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REVIEW

Modulating inflammation for cancer therapy

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A link between chronic inflammation and development of tumors is well established. Moreover, it has become evident that tumorigenesis is not a cell autonomous disease, and an inflammatory microenvironment is a prerequisite of basically all tumors, including those that emerge in the absence of overt inflammation. This knowledge has led to the development of anti-inflammatory concepts to treat and prevent cancer. In contrast, immunotherapies, in particular checkpoint inhibitors, representing the most significant progress in the therapy of several malignancies depend on the presence of a pro-inflammatory "hot" environment. Here, we discuss pro- and anti-inflammatory concepts for the treatment of cancer.

Introduction

The clinical connection of inflammation and cancer reaches back to the late 19th century, when Rudolf Virchow postulated sites of chronic inflammation as origin of neoplastic malignancies after he had noticed the presence of leukocyte infiltrates in cancerous tissues (Balkwill and Mantovani, 2001). Nearly at the same time, the German physician Wilhelm Busch employed an inflammatory immune response as a treatment for cancer, partially curing a patient suffering from soft-tissue sarcoma of the neck with an erysipelas infection. He was followed by the American bone surgeon William Coley, who used a mixture of heat-killed bacteria, later called "Coley's toxins," to successfully treat sarcomas (Coley, 1893), making him the father of immunotherapy. These historic examples depict vividly what we know today: while inflammation can promote carcinogenesis, it may as well be used for tumor therapy. Initially, the underlying mechanisms were completely unknown, and the original forms of pro-inflammatory therapy bore severe side effects. During the following century, radiation therapy and chemotherapy emerged, and because cancer was increasingly considered a cell-intrinsic genetic disease, new treatment modalities focused on killing tumor cells directly, while "inflammatory" therapies were neglected (Fig. 1; Faguet, 2015). This view has changed again over the last two decades. It became clear that cancer resembles complex organs, consisting of tumor cells and host-derived stroma, which is composed of resident as well as recruited cells (Hanahan, 2014; Weinberg, 2014). Thus, it has become unequivocally evident that tumor development depends on the intricate reciprocal interplay of mutagenized tumor cells with their local and distant microenvironment (Balkwill and Mantovani, 2012; Quail and Joyce, 2013).

Chronic inflammation shapes the tumor microenvironment, affecting cell plasticity through epithelial–mesenchymal transition, dedifferentiation, polarization of immune cells, ROS, cytokines, epigenetic mechanisms, miRNAs, and complex regulatory cascades in tumor and stromal cells (Varga and Greten, 2017). Curiously, not all inflammatory diseases or persistent infections are correlated to increased cancer risk, and although allergic diseases also embody a state of constant or recurring inflammation, this type of inflammation may be even inversely correlated with cancer progression (Turner et al., 2006; Kozłowska et al., 2016). Thus, an important open question remains why certain organs with ongoing inflammation, such as rheumatoid arthritis or myocarditis, are not susceptible to tumor induction. The formation of inflammation-induced reactive oxygen or nitrogen species, produced by activated myeloid cells, that can directly mediate DNA damage and chromosomal instability in neighboring cells (Canli et al., 2017) cannot account for this phenomenon, considering that this would occur in all types of organs. Interestingly, organs with high tumor incidence in the context of chronic inflammation are those that usually interact closely with microbial products or directly with microbiota, pointing to the role of the microenvironment, potentially carcinogenic microbe-derived metabolites, or host immune responses in cancer initiation.

In addition to cytotoxic therapies that induce a pro-inflammatory response (Grivennikov et al., 2010), surgery can act in an immunomodulating way, contributing to the outgrowth of metastases even when surgery is performed years after removal of a primary tumor. Here, the concept of pre-metastatic niches and circulating tumor cells (CTCs) is considered to play an important role, and dormant CTCs seem to be essential for the formation of metastases upon surgery (Murthy

