

Immunity, inflammation, and cancer: an eternal fight between good and evil

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Cancer development and its response to therapy are strongly influenced by innate and adaptive immunity, which either promote or attenuate tumorigenesis and can have opposing effects on therapeutic outcome. Chronic inflammation promotes tumor development, progression, and metastatic dissemination, as well as treatment resistance. However, cancer development and malignant progression are also associated with accumulation of genetic alterations and loss of normal regulatory processes, which cause expression of tumor-specific antigens and tumor-associated antigens (TAAs) that can activate antitumor immune responses. Although signals that trigger acute inflammatory reactions often stimulate dendritic cell maturation and antigen presentation, chronic inflammation can be immunosuppressive. This antagonism between inflammation and immunity also affects the outcome of cancer treatment and needs to be considered when designing new therapeutic approaches.

Introduction

Inflammation has been recognized since the beginning of recorded medical knowledge (1–3). It is a part of a complex biological response to cellular damage caused either by sterile injury (cell death) or infection, in which the immune system attempts to eliminate or neutralize injurious stimuli and initiates healing and regenerative processes. For example, IL-6, a key tumor-promoting inflammatory cytokine produced by innate immune cells, activates at least three regeneration-promoting transcription factors — YAP, Notch, and STAT3 — which are also involved in stem cell activation (4). It is likely that all tumor-promoting inflammation, whether it precedes or follows tumor development, is part of the normal response to injury and infection that has been usurped by cancer cells to their own advantage.

Inflammation is classically viewed as a feature of innate immunity, which differs from adaptive immunity by the receptors mediating its activation and its rapid onset. Innate immunity is also more evolutionarily ancient than adaptive immunity and is triggered by foreign microbial and viral structures, known as pathogen-associated molecular patterns (PAMPs), or normal cellular constituents released upon injury and cell death, known as damage-associated molecular patterns (DAMPs). Both PAMPs and DAMPs are recognized by pattern-recognition receptors (PRRs), many of which belong to the TLR family (5, 6). Once activated, innate immunity results in upregulation of MHC class I and II and costimulatory molecules, as well as numerous inflammatory chemokines and cytokines that attract and prime T cells for activation through diverse antigen receptors (7). Activated adaptive immune cells, including T and B lymphocytes, further amplify the initial inflammatory response. Thus, type 1 helper T cells (Th1 cells) activate macrophages both through cell-to-cell contact and IFN- γ secretion (8), Th2 cells activate eosinophils through cytokine release, and

B cells secrete antibodies that activate the complement cascade — as well as phagocytes, NK cells, and mast cells — through Fc receptors (7, 9–12). However, certain adaptive immune cells, especially Tregs, can turn off the inflammatory response (13).

The major driving forces that contribute to evolution of the immune system are infectious organisms capable of eliciting direct damage to the host. Yet, despite its sophistication, the immune system can cause substantial collateral damage (immunopathology) when over-activated or not properly terminated. To minimize immunopathology and maximize host defense, innate and adaptive immune cells are equipped with negative regulatory mechanisms (14–18). In fact, maximal immunity is achieved only when innate and adaptive immune cells act in concert and harmony, which also depends on negative control or immunosuppressive mechanisms. For instance, during chronic viral infections, viruses are held at bay while avoiding immunopathological damage by immune checkpoints that prevent an overzealous antiviral response (19). These evolutionarily conserved controls may also be involved in T cell tolerization during cancer-associated chronic inflammation (20, 21), although the underlying mechanisms remain obscure (22–24). In this review, we will discuss how innate and adaptive immune cells control tumor progression and the response to therapy, and we will try to avoid extensive discussion of the entire inflammation and cancer field, which has been reviewed elsewhere (20, 25, 26).

The evil: chronic inflammation and cancer

The first documented proposition of an association between inflammation and cancer has been attributed to the German pathologist Rudolf Virchow, who was active in the mid-19th century. This hypothesis, based on Virchow's detection of inflammatory infiltrates in solid malignancies, has gained strong epidemiological and mechanistic support in the past dozen years (20), leading to recognition of tumor-associated inflammation as a key feature (hallmark) of cancer (20, 27, 28). While early work has mainly addressed the link between preexisting inflammation and subsequent tumor develop-

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ment, which may account for 15%–20% of cancer deaths (25), more recent efforts have been dedicated to understanding tumor-elicited inflammation, the inflammatory reaction that follows tumor development and is detected in nearly all solid malignancies.

