecules could simultaneously counteract the metastatic potential of cancer cells and restore antitumor immune surveillance. The above-mentioned cancer therapeutic targets and their beneficial effects are briefly outlined in Fig. 4.

6.3. Vaccination therapy (peptide, DNA, and DC)

Several studies demonstrated the efficacy of therapeutic viral vaccines [178]. Peptide vaccines derived from tumor-associated antigens (TAA) may significantly contribute to immune enhancement or tumor regression. Many TAAs have been identified and molecularly characterized. However, so far only a limited number of TAA peptides, mostly recognized by $CD8^+$ T cells in melanoma patients, have been clinically tested. In some clinical trials, partial or complete tumor regression was observed in 10–30% of patients [179]. Peptides such as melan-A/MART-$1_{27–35}$ and gp100, which readily activate specific T cells in vitro [180] and in vivo [181,182], show limited immunogenicity when used as vaccines for cancer patients [183,184]. Alternatively, DNA cancer vaccines may also represent an effective approach [185]. Such vaccines, although

Table 1
Cross-validation of potential targets that may enhance anticancer immune responses to other cancer hallmarks.

Potential targets for immune-modulation Other cancer hallmarks	(Promote/enhance) Th1 responses via increase number of NK cells	(Promote/enhance) γδ T cell activities	(Promote/activate) macrophages	(Inhibit) Treg lymphocytes	(Promote/enhance) NK cell activity	(Promote/induce) IL-12
Genomic Instability	0	0	0	0	0	0
Sustained Proliferative Signaling	0	0	– [206]	0	0	0
Tumor-Promoting Inflammation	– [207,208]	– [209]	+ [210]	+/– [211–213]	+ [214,215]	+ [216,217]
Evasion of Anti-growth Signaling	0	+ [218]	0	+ [219]	+ [220]	0
Resistance to Apoptosis	0	0	+ [221]	+ [222]	0	– [223]
Replicative Immortality	+ [224]	0	0	0	+ [224]	0
Dysregulated Metabolism	0	0	0	0	0	0
Angiogenesis	+ [225–228]	– [229–232]	+/– [233]	+ [234]	+ [225]	+ [235]
Tissue Invasion and Metastasis	+ [236]	+ [237]	– [238]	+ [239]	+ [240]	+ [241]
Tumor Microenvironment	+ [242]	+ [243]	+/– [244–246]	+ [247]	+ [248]	+ [249]

The symbols presented above represent as follows: +, complementary; –, contrary; +/–, controversial; 0, no known relationship.

having many variants, utilize the same basic principle involving the isolation of DNA from cancer cells and subsequent transfer, most commonly via the intramuscular route, into tumor-bearing individuals. It has been shown that the administration of DNA vaccines via the intramuscular route effectively primes both the adaptive as well as innate arms of the immune system [186]. While naked DNA is quite sturdy and stable at different temperatures, and retains immune activating abilities, plasmid DNA vaccines are less immunogenic [187]. Refinements to the existing DNA vaccination strategies are showing promising results. Among these, the use of an electrical pulse, commonly called electropermeabilization, electroporation or electrotransfer [188] is currently used in preclinical protocols and has been shown to have strong immune activating abilities [189]. Recent therapeutic studies involving DNA vaccines have shown promise, for example, for the treatment of glioma. Incorporation of cancer cell DNA into healthy immune competent cells and subsequent transfer into tumor-bearing mice showed decreased tumor burden and increased survival of both spontaneous as well as established tumors. Further analysis revealed that DNA vaccine-mediated antitumor activity in the above case involved over-production of IFN-γ and participation of T and NK/lymphokine activated killer (LAK) cells [190,191]. Adoptive transfer of peptide-pulsed DC [192] is also an option. In all cases, it takes a long time to develop such therapies and the newest results now being published suggest that peptide vaccinations with selected multi-peptide vaccines, combined with immunomodulatory agents, may indeed achieve impressive results. Thus, a phase II multi-center granulocyte macrophage colony stimulating factor (GM-CSF)-adjuvanted multipeptide vaccine for refractory late-stage renal cancer patients has yielded unprecedented 3-year survival benefits especially in those patients able to respond to more than one peptide, provided they had received a pulse of low-dose cyclophosphamide prior to vaccination. It was proposed that the cyclophosphamide reduced the Tregs in the patients, for which some evidence was presented [193,194]. The United States FDA has approved the use of sipuleucel-T, a cellular product made of blood APCs cultured with a fusion protein of prostatic acid phosphatase (PAP) and GM-CSF [195]. Efficacy studies revealed a 4-month extended median survival in patients with prostate cancer [196].