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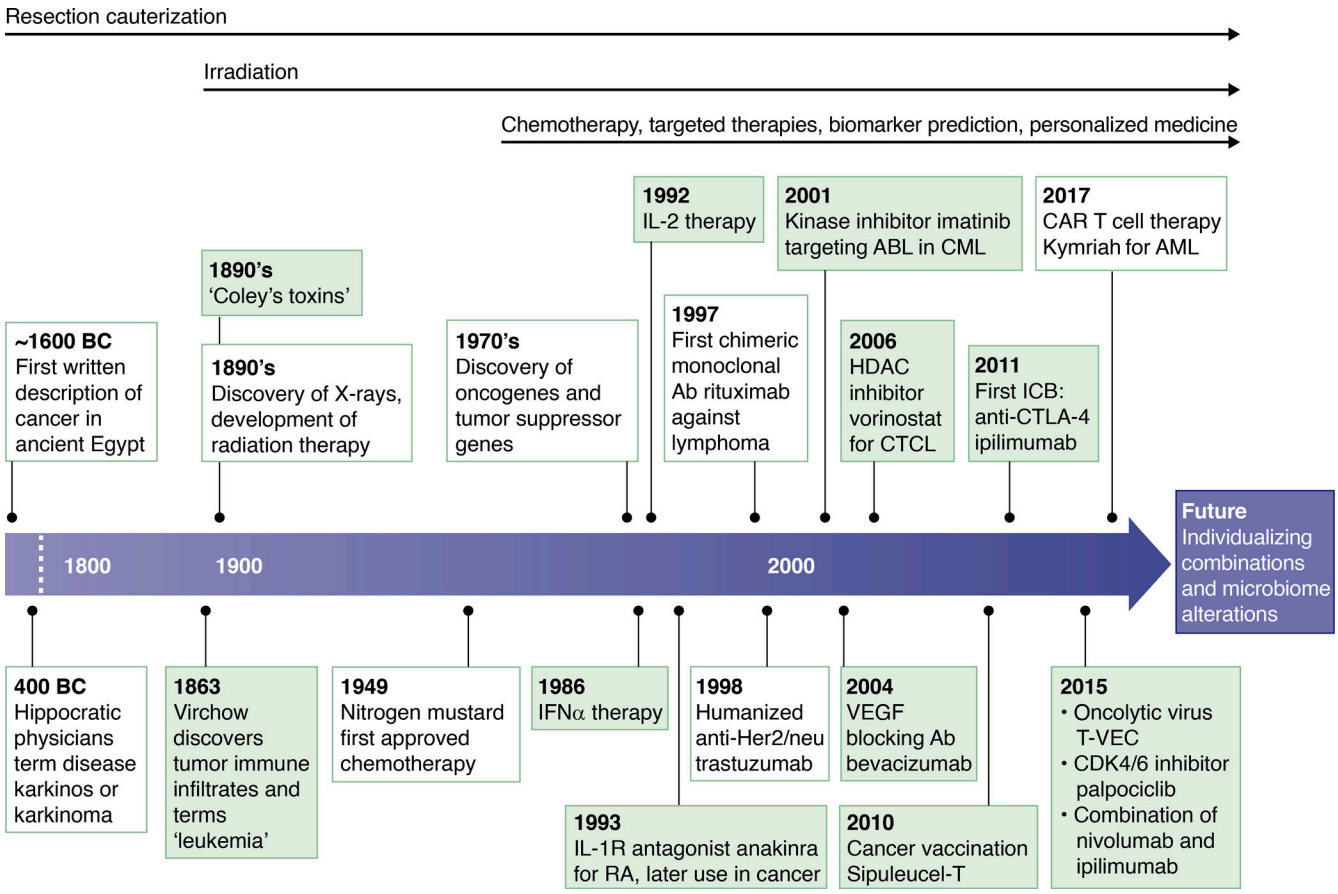

Figure 1. **Time course from first documented cancer cases to modern therapy.** Ab, antibody; ABL, Abelson murine leukemia viral oncogene homologue 1; AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CML, chronic myeloid leukemia; CTCL, cutaneous T cell lymphoma; RA, rheumatoid arthritis; T-VEC, talimogene laherparepvec; VEGF, vascular endothelial growth factor.

et al., 1989; Demicheli et al., 2008; Tohme et al., 2017; Castaño et al., 2018). One reason for this is the loss of tumor-derived angiogenesis inhibitors after removal of the primary tumor; others may comprise shedding of mediators that promote wound healing and neoangiogenesis to promote the outgrowth of formerly dormant CTC or micrometastases (Hofer et al., 1998; Demicheli et al., 2008). Through the surgery itself, inflammatory cells and cytokines are released into the blood, helping to create premetastatic niches, where CTCs can settle and prosper (Lim et al., 2013; Peinado et al., 2017). These findings already give some insight into the complex nature of inflammatory processes connected to tumor development, progression, and classical treatment.