One of the best-studied cancers from a genetic perspective has been colorectal cancer (CRC), where the majority of cases follow a well-charted genetic pathway in which premalignant lesions, called advanced crypt foci (ACF), are formed as a result of β -catenin activation, mainly due to loss of the antigen-presenting cell (APC) tumor suppressor (29). Additional K-Ras activating mutations lead to formation of adenomas, which progress to invasive carcinomas upon loss of p53 and components of the TGF- β signaling pathway (30). The elucidation of this process led to the view that cancer is a genetic disease in which environmental factors come into play solely through induction of new somatic mutations. For instance, chronic inflammation due to inflammatory bowel disease (IBD), which increases CRC risk, was thought to act mainly through production of mutagenic ROS and reactive nitrogen species (RNS) (30). Although expression of inducible NO synthase (iNOS) induces oxidative DNA damage and accelerates loss of heterozygosity at the *Apc* locus to contribute to CRC induction (31), IBD promotes CRC development mainly through activation of NF- κ B and STAT3 (32, 33), and perhaps YAP and Notch (4), transcription factors that activate genes that promote the survival of initiated epithelial cells and expose them to growth-promoting inflammatory cytokines (30). More recently, it became clear that even without preexisting IBD, inflammation occupies a key position in the development of sporadic CRC. As soon as the *Apc* locus is lost in mice and ACF lesions appear, there is an accompanying loss of mucin2 production and junctional adhesion molecules, resulting in barrier defects and invasion of ACF lesions and early adenomas with commensal enteric bacteria or their products (34). The latter activate nearby macrophages through TLR2, -4, and -9 to secrete IL-23, which stimulates the production of IL-17A through its effects on Th17 cells and innate lymphoid cells (34). IL-17A, in turn, directly stimulates the proliferation and growth of ACF lesions into adenomas and adenocarcinomas (35). Early human adenomas also exhibit loss of the epithelial barrier, microbial invasion, and upregulation of IL-23 and IL-17A (34). Furthermore, elevated expression of IL-17A and IL-23R in stage I and II human CRC correlates with rapid progression to lethal metastatic disease (36). Moreover, IL-11, an IL-6 family member mainly produced by myeloid cells and cancer-associated fibroblasts (CAFs), also supports tumor promotion and progression by activating gp130/STAT3 signaling in gastrointestinal cancers (37, 38). Another cytokine, IL-22 — an IL-10 family member that is mainly secreted by T cells, innate lymphoid cells, and DCs — also acts through STAT3 to promote tissue repair and tumorigenesis in colon and liver (39–41). In addition, IL-6 and related cytokines are induced upon IL-17R reengagement and may enhance tumor progression at later stages (35). Neutralization of IL-17A, IL-11, or IL-22 can inhibit colonic tumorigenesis at an early stage, underscoring the fundamental importance of tumor-elicited inflammation in the malignant progression of colorectal tumors. Such findings and others counter the recent suggestion that cancer rates and risks are purely dictated by the number of cancer-initiating cell divisions (42). We suggest, instead, that the key rate-limiting step in cancer

development is the progression of premalignant lesions, many of which (excluding ACF lesions) can exist in a dormant state for years before becoming malignant growths. This step is controlled both by intrinsic (tumor-elicited) and extrinsic inflammation, and may be attenuated by antitumor immunity, which was suggested to maintain dormancy (23).