6.4. Cross validation

A cross-validation team conducted a peer-reviewed literature review of the targets and approaches listed in Tables 1 and 2, and these evidences of cross- hallmark activity are referenced accordingly. This process led to the creation of two unique matrices, whereby a series of candidate compounds and molecular/cellular targets were identified for having immune system evasion mechanistic relevance. The complete mapping of these candidate targets and actions was screened for known complementary, contrary or combinations of actions across all cancer hallmarks described in Hanahan and Weinberg [1]. For example, inhibiting or stimulating an immune evasion target may or may not have been examined in other hallmark mechanism. Each potential target-hallmark or approach-hallmark interaction was considered to have either a pro- or anti-chemotherapeutic effect. There were also mixed indications or many instances where no known relationship existed. In summary, the findings gathered in this effort varied considerably by each hallmark. These tables provide information that can serve as a starting point for future basic and translational research on phytochemical combinations for immune evasion targets and for chemotherapeutic applications.

6.5. Phytochemicals

Besides these conventional immunotherapeutic approaches, several phytochemicals have been shown to facilitate tumor regression. Prominent among these are isothiocyanate, curcumin, genistein, epigallocatechin gallate, lycopene, resveratrol, and glucosinolates. Some have entered clinical trials and are beginning to yield encouraging results [197]. There are other natural, plant-derived or nutrient substances, including flavonoids, omega-3 fatty acids, zinc, and vitamin C, that are purported to strengthen the immune system [198–201], yet their roles as nutrients to resolve inflammation or assist in suppressing tumorigenesis are not clear

Table 2
Cross-validation of phytochemicals that may enhance anticancer immune responses to other cancer hallmarks.

Approach Other cancer hallmarks	*Ganoderma lucidum* (polysaccharide fraction)	*Trametes versicolor* (protein-bound polysaccharide-k)	*Astragalus membranaceus* (polysaccharide fraction)	*Lentinus edodes* (polysaccharide L-II, lentinan)	Astaxan-thin	Polyphenol-resveratrol analog HS-1793
Genomic Instability	0	0	0	0	0	0
Sustained Proliferative Signaling	+ [250]	0	0	+ [251,252]	+ [253–255]	0
Tumor-Promoting Inflammation	+ [256,257]	0	+ [258]	+ [259,260]	+ [261,254]	0
Evasion of Anti-growth Signaling	+ [262,263]	+ [264]	+ [265]	+ [266]	+ [267]	0
Resistance to Apoptosis	+ [268]	0	+ [269]	+ [270]	+ [271]	+ [272]
Replicative Immortality	+ [273]	0	0	0	0	0
Dysregulated Metabolism	0	0	0	0	0	0
Angiogenesis	+ [274,275]	0	– [276]	+ [277]	0	+ [278]
Tissue Invasion and Metastasis	+ [279]	0	+ [280]	+ [281]	+ [282]	+ [283,284]
Tumor Microenvironment	+ [285]	+ [286]	+ [287]	+ [288,259]	+ [289]	+ [290]

The symbols presented above represent as follows: +, complementary; –, contrary; +/–, controversial; 0, no known relationship.

from human studies. Too often, these alternative or complementary agents are not evaluated with standard sets of clinical outcomes that are needed to advance our understanding of how nutritional components and phytochemicals may enhance tumoricidal immunity or inhibit tumor immune evasion mechanisms described above. While some dietary supplements have been shown to enhance the ability of NK cells to identify and destroy dysfunctional cells, such as infected or cancerous cells [202,203], these studies have not comprehensively assessed increased T cell production of cytokines such as IFN and TNF, or reduced secretion of immune suppressive factors from tumors. The emerging evidence for dietary supplement doses that far exceed physiological nutrient exposures suggests that some bioactive food components can even be hazardous [204], and are now largely discouraged for consumption during cancer treatment [205]. Table 2 summarizes potential targets and approaches that may enhance anticancer immune responses.