Although the importance of the tumor microenvironment for tumor progression is undisputed, most current cytotoxic treatments or recently developed small-molecule inhibitors target specific signaling pathways within tumor cells. Undoubtedly, several of these promising new compounds have proven extremely successful (McCubrey et al., 2012; Hengel et al., 2017; Whittaker et al., 2017). However, many patients that initially benefit from these very effective compounds rapidly develop therapy resistance, leading to even more aggressive tumors. The clinical approval of antiangiogenic tumor therapy nearly 15 yr ago marked a breakthrough paradigm change as the first clinically effective antistroma therapy (Ferrara et al., 2004). However, the efficacy of antiangiogenic therapies continues to be limited, and the mechanism of action (vascular regression vs. vascular normalization) is poorly understood (Klement et al., 2000; Jain, 2001). Today, a variety of molecular pathways and stroma cells are targeted ranging from epigenetic factors, hypoxia, neoangiogenesis, and cytokines over tumor and tumor-associated cells to the microbiota of the gut. Although certain anti-inflammatory therapies show very promising results in various malignancies, the real breakthrough of the last years was the development and clinical approval of antibody-based immunotherapies targeting CTLA-4 or PD-1/PD-L1. While immune checkpoint blockade (ICB) is clinically very effective, leading to durable treatment responses in a few tumor entities, the majority of tumor patients do not respond for a wide range of potential reasons (Chen and Mellman, 2017). So-called infiltrated–inflamed tumors are considered "hot" tumors that contain a high number of infiltrating cytotoxic lymphocytes expressing PD-1 and that usually respond well to ICB. In contrast, infiltration-excluded tumors are characterized by accumulation of CTLs along the border of the tumor mass and a lack of CTL infiltration into the tumor core. These tumors are generally considered "cold" tumors with poor sensitivity to ICB (Fig. 2; Gajewski, 2015). Several promising strategies have been