The good: immunity and cancer

In recent years, tumor immunologists and practicing oncologists have seen a dream come true with the clinical implementation and regulatory approval of cancer immunotherapies (43). It was first suggested by Paul Ehrlich, 50 years after Virchow, that the immune system can fight tumors (44), a suggestion reiterated by the immunosurveillance hypothesis of Burnet and Thomas (45). These hypotheses are based on the notion that cancer-associated genetic alterations, together with aberrant quality-control mechanisms and epigenetic reprogramming, result in expression of tumor-specific antigens (neoantigens) and tumor-associated antigens (TAAs), which are nonmutated proteins to which T cell tolerance is probably incomplete due to their restricted tissue expression pattern (46). These antigens can activate antitumor immunity and, under certain circumstances, may also induce rejection of early neoplasms, a concept known as immunosurveillance (23, 46). However, the tumor-controlling ability of the immune system was not widely accepted until the successful development of immune checkpoint inhibitors that trigger tumor rejection by activating cytotoxic T lymphocytes (CTLs). The response to such immunotherapeutics and their clinical benefit were shown to depend on the intrinsic mutational rate for the cancer being treated (47). However, it is still not clear which type of neoantigen induces a better protective immunity, as tumors with immunogenic passenger mutations are most likely to develop resistance, compared with those with immunogenic driver mutations (48, 49). Based on these data, one would assume that early neoplasms might have too few mutations to be recognized by our T cells. Furthermore, established tumors with higher mutation rates use various escape mechanisms to bypass immunosurveillance, including immunoediting, antigen loss variants, MHC downregulation (23), and induction of immunogenic tolerance (24, 50–52). Tolerance induction can be achieved by production of negative regulatory signals and recruitment of immunosuppressive cells to the tumor microenvironment (24, 50, 52). In addition to Tregs, this population of immunosuppressive cells includes so-called myeloid-derived suppressor cells (MDSCs), regulatory B cells (Bregs), and immunosuppressive plasmacytes (ISPC) (24, 51–53).

The recent success of immune checkpoint inhibitors in the treatment of melanoma, non-small cell lung carcinoma (NSCLC), and bladder and kidney cancers suggests that a fraction of these cancers still display or release sufficient amounts of potent tumor antigens. It is the elevated expression of negative regulatory signals and the presence of immunosuppressive cells that account for establishment of immune tolerance in such cancers. However, while immune checkpoint blockade and adoptive T cell transfer strategies can result in a clinical benefit in a subset of patients, most patients are still refractory to such therapies (43, 54, 55). Thus, future effort should be directed toward increasing response rates and expanding the applicability of immunotherapy to all types of cancer.

We will discuss how tumor-related chronic inflammation shapes local and systemic innate and adaptive immunity to promote formation of an immunosuppressive tumor microenvironment, especially during cancer therapy. We also review the dual roles played by different immune cell types in promoting tumor inflammation or immunity, and progression or regression.

Innate immune cells: the good APC and the evil TAM, TAN, and MDSC

Myeloid cells, including macrophages and neutrophils, are the most abundant immune cells in the tumor microenvironment (56, 57). Tumor-associated macrophages (TAMs) acquire protumorigenic properties in primary and metastatic sites, and they play supportive roles in cancer development and progression by stimulating cell proliferation, cell survival, angiogenesis, invasive and motile behavior, and suppression of CTL responses (56, 58–60). At early stages of tumor development, TAMs appear to undergo classical activation and exhibit an M1 phenotype (referred to as TAM1) (61), rather than the alternatively activated M2 phenotype (TAM2), which may form as tumors accumulate lactic acid and acquire hypoxic cores (62). Exposure of macrophages to IL-4 produced by CD4⁺ T cells and/or cancer cells (59, 63), growth factors such as colony stimulating factor-1 (CSF1) (64), GM-CSF (65), and TGF β secreted by cancer cells, can also induce the M2 switch. It remains to be determined which TAM type is more important in tumor promotion, but it should be noted that TAM1 cells express and secrete classical proinflammatory cytokines, chemokines, and effector molecules, including IL-1, IL-6, TNF, IL-23, and iNOS, which are known to contribute to tumor initiation and early promotion (20). TAM2 cells produce VEGF and antiinflammatory molecules, such as IL-10, TGF- β , and arginase 1 (ARG1) (57, 60). The blood vessels that provide oxygenation and nutrition dramatically increase in most tumors during malignant conversion, a process known as the angiogenic switch, and a similar process may occur during cancer therapy. TAMs that express TIE2 regulate this process mostly via production of VEGF and are mainly considered to be TAM2 cells (66, 67). TIE2⁺ macrophages also promote cancer cell migration and intravasation (68), which come into play during late stages of tumor progression. Based on such observations, we propose that TAM2 cells may be more important in later stages of tumor growth, which depend on angiogenesis and immunosuppression. Macrophages are plastic in nature and easily alter their gene expression program during tumor progression rather than assume irreversible fates. Additionally, TAM2 cells express membrane-bound or soluble forms of HLA molecules that can directly inhibit activation of NK cells and certain T cell subsets (69). TAMs can also express programmed death-1 ligand (PD-L1) upon activation of HIF-1 α in hypoxic tumor regions, further inhibiting CTL activation (70). However, tumors lacking T cell-based inflammation may require innate immune cells to promote T cell recruitment and activation (50, 71, 72).