6.6. Adoptive T cell therapy

Autoreactive T cells are potentially tolerant to self-tissues, due to diverse mechanisms in the periphery [291]. Adoptive T cell therapy involves the isolation and expansion of autologous T cells specific for tumor antigen and their subsequent re-infusion into the patient. Tumor-reactive T cells such as tumor-infiltrating lymphocytes (TIL) combined with IL-2 showed potentially interesting results already in the 1980s, but objective response rate was low in metastatic melanoma patients [292,293]. In 2002, Rosenberg and colleagues [294,295] introduced a lymphodepletion regimen before administering adoptive T cell therapy, resulting in elimination of the immune-suppressive cells, increase of key cytokines for T cells such as IL-7 and IL-15, and creation of a space for T-cell proliferation. When lymphopenia is induced, remaining peripheral T cells initiate homeostatic proliferation to reconstitute the lost T cells, and the tolerant autoreactive $CD8^+$ T cells acquire an opportunity to proliferate and become functional [296,297]. This may be one mechanism by which self-tumor Ag-specific T cells are increased in cancer patients after chemo- or radio-therapy [298,299]. This lymphodepletion treatment markedly improved the clinical efficacy of adoptive cell therapy using TILs, with an objective response in ~70% of melanoma patients and complete durable regressions were found in ~50% [300]. Rosenberg et al. [301] have demonstrated objective cancer regression in patients with metstatic melanoma. Though good clinical outcome has been observed by Rosenberg et al. [301], generating T cells for adoptive T cell therapy is a cumbersome process. There have been many efforts to develop a practical protocol to produce autologous self-tumor Ag-specific T cells, but most of them are still complicated and time-consuming because self-tumor Ag-reactive T cells exist as a minor population. Recently, however, an efficient method has been developed to produce tumor-specific $CD8^+$ T cells from ~50 ml of peripheral blood mononuclear cells based upon the unique property of 4-1BB (CD137) to be selectively expressed on antigen-engaged T cells [302]. Clinical trials with various solid tumors are underway to test the safety and efficacy of the CTLs thus generated. To overcome major hurdles in the preparation of autologous self-tumor Ag-specific T cells, gene-modified T cells like TCR or chimeric Ag receptor (CAR)-modified T cells were developed [303]. Currently, these gene-modified T cells are being tested for safety and efficacy in the clinic and clinical results will tell us whether adoptive T cell therapy could provide a new opportunity for cancer patients who failed to respond to standard therapies. However, the many mechanisms of tumor escape discussed above (tumor suppression, downregulation of target antigens etc.) need to be considered and counteracted in combination with these modalities.

7. Conclusions

Here we wish to emphasize that immunotherapeutic approaches may advance via the inclusion of holistic or integrative therapy of cancer. Especially, we want to emphasize that dual approaches which seek to (1) eliminate immune suppressing factors, and (2) enhance tumor-killing activities will be necessary to achieve successful cancer therapy. In view of the immune suppressive factors present in the tumor microenvironment from the very earliest stages of tumor formation, nontoxic agents that control or eliminate the immunosuppressive factors can be used for therapy of cancer or also utilized as cancer control and chemopreventive agents. A tumor-killing agent requires us to aim at cross-clonal common targets, which overcome the intra- and inter-tumoral heterogeneity.

An in-depth understanding of how tumors evade immune surveillance will help develop effective therapeutic strategies that can be used for the benefit of cancer patients.

Disclosure

BSK: patents for methods regarding anti-CD137 and adoptive CTL therapeutics. RLW: patent for use of IGFBP-3 as anticancer therapy; FDA murine work for Arrium Corporation for Omega 3 fatty acid anti-adhesion product; Consultant for Ethicon Endosurgery and Olympus Corporation regarding surgical staplers and advanced endoscopic polypectomy methods. TL: worked with Medtronic in developing a passive immunotherapeutic strategy for treatment of Alzheimer's disease. WKD: patent for methods and compositions regarding Th-1 dendritic cells; Consultant of Gerson Lehrman Group; Medical advisor of Texans for stem cell research.

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