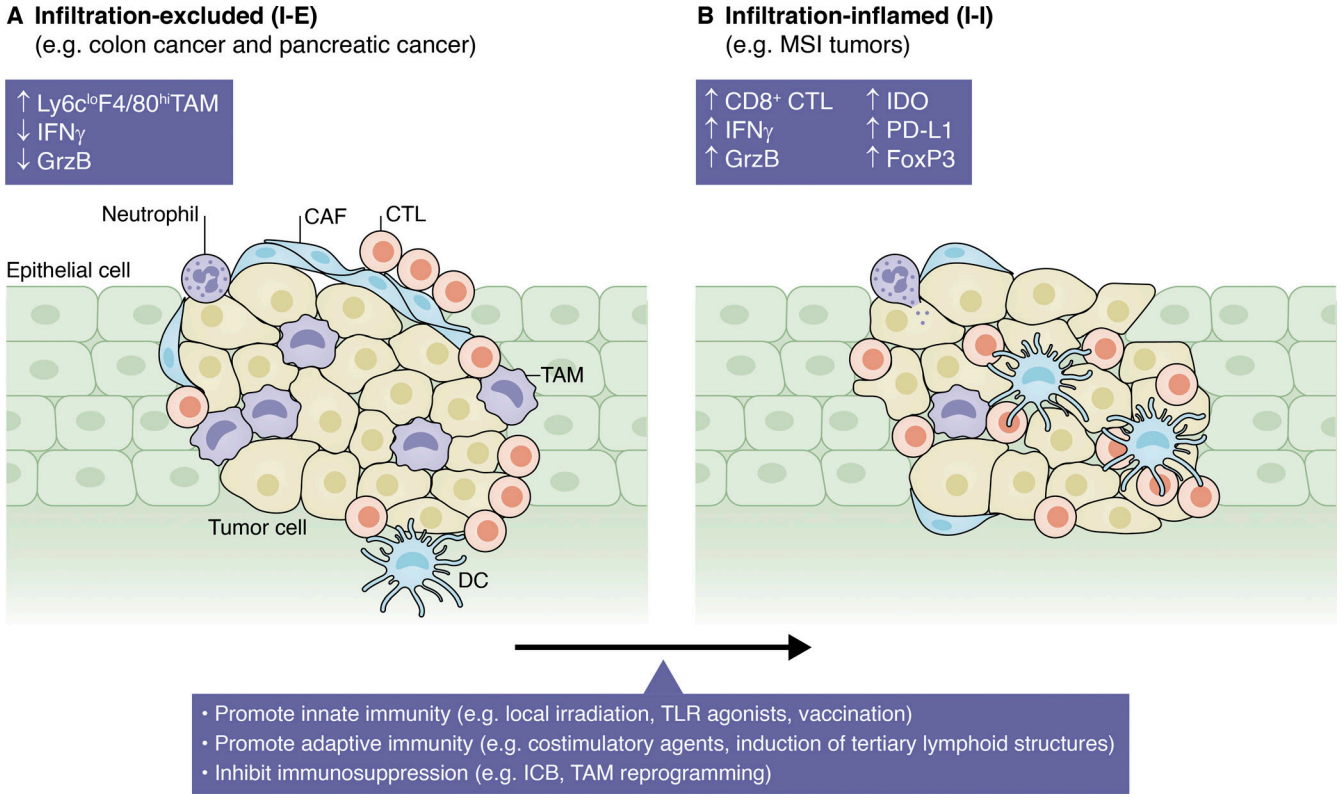

Figure 2. **Tumor immune statuses.** Infiltration-excluded tumors (left) accumulate cytotoxic T lymphocytes (CTLs) around their margins, where they interact with Ly6c^{lo}F4/80^{hi} TAMs or are impeded by cancer-associated fibroblasts (CAFs). Infiltration-inflamed tumors (right) show activated PD1^{+} CTLs in their core that express IFNγ and granzyme B (GrzB). They may form tertiary lymphoid structures and are generally associated with good prognosis and response to ICB. Therefore, therapies aim to promote this state. DC, dendritic cell; IDO, indoleamine (2,3)-dioxygenase; MSI, microsatellite instability.

suggested to change a cold into a hot tumor, which can render these tumors sensitive to ICB (Table 1), yet there is certainly an unmet need to unravel further mechanisms that would allow such conversion. Moreover, it remains one of the biggest challenges to identify biomarkers that will allow assessment of individual patients' ICB sensitivity or that will help to decide about the most promising combinatorial approach for an individual patient.

Inhibiting inflammation

Because tumors and their constant smoldering inflammation resemble and are promoted by chronic inflammatory diseases, it seems logical to employ anti-inflammatory drugs. Aspirin is one of the oldest anti-inflammatory drugs. Its anticoagulant properties were noted in the 1950s, and its metastasis-reducing capacity was tested in animal models in the 1970s, when its suppressive effect on prostaglandin production had been discovered (Henschke et al., 1977). More evidence of aspirin or other nonsteroidal anti-inflammatory drugs, targeting cyclooxygenases, came from the observation that taking these drugs as pain killers for cancer-elicited pain or therapy side effects had an overall survival benefit. Today, several clinical trials are still ongoing, showing modest results in different kinds of cancer, such as breast, prostate, and especially colon, although the positive effect on cardiovascular-caused death, which could influence these results, should be kept in mind (Jacobs et al., 2014; Chen and Holmes, 2017; Frouws et al., 2017).

Neutralizing pro-inflammatory cytokines or blocking their receptors represents a more direct targeted approach. In 1993, the first IL-1 receptor antagonist was approved for the treatment of rheumatoid arthritis (anakinra from Amgen). Since then, its application has been extended to a variety of other diseases. Today, several mediators blocking or neutralizing the IL-1 pathway (e.g., antibodies, soluble receptors, and small-molecule inhibitors) are in use or being tested for cancer treatment (Dinarello et al., 2012; Molgora et al., 2018). In a recently completed trial, the IL-1β blocking antibody canakinumab was shown to ameliorate inflammation in patients suffering from atherosclerosis (Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CANTOS). Interestingly, a secondary analysis of the obtained data including a 5-yr follow-up revealed that canakinumab-receiving patients showed a significant dose–dependent reduction in lung cancer incidence and mortality compared with placebo-treated patients (Ridker et al., 2017). Similar positive results of blocking inflammatory IL-1 pathways were observed in different murine models of breast cancer in both primary tumors and metastases formation (Guo et al., 2016; Dagenais et al., 2017). In contrast, a recent preclinical study could demonstrate an IL-1β–dependent suppression of metastasis-initiating cancer cells, which was lost upon its neutralization. This was underscored by database analysis that showed a beneficial effect of high levels of IL-1β on overall survival of breast cancer patients with lymph node metastases