Tumor-associated neutrophils (TANs) exhibit both antitumoral and protumoral functions. TANs can mediate cancer cell killing and promote metastasis by releasing ROS and neutrophil elastase, and potentiate antitumoral T cell responses by inhibiting TGF- β signaling (66). TANs promote genetic instability

through ROS and RNS release; sustain angiogenesis by releasing VEGF, MMP-9, or prokineticin 2 (Bv8); and enhance neoplastic cell invasiveness through soluble mediators (e.g., oncostatin M [OSM] and HGF) (56, 73, 74).

MDSCs are an ill-defined population of cells that express markers of monocytes, macrophages, and neutrophils (75). Most of their immunosuppressive activities are similar to those of TAM2 cells and TANs, and it may be difficult to distinguish between these cells, since they express several common markers. Furthermore, immunosuppression in the tumor bed is primarily mediated by TAMs and TANs that contribute to the inhibition of CTL (60), and it is not clear whether MDSCs are a truly distinct population or immature inflammatory monocytes that were recently recruited into the tumor.

DCs, the main type of professional APCs, play an important role in T cell priming. The generation of protective antitumor immunity depends on DC maturation and antigen presentation (72, 76). DC and macrophages express MHC class I molecules, which present antigens to CD8⁺ T cells. Host type 1 IFN signals are required for mounting an antitumor CTL response through CD8 α ⁺ DCs. Notably, some conventional chemotherapeutics, when administered at a low dose, and certain forms of radiation therapy induce tumor rejection through immunogenic cell death (ICD), which depends on the release of DAMPs and antigens (77–79). The DAMPs bind to receptors expressed on the surface of APCs and stimulate their maturation and ability to present TAAs through an acute proinflammatory pathway (77). Such APCs acquire the ability to support cancer-specific immune responses and promote tumor regression (80). Based on this knowledge, DC-based therapeutic vaccination has been developed, but so far only a modest transient response has been observed (81–83).

Janus-faced innate lymphocytes: NK, NKT, and $\gamma\delta$ T cells

NK cells, natural killer T (NKT) cells, and $\gamma\delta$ T cells populate many tumors (84–86). NK cells recognize mouse cancer cells via ribonucleic acid export-1 (RAE-1) family ligands and human cancer via MHC class I-related genes A and B (MICA and MICB), all of which bind the NK cell-activating receptor NKG2D (84, 87, 88). These NKG2D ligands are upregulated during the DNA damage response and cell cycle progression via E2F transcription factors (89). The antitumor activity of NK cells was mainly observed in hematopoietic malignancies, but it was recently shown that in mice, MULT1, a high-affinity NKG2D ligand that is released by cancer cells, causes NK cell activation and rejection of solid tumors (90). NK cells have a dual role during liver inflammation and injury, where they contribute to both antiviral defense and tumor-promoting tissue damage. NK cells control liver fibrosis by killing early or senescence-activated hepatic stellate cells and produce antifibrogenic IFN- γ (91). However, CD8⁺ T cells and NKT cells also promote nonalcoholic steatohepatitis (NASH) and accelerate its progression to hepatocellular carcinoma (HCC) (92). CD1d-restricted NKT cells have both innate and adaptive characteristics (93), and a subset of NKT cells was reported to suppress antitumor immunity, in part via production of IL-13, which in turn induces TGF- β production by myeloid cells (94). $\gamma\delta$ T cells also have dual functions; they are antitumorigenic after chemotherapy (95, 96) and immunosuppressive in isolated breast

cancer tissue (97). IL-17 expression from $\gamma\delta$ T cells was shown to induce a T cell-suppressive TAN phenotype in mice bearing mammary tumors that promote metastatic spread (98).