Table 1. **Mechanisms to improve anti-tumor response and immune infiltration with selected examples**

Promote innate immunity		
Local inflammation	Local irradiation	Liu et al., 2018
	Oncolytic viruses	Raja et al., 2018
Macrophage/DC activation	CD40	Vonderheide, 2018
	TLR or RLR agonists	Li et al., 2017
Pro-inflammatory cytokines	IFNα	Medrano et al., 2017
Promote phagocytosis	CD47/SIRPα	Liu et al., 2017
Vaccination	DC vaccination	Palucka and Banchereau, 2013
	Peptide vaccination	Kumai et al., 2017
	Tumor cell vaccination	Srivatsan et al., 2014
Promote adaptive immunity		
Induction of tertiary lymphoid structures	LIGHT	Johansson-Percival et al., 2017
Costimulatory agents	CD40, CD137, GITR, ICOS, OX40	Dempke et al., 2017
T cell activation	IL-2	Jiang et al., 2016
	Pegylated IL-10	Naing et al., 2018
	STING	Rivera Vargas et al., 2017
Inhibition of immunosuppression		
ICB	CTLA-4, PD-1/PD-L1	Seidel et al., 2018
	IDO, KIR, LAG-3, Tim-3, VISTA	Dempke et al., 2017
TAM reprogramming	BTK	Gunderson et al., 2016
	Class IIa HDAC	Guerriero et al., 2017
	CD40	Majety et al., 2018
Blocking immunosuppressive cytokines	TGFβ	Haque and Morris, 2017

DC, dendritic cell; ICOS, inducible costimulator; IDO, indoleamine (2,3)-dioxygenase; KIR, killer cell immunoglobulin-like receptor; RLR, RIG-I-like receptor.

(Castaño et al., 2018). Admittedly, the murine studies differed in model and cells used and the suppressive effect was restricted to early stages of metastases outgrowth. Although most of the available data support the concept to block IL-1, there is no doubt that further research is needed, as well as for other pro-inflammatory cytokines that are targeted in anticancer therapy, including IL-6 (Kitamura et al., 2017), IL-23, TNFα, and CC-chemokine ligand 2 (CCL2), to dampen inflammation and/or leukocyte recruitment (Todoric et al., 2016).

Interestingly, although IL-17 is known to be one of the most potent inflammatory cytokines and the culprit in many autoimmune diseases, patients suffering from different kind of cancers showed prolonged survival when they expressed high levels of IL-17 (Qian et al., 2017). While IL-17 was originally considered to promote neovascularization and tumor cell proliferation, its anti-tumorigenic function, achieved by, e.g., activation of tumoricidal T cells, natural killer cells, or neutrophils and upholding barrier integrity, is undisputable (Kryczek et al., 2009; Wang et al., 2014; Fabre et al., 2016). Since more and more is known about the molecular mechanisms linking inflammation and tumor progression, the respective intracellular signaling cascades constitute a novel target for therapeutic intervention. This is practiced indirectly by cytokine blocking antibodies mentioned above, many of which impinge on protumorigenic STAT3 or NF-κB signaling. Several direct STAT3 inhibitors are currently tested in clinical trials (Johnson et al., 2018). Unfortunately, various side effects, including development of neutrophilia and elevated IL-1β serum levels (Greten et al., 2007; Mankan et al., 2011), led to the discontinuation of IKKβ inhibitor development by many pharmaceutical companies.

Inducing inflammation and modulating immune cell activation

Less than 25% of all patients respond to immune-oncology compounds. Exhaustion of T cells, PD-1/PD-L1 gene amplification, MHC-I/II mutations, β-catenin overexpression, and other reasons have been described to be responsible for such resistance (Dempke et al., 2017). One concept to improve response to ICB has simply been the combination of anti–CTLA-4 plus anti–PD-1/PD-L1. This prolongs survival of metastatic melanoma patients and led to Food and Drug Administration approval of nivolumab (anti–PD-1) plus ipilimumab (anti–CTLA-4) in 2015 (Fig. 1). Yet, while single administration of anti–CTLA-4 induces PD-L1 expression on tumor cells (Hu-Lieskovan and Ribas, 2017), the advantage of additional CTLA-4 blockade is often only moderate, accompanied by more severe cytotoxic side effects compared with PD-1 blockade alone.

One of the greatest obstacles in immune therapy is the immune-deserted or cold state of certain tumors that lack an appropriate anti-tumor immune response (Chen and Mellman, 2017). To increase T cell infiltration into tumors, various combination therapies now aim to induce a pro-inflammatory response that would overcome T cell exclusion, turning tumors into hot tumors (Fig. 2). One of these approaches comprises the likewise relatively novel oncolytic viruses. Talimogene laherparepvec is the first approved oncolytic virus for use in melanoma. Its lytic traits, together with the expression of GM-CSF, lead to increased tumor cell lysis and release of danger signals and antigens, promoting T cell responses, which showed beneficial effects in combination with anti–CTLA-4 or anti–PD-1 therapy (Zamarin et al., 2014; Ribas et al., 2017; Chesney et al., 2018). Further attempts to increase T cell activity include irradiation, GM-CSF–expressing tumor vaccine GVAX, or cytostatics as combinatorial therapies (Robert et al., 2011; van den Eertwegh et al., 2012; Le et al., 2013; Rech et al., 2018). Not only does irradiation induce a local inflammatory milieu with increased IFNγ production, cell death, antigen release, and broadened T cell receptor repertoire, its combination with PD-1 blockade can exert an abscopal effect, with tumor regression in non-irradiated secondary tumors (Liu et al., 2018). Furthermore, irradiation-induced DNA damage activates pattern recognition receptors like the cytosolic DNA sensor cyclic GMP-AMP synthase, which further activates STING (stimulator of interferon genes) and leads to a type I IFN response, responsible for

anti-tumor immunity (Deng et al., 2014). Interestingly, cyclic GMP-AMP synthase/STING seems to be essential for anti–PD-L1 and anti–CTLA-4 to act when combined with irradiation in murine models of melanoma (Harding et al., 2017; Wang et al., 2017). Another promising approach comprises direct interference with cytokines. TGFβ promotes T cell exclusion and is correlated with poor prognosis (Calon et al., 2012, 2015; Tauriello et al., 2018). Blocking TGFβ along with PD-1 provided excellent results in preclinical models of colorectal and mammary carcinoma (Mariathasan et al., 2018; Tauriello et al., 2018). While the anti-inflammatory cytokine IL-10 is one of the main mediators secreted by regulatory T cells to inhibit tumor-specific immune responses, the contradicting observation that block or deficiency of IL-10 increases tumor growth led to the development of PEGylated IL-10 (Pegilodecakin; Oft, 2014; Naing et al., 2016). Interestingly, while dampening pro-inflammatory macrophages and Th17 cells, a simultaneous induction of anti-tumorigenic CD8 T cell responses and CD8-derived IFNγ was observed following administration of Pegilodecakin in mice. More importantly, Pegilodecakin promoted expansion of underrepresented T cell clones as well as LAG-3$^+$ PD-1$^+$ CD8$^+$ T cells, which are further induced by anti–PD-1 in various solid tumors (Naing et al., 2018). Intratumoral applications of TNFα "TNFerade" seemed not to be as effective as initially hoped, and clinical trials have been stopped despite first promising results (Kali, 2015). To date, IL-2 and IFNα are the only cytokines approved for use in cancer. They aim for increased T cell proliferation and MHC-I/HLA expression by tumor cells (Lee and Margolin, 2011).

Several other compounds that trigger innate and adaptive immune responses have now found their way into the clinics and are being tested in combination with ICB. Apart from Toll- and RIG-like receptor or STING activation (Li et al., 2017) current strategies employ inhibitory compounds targeting V-domain immunoglobulin suppressor of T cell activation (VISTA), TIM-3, LAG-3, indoleamine (2,3)-dioxygenase, or killer cell immunoglobulin-like receptor as well as costimulatory antibodies including CD40, OX40, inducible costimulator, CD137, or glucocorticoid-induced TNFR family-related gene (GITR). Initial concerns regarding the potential development of cytokine-release syndromes, autoimmune reactions, and hyperimmune stimulation have not been confirmed in early phase I/II clinical trials so far (Dempke et al., 2017). Moreover, cyclin-dependent kinase (CDK) inhibitors targeting CDK4 and CDK6 (Goel et al., 2017; Deng et al., 2018), histone deacetylase (HDAC), or DNA methyltransferase inhibitors (Fraga et al., 2005; Goel and Boland, 2012; Lee and Huang, 2013) showed promising results while maintaining tolerable side effects. Several recent excellent reviews have summarized these results in greater detail (Hu-Lieskovan and Ribas, 2017; Patel and Minn, 2018).