CAFs: underappreciated immune regulators

Inflammatory responses are often accompanied by recruitment of fibroblasts and induction of fibrosis. CAFs are responsible for deposition of collagen and various extracellular matrix components (ECM components) in the tumor microenvironment, where they stimulate cancer cell proliferation and angiogenesis (99, 100). CAFs also have a critical but underappreciated immune function as they produce numerous cytokines and chemokines, including osteopontin (OPN), CXCL1, CXCL2, IL-6, IL-1 β , CCL-5, stromal-derived factor-1 α (SDF-1 α), and CXCL13 (101, 102). During early tumorigenesis, fibroblasts sense changes in tissue architecture caused by increased proliferation of neighboring epithelial cells and respond to these changes by producing proinflammatory mediators (103). The proinflammatory properties of CAFs are enhanced by mediators secreted by resident immune cells (102), such as IL-1, which activates Fc receptors (104). CAFs are also activated during therapy-induced hypoxia and produce copious amounts of TGF- β and numerous chemokines, including B cell-recruiting CXCL13 (105). CAF-secreted CCL2 recruits macrophages to the tumor microenvironment (106), whereas CAF-derived TGF- β inhibits NK cell and CTL activation, and induces Treg and ISPC differentiation (53, 107). CAF-derived CXCL13 mediates recruitment of B cells into androgen-deprived prostate cancer, leading to development of hormone resistance (105, 108). Activated CAFs expressing fibroblast activation protein- α (FAP) were also reported to suppress antitumor immunity in Lewis lung carcinoma (109). In contrast, in a mouse model of pancreatic cancer, depletion of activated α SMA⁺ CAFs induced immunosuppression that correlated with increased recruitment of CD4⁺Foxp3⁺ Tregs (110). Moreover, mesenchymal stem cells (MSC), which are multipotent stromal cells that can give rise to CAFs (111), exist in many tissues, especially tumors, and their contribution to tissue regeneration and modulation of inflammation has been described (112, 113). MSCs suppress immunity in some cases and enhance it in others by producing factors like TGF- β ; indoleamine 2,3-dioxygenase (IDO); IL-7; or IL-15 (113, 114). MSCs and CAFs also secrete IL-6 and orchestrate lymphoid tissue growth and responses (115).

Dual roles of T cell subsets in cancer

Many tumors express antigens that can be recognized by T lymphocytes, and analysis of the tumor microenvironment often reveals T cell infiltrates (116). Although CD8⁺ T cells are generally antitumorogenic, CD4⁺ T cell subpopulations can either promote or inhibit tumor progression. For example, CD4⁺Foxp3⁺ Tregs play a pivotal role in maintenance of immunological tolerance (117) and also produce cytokines, such as RANKL, that promote breast cancer progression and metastasis (118). Th17 cells produce IL-17A and IL-17F, which accelerate CRC progression (discussed above, ref. 34) but may also possess an antitumorogenic function in other malignancies (119, 120).

CTL activation involves DAMP release upon ICD, which promotes DC maturation and antigen presentation (53, 77, 121). Despite an active CTL response in a subset of patients, established

tumors that progress are obviously not rejected. This indicates the existence of potent immunosuppressive mechanisms that neutralize antitumor immunity, including induction of an exhausted/nergic-like CD8⁺ T cell phenotype, which may be a product of ongoing cancer-associated inflammation, as well as chronic inflammation caused by multiple rounds of cancer therapy. After acute infection, naive, antigen-specific CD8⁺ T cells become activated, proliferate, and acquire effector functions. After pathogen clearance, 5%–10% of effector CD8⁺ T cells survive and differentiate into memory cells (122). During persistent infections, chronic inflammation, and tumor development, antigen-specific CD8⁺ T cells often fail to form effector or memory cells (24, 123) and instead undergo exhaustion, as first described during viral infection (124). Importantly, CD8⁺ T cell effector functions are lost in a hierarchical manner during chronic inflammation, with some functions exhausted earlier (e.g., IL-2 production, cytotoxicity, and proliferation) than others (e.g., IFN- γ) (125). Anergic/exhausted CD8⁺ T cells accumulate when antigen load is high and CD4⁺ T cell help is lacking (126).