PD-1–PD-L1 therapies may also function through a direct effect on macrophages, since PD-1 expression can be observed on tumor-associated macrophages (TAMs), where its engagement dampens tumor cell phagocytosis and acts in an immunosuppressive manner on CD8 T cells (Gordon et al., 2017; Wang et al., 2018). Interestingly, blocking either PD-1 or PD-L1 may even have distinct effects on macrophage activation that could be targeted synergistically (Hartley et al., 2018).

TAMs with an M2-like phenotype comprise one cell type that is associated with poor prognosis in many solid cancers (Shabo et al., 2008; Kurahara et al., 2011). Their recruitment can be inadvertently induced by affected tissue following chemotherapy (DeNardo et al., 2011). Inhibitors targeting colony-stimulating factor-1 receptor (CSF-1R), a critical macrophage survival factor, were shown to have positive outcomes in xenograft models of glioblastoma, by reprogramming the M2-like phenotype (Pyonteck et al., 2013). CSF-1R–targeting antibodies showed clinical response in diffuse-type giant cell tumor of human patients (Ries et al., 2014). Alternative targets that are involved in polarization of TAMs comprise Bruton tyrosine kinase (BTK) and PI3Kγ. In a preclinical model of pancreatic ductal adenocarcinoma, the BTK inhibitor ibrutinib reprogrammed macrophages toward a M1 phenotype and thereby stimulated CD8$^+$ T cells in a macrophage-dependent manner (Gunderson et al., 2016). Inhibition of PI3Kγ in macrophages prolongs NF-κB activation and inhibits C/EBPβ to induce an immunostimulatory program that enhances cytotoxic CD8$^+$ T cell recruitment and activation, thus improving anti-tumor function (Kaneda et al., 2016). A recent report demonstrated reprogramming of TAMs and recruitment of non-TAM macrophages by class IIa HDAC inhibition, resulting in cytotoxic T cell response and regression of breast tumors and metastases (Guerriero et al., 2017). Although the inhibitor was acting specifically on myeloid cells, the exact mechanism was not yet clear. TAM reprogramming into an immune-stimulating phenotype can also be achieved by agonistic CD40 therapy, which enhances macrophage activation and activity (Beatty et al., 2011; Vonderheide, 2018) and which showed promising results in combination with the aforementioned CSF-1R blockade (Hoves et al., 2018; Perry et al., 2018), checkpoint inhibitors, and chemo- or radiotherapy (Byrne and Vonderheide, 2016; Bajor et al., 2018; Rech et al., 2018). Another approach to enhance macrophage function consists of blocking antiphagocytic signals from tumor cells. CD47 depicts the most advanced target in this category. Blocking the interaction with its ligand SIRPα leads to increased phagocytosis and tumor regression in several models (Chao et al., 2010; Goto et al., 2014; Gholamin et al., 2017; Liu et al., 2017; Métayer et al., 2017). Currently, different strategies aiming at TAM recruitment, function, or activation are tested in clinical trials (Ruffell and Coussens, 2015; Cannarile et al., 2017). Among these are mediators, blocking the CCL2/CCR2 axis, that prevent chemoattraction of monocytes/macrophages and their subsequent effects including metastasis (Lim et al., 2016). An interesting discovery was that the cytostatic trabectedin exerts some of its function by selective depletion of monocytes and macrophages apart from its direct effect on tumor cells (Germano et al., 2013). Of note, however, was the observation that termination of anti-CCL2 treatment caused a dramatic increase of metastases and death in syngeneic breast cancer models (Bonapace et al., 2014). Furthermore, macrophages exert critical Fc-mediated effector functions like antibody-dependent cellular cytotoxicity of, for example, anti-CTLA-4–targeted T reg cells (Simpson et al., 2013), which should be considered in the context of a clinical use of monocyte/macrophage blocking agents.

While the concept to employ bacteria for cancer therapy was initiated by Wilhelm Busch and William Coley, nowadays the microbiome, and particularly the intestinal microbiome, has to be considered for tumor therapy due to its important role in host physiology and metabolism. Either through changes in the microbial composition (dysbiosis) or through a barrier defect, the microbiome has a significant impact on the development of the immune system (Chung et al., 2012) as well as carcinogenesis (Quante et al., 2013). Importantly, however, the microbiome can also directly affect the efficacy of various cancer therapies (Zitvogel et al., 2018), including administration of platinum-based agents (Iida et al., 2013), alkylating agents such as cyclophosphamide (Viaud et al., 2013), innate immunity modulators such as TLR9 stimulating CpG-DNA (Iida et al., 2013), or immune checkpoint inhibitors (Sivan et al., 2015; Vétizou et al., 2015; Gopalakrishnan et al., 2018). Furthermore, intratumor Gammaproteobacteria can metabolize the chemotherapeutic gemcitabine to an inactive form, dampening its efficacy (Geller et al., 2017). So far, mechanistic studies clearly defining the exact mechanisms for the beneficial or detrimental effects of microbes in cancer immunotherapy are mostly missing, and conclusions rather depend on correlative results showing effects, or the lack thereof, on antibiotic treatments or gnotobiotic experiments. Furthermore, it remains to be proven that these studies, which have been mostly performed in mice using syngeneic cancer cell lines that had previously been immune edited, can be recapitulated in (humanized) models of spontaneous tumorigenesis. Although there is clear evidence that the microbiome has an immunostimulatory function, it also remains to be defined which and if individual bacteria, or rather bacterial communities, are responsible for this and whether direct stimulation of T cell receptors, engagement of pattern recognition receptors, or system metabolic effects are the key drivers (Zitvogel et al., 2018). Nevertheless, these recent studies underscore the potentially adverse effects of antibiotic use in patients during anticancer therapy, and they further suggest that, for example, pre-existing diet-dependent changes in the intestinal microbiome are not only important for the development of tumors (Arkan, 2017), but may also affect the responsiveness to chemo- or immunotherapy to a much greater extent than previously anticipated. However, a better understanding of the microbiome-induced effects on the host during cancer therapy as well as the identification of a possibly beneficial microbiome (Tanoue et al., 2019) may lead to concepts aiming at altering the microbiome by either fecal transplantation, supplementation of distinct bacterial strains, or targeted antibiotic therapy.

Conclusion

Over the last years, the field of cancer-related inflammation has tremendously expanded, and a multitude of different cellular and molecular mechanisms have been discovered, so far nicely illustrating the intricate interaction of immune cells, vascular cells, stromal cells, and tumor cells and the influence of various external factors. Essentially all immune cells have been shown to be involved in the different stages of tumorigenesis, and this has unraveled various exciting new strategies for tumor therapy, some of which we have highlighted above. Individualized multimodal combinatorial approaches targeting both tumor cell intrinsic and extrinsic pathways will most likely represent the future of modern cancer therapy. The biggest challenge will be the timely identification of the most efficient combination for each individual cancer patient and the identification of biomarkers that will allow prediction of immunotherapeutic response. Better characterization of individual immune and stromal cells in the tumor microenvironment using single-cell analysis that will particularly help to address the plasticity of these cells will be important. Development of technological platforms that allow interactions of T cells with matched tumor organoids in a personalized manner to assess killing efficiency (Dijkstra et al., 2018) will prove extremely helpful in this regard. Nevertheless, novel, original approaches that will help overcome T cell exclusion from tumors remain an unmet need. In this context, CRISPR-mediated genetic in vivo screens represent a promising approach, as they have recently unraveled pathways that may lead to innovative concepts that could render unresponsive cold tumors sensitive to ICB (Manguso et al., 2017; Ishizuka et al., 2019). Another important task and the basis for proper preclinical validation of novel immunotherapeutic concepts is the development of improved in vivo tumor models and the use of humanized mice that enable an adequate recapitulation of tumor evolution and that sufficiently take into consideration other external factors such as age, diet, and the microbiome. However, also recently developed microfluidic human organs-on-chips that can be used to model cancer cell behavior within human-relevant tissue and organ microenvironments in vitro (Sontheimer-Phelps et al., 2019) represent a promising alternative to evaluate personalized therapy responses.

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