Multiple regulatory pathways were shown to mediate T cell exhaustion in a context-dependent manner. The inhibitory receptor PD-1 is an important regulator of virus- and cancer-specific CD8⁺ T cell exhaustion during chronic inflammation in mice, primates, and humans (127, 128). IL-10 was also implicated in CTL dysfunction (129). Additional pathways, including CTL antigen 4 (CTLA-4), seem to influence CTL function and differentiation during persistent chronic inflammation and cancer. Importantly, tolerance and exhaustion are not irreversible fates, and depending on external conditions, anergic/exhausted cells can be reprogrammed and their immune effector function can be resumed. Many of the factors involved in T cell suppression are expressed or secreted by cancer- and tumor-associated cells, including IL-10, TGF- β , iNOS, ROS, and IDO. Tumor-specific CD8⁺ T cells showed an exhausted phenotype not only in primary tumors but also in metastases (130, 131). Furthermore, ZEB1, an epithelial-to-mesenchymal-transition (EMT) activator, increased PD-L1 expression on cancer cells, thereby causing CD8⁺ T cell exhaustion, which promotes metastasis (132). Curiously, upregulation of PD-L1, IDO, and Tregs in the melanoma microenvironment may be driven by CD8⁺ T cells (133). We found that activation and infiltration of ISPCs requires the presence of CD8⁺ T cells, even though ISPCs eventually suppress CTL activation (53). Chemotherapy-induced ICD results in tumor infiltration with CD8⁺ T cells, but these cells exhibit an anergic/exhausted phenotype unless ISPCs are removed from the tumor bed through genetic or immunological manipulations (53). Inflammation-induced resistance to immunotherapy was also described in melanomas, which acquire resistance to adoptive T cell therapy (ATCT) through TNF-dependent loss of melanocytic antigens and IFN- γ -dependent PD-L1 expression (134). These data suggest that the majority of observed immunosuppressive pathways, whose molecular nature is discussed below, are intrinsically driven by the immune system rather than being orchestrated by cancer cells, and may be driven by the negative feedback mechanisms that limit an overactive immune response. These are the remnants of the ancient protective mechanisms that had evolved to limit collateral damage during eradication of viral and microbial infections.

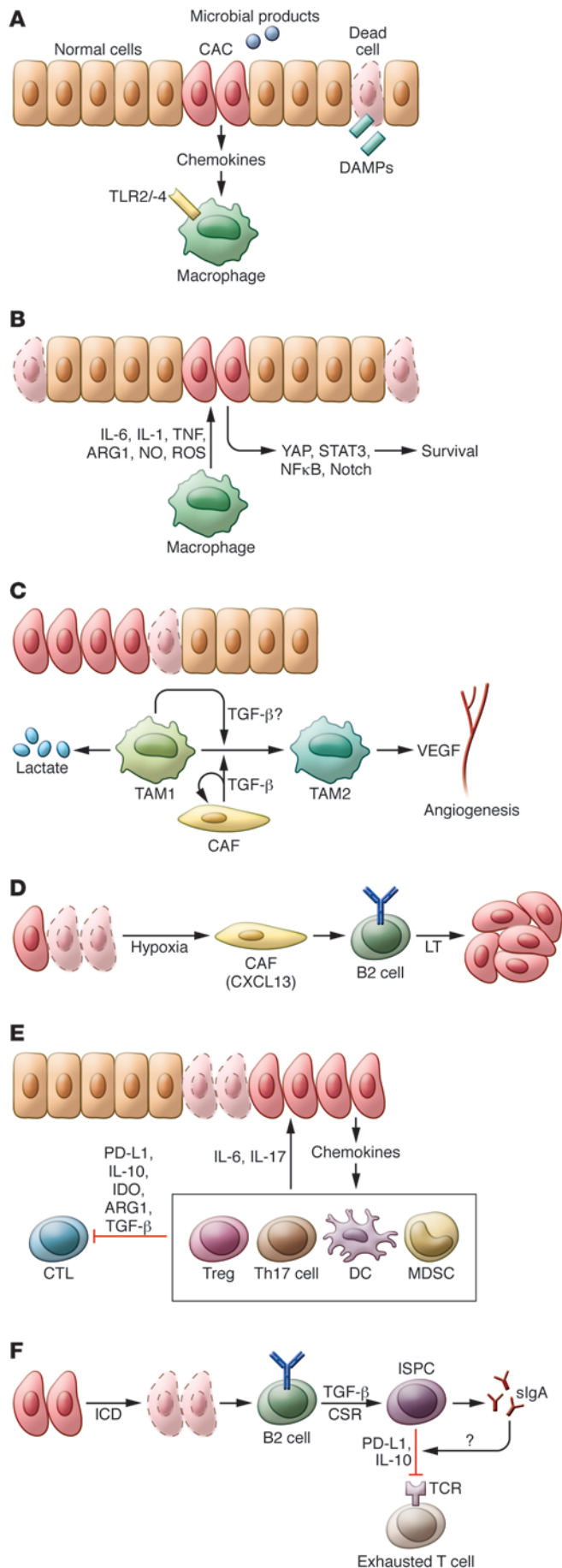


Figure 1. Inflammation promotes tumor development. (A) Microbial products that penetrate through the defective barrier associated with early tumors or DAMPs released by dying cancer cells (CACs) activate myeloid cells that are recruited into the tumor due to production of chemokines by CACs. (B) TAMs and TANs express cytokines, such as IL-1, IL-6, and TNF, which act directly on CACs, leading to activation of NF-κB, STAT3, YAP, and Notch. The cytokines thereby promote CAC survival and proliferation. (C) The growing tumor secretes lactate and acquires a hypoxic core due to insufficient O₂ supply. The hypoxia results in CAF activation due to HIF-1-induced TGF-β production and may convert TAM1 cells to a TAM2 phenotype, which produces VEGF to support neo-angiogenesis. (D) CAFs, which express TGF-β and CXCL13, recruit lymphotoxin-producing B2 cells that support further tumor growth. (E) Chemokines expressed in the inflamed tumor bed recruit tumor-promoting Th17 cells and immunosuppressive Tregs and MDSCs. (F) Tumor-infiltrating B cells undergo class-switch recombination (CSR) and become ISPCs that induce an exhausted/ anergic-like phenotype in cytotoxic T cells.

Good and bad B cells

Immunoglobulins specific for more than 2,000 antigens, which are often overexpressed by cancer cells, were detected in the sera of cancer patients (135, 136); however, antibody-mediated cancer cell killing is impaired. Notably, antibody effector functions that are mediated by Fcγ receptors are also compromised during persistent infections, an effect attributed to formation of antigen/antibody immune complexes (ICs), suggesting that high concentrations of preexisting ICs can limit the effectiveness of antibody therapy in human cancer (137). Moreover, certain immunoglobulins exhibit an antitumorigenic function (138). B lymphocytes are also present in the tumor microenvironment and in mouse models of squamous cell carcinoma, where they promote progression by activating mast cells and other myeloid cells (139). In prostate cancer, however, newly recruited B cells promote aggressive hormone-resistant tumors by producing the proinflammatory cytokine lymphotoxin (108). Recently, B cells including Bregs and ISPCs were shown to attenuate the development of autoimmune disease (140) and antitumor immunity (53, 141–143). We found a subpopulation of ISPCs that produce IgA, PD-L1, and IL-10 and strongly inhibit CTL activation in prostate cancer-bearing mice treated with the immunogenic chemotherapeutic agent oxaliplatin (53). These cells are also present in human prostate cancer, especially in treatment refractory and metastatic tumors. Unlike B cells in skin cancer (143), ISPCs in prostate cancer directly inhibit CTL activation by expressing IL-10 and PD-L1 (53). Elimination of ISPCs, whose development depends on TGF-β signaling, strongly enhances the immunogenic response to low-dose oxaliplatin and results in tumor rejection (53).

The molecular “Yin-Yang” of cancer inflammation and immunity

Although induction of T cell exhaustion through inhibitory receptors like PD-1, TIM-3, LAG3, CTLA-4, and BTLA has been extensively described (144), little is known about the factors that regulate receptor and ligand expression in chronically inflamed tissues or tumors. So far, STAT3, STAT4, and SMAD transcription factors, which are also involved in regulation of chronic inflammation (20), seem to control expression of most of these inhibitory receptors (144). These factors are activated by TGF-β and IL-10, both of which are present in the tumor microenvironment. TGF-β,

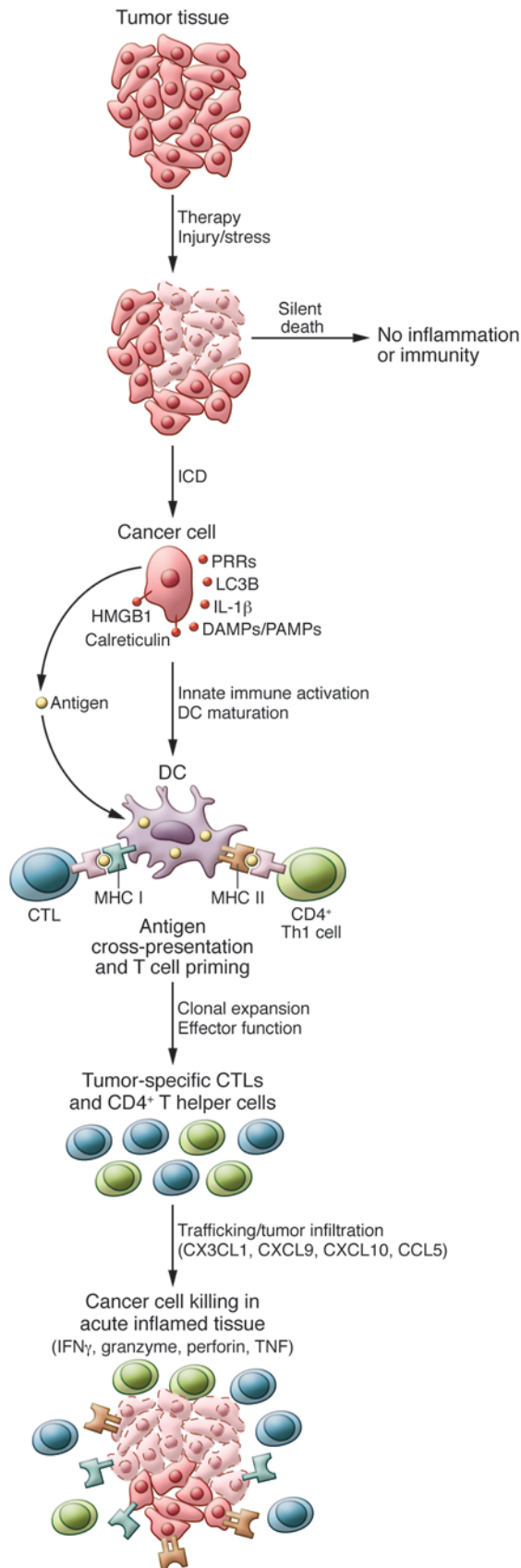


Figure 2. Acute inflammation promotes antitumor immunity in response to immunogenic chemotherapy in noninflamed tumors. ICD is induced by injury, stress, and certain chemotherapeutic agents. ICD can induce expression of surface calreticulin and HMGB1 in cancer cells, thereby activating innate immune cells through PRRs. DC maturation and antigen cross-presentation, together with secretion of inflammatory cytokines, can efficiently prime cytotoxic T cells, resulting in effective antitumor immune responses. However, in tumors with a chronically inflamed microenvironment rich in immunosuppressive factors, antitumor immunity cannot be activated unless the immunosuppressive factors are neutralized or eliminated.

for instance, is a key regulator of the wound-healing and fibrotic response. Its expression in CAFs is induced by tumor hypoxia that occurs either in response to O_2 shortage during rapid tumor growth or blood vessel collapse induced by therapy (105). TGF- β may suppress CTL activation through SMAD activation and direct binding of SMAD/activating transcription factor-1 (ATF1) complexes to the granzyme B and *IFNG* promoter regions (145). TGF- β also suppresses CTL activation indirectly by inducing regulatory cells including Tregs, ISPCs, and tolerogenic APCs (53, 146, 147). In this context, TGF- β signaling may synergistically interact with IL-6 or IL-10 through STAT3. We found that TGF- β signaling in combination with STAT3, which may be activated by IL-21 and auto-crine IL-10, induces formation of IgA⁺ ISPCs through class-switch recombination (53). Galectin-9, a TIM-3 ligand, promotes TGF- β -dependent induction of Tregs by activating SMAD and ERK (147). Moreover, activation of STAT3 together with ERK or p38 induces IL-10 expression in B cells (148). In addition to suppressing CTL effector functions, IL-10 induces tolerogenic macrophages and APCs by elevating their PD-L1 expression (149). PD-L1 expression by MDSCs is another direct target for HIF-1 α (70), which is responsible for CAF activation in prostate cancer (105).

Conclusions and prospects

In addition to its well-studied effects on cancer cell proliferation and survival, tumor-associated inflammation also plays an important role in the suppression of antitumor immunity (Figures 1 and 2). As discussed above, the immunosuppressive mechanisms triggered by tumor-associated inflammation are just beginning to be elucidated. Clearly, further investigation into this new crosstalk between innate and adaptive immunity will facilitate the development of new therapeutic strategies that boost antitumor immunity by targeting immunosuppressive chronic inflammation. In addition to combining immunogenic chemotherapeutics that induce tumor antigen release and presentation with immune checkpoint inhibitors, it should be possible to identify small molecules or neutralizing antibodies that inhibit the induction, accumulation, and function of immunosuppressive cell types in response to cancer-associated inflammation. All of these manipulations may prevent CTL exhaustion and support antitumor immunity. The availability of such reagents is likely to expand the new era in cancer therapy brought about by immune checkpoint inhibitors.

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