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Overcoming immunotherapeutic resistance by targeting the cancer inflammation cycle

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Abstract

Inflammation is a hallmark of cancer and supports tumor growth, proliferation, and metastasis, but also inhibits T cell immunosurveillance and the efficacy of immunotherapy. The biology of cancer inflammation is defined by a cycle of distinct immunological steps that begins during disease conception with the release of inflammatory soluble factors. These factors communicate with host organs to trigger bone marrow mobilization of myeloid cells, trafficking of myeloid cells to the tumor, and differentiation of myeloid cells within the tumor bed. Tumor-infiltrating myeloid cells then orchestrate an immunosuppressive microenvironment and assist in sustaining a vicious cycle of inflammation that co-evolves with tumor cells. This Cancer-Inflammation Cycle acts as a rheostat or “inflammostat” that impinges upon T cell immunosurveillance and prevents the development of productive anti-tumor immunity. Here, we define the major nodes of the Cancer-Inflammation Cycle and describe their impact on T cell immunosurveillance in cancer. Additionally, we discuss emerging pre-clinical and clinical data suggesting that intervening upon the Cancer-Inflammation Cycle will be a necessary step for broadening the potential of immunotherapy in cancer.

Keywords

Cancer; Inflammation; Inflammostat; Macrophage; Myeloid Cells; T cells; Immunotherapy

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Disclosure of Potential Conflicts of Interest

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1. Introduction

The immune system is hardwired with multiple checks and balances that combine to regulate the decision between elimination of non-self and the preservation of self. In cancer, immune surveillance is dependent on a balance of activating and inhibitory signals. For example, strategies to disrupt inhibitory signals (e.g. CTLA4 and PD1/PDL1) that negatively impact immunosurveillance in cancer have yielded promising treatments for patients. However, despite increasing indications for these therapies, only a minority of patients with cancer achieve significant clinical benefit. This observation reflects significant heterogeneity in the immune reaction to cancer that is detected across a wide-range of tumor histologies and even within the same tumor type. For instance, even in cancers where immunotherapy has demonstrated remarkable activity, such as non-small cell lung cancer (NSCLC) [1-4], kidney cancer [5-7], and melanoma [8, 9], many patients do not respond or ultimately relapse after initial disease control. Moreover, for several malignancies, including gastrointestinal cancers [10], brain cancers [11], and sarcoma [12], profound resistance to immunotherapy is the norm. Thus, in an effort to extend the benefits of immunotherapy, active investigations aim to identify determinants of response and resistance. One such determinant that has consistently emerged as a key mechanism of resistance is inflammation.

Inflammation is a hallmark of cancer and develops agnostically to tumor histology [13]. In this context, cancer-associated inflammation is defined by the recruitment of leukocytes to tumors and their release of soluble factors. Historically, inflammatory cells and the factors that they release within the tumor microenvironment have been perceived as the main mediators of cancer progression, metastasis and resistance to therapy. However, cancer-associated inflammation extends beyond the tumor microenvironment giving rise to chronic systemic inflammation which is characterized by increases in inflammatory cells and proteins detected in the peripheral blood of patients. Systemic chronic inflammation associates with poor outcomes to immunotherapy [14]. Moreover, accumulating evidence demonstrates that markers of systemic chronic inflammation are not only predictive of outcomes, but may directly mediate resistance to cytotoxic therapies (e.g. chemotherapy and radiotherapy) [15] and enforce immunosuppression by impinging upon the development of productive anti-tumor immunity [16, 17]. Taken together, inflammation has emerged as a major therapeutic target that will need to be reconciled to extend the benefit of cancer immunotherapy.

In this review, we discuss recent insights into the impact of inflammation on resistance to cancer immunotherapy. In our discussion, we highlight elegant studies in mice and humans to illustrate that factors secreted by tumor and host cells align to coordinate a systemic inflammatory reaction, acting as an inflammatory rheostat, which we call the “inflammostat”. As discussed in detail in subsequent sections, these molecules trigger mobilization of myeloid cells from the bone marrow, myeloid cell trafficking and infiltration into tumors, and the differentiation of infiltrating myeloid cells which then orchestrate immune suppression in the tumor microenvironment [18]. Within tumors, the myeloid cell reaction sustains the inflammostat creating a vicious cycle that fosters tumor cell survival, invasion and metastasis as well as evasion of the adaptive immune system [13, 19]. This biology emphasizes the complexity of the cancer-host interaction and identifies a series of

well-defined events that may be targeted therapeutically to divert the inflammatory reaction to cancer from tumor-promoting to tumor-suppressive. A major challenge moving forward is in how to combine and sequence drugs to disrupt cancer inflammation and to prevent the emergence of compensatory mechanisms of inflammation that are equally supportive of cancer progression. It is important to be mindful that the inflammatory reaction in cancer may differ across tumor histologies and even within the same histology. As a result, our focus in this review is on fundamental mechanisms that define elements of the inflammatory process in cancer without an emphasis on any specific tumor histology.

2. The Cancer Inflammation Cycle

Cancer biology is defined by multiple hallmarks that coalesce to instruct its complexity [13]. These hallmarks include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Inflammation and genomic instability are key determinants and enablers of these hallmarks [13]. However, tumor cells must also evade immune elimination. Accordingly, cells arising from both the innate (e.g. myeloid cells) and adaptive (e.g. T and B lymphoid cells) arms of the immune system influence the evolution and biology of cancer. In this regard, myeloid cells, including monocytes, macrophages, dendritic cells, neutrophils, eosinophils and mast cells, are fundamental determinants of cancer biology [14, 20]. Myeloid cells are recruited almost universally to a developing tumor [18]. Within the tumor, myeloid cells secrete survival factors and remodel the surrounding microenvironment to promote tumor cell growth and to protect the tumor from immune attack. In addition, myeloid cells assist in tumor cell invasion of the surrounding extracellular matrix and in doing so, direct tumor cells to intravasate into the bloodstream and begin the metastatic journey to distant organs [21]. Overall, myeloid cells co-evolve with tumor cells and serve as major proponents for cancer development and progression.

Within tumors, macrophages represent the predominant recruited myeloid cell type [18]. Macrophages can be detected at the earliest stages of carcinogenesis where they persist through development of invasive disease and accompany tumor cells in the formation of metastatic lesions [22-24]. The life cycle of macrophages and their precursors is fundamental to cancer biology. This process, which we call the Cancer-Inflammation Cycle (Figure 1), is integral from cancer conception. Indeed, the initiation of the Cancer-Inflammation Cycle can precede the emergence of a tumor cell. For example, inflammation (e.g. gastritis, esophagitis, colitis, pancreatitis, hepatitis, etc) is a major risk factor for cancer development in humans [25]. Cancer inflammation is also a determinant of immunoediting (reviewed in detail elsewhere [26, 27]), a process during which tumor cells are sculpted, or edited, with decreased susceptibility to immune recognition and elimination. Immunoediting proceeds sequentially through distinct phases, termed “elimination”, “equilibrium”, and “escape”. This process is dependent on a dynamic interconnection between innate and adaptive immunity. During the elimination phase, innate immunity may contribute to productive anti-tumor immunity via cross-presentation of antigens by dendritic cells for priming of tumor-specific T cells [26, 27]. However, innate and adaptive immunity eventually vie for dominance in the equilibrium phase [26, 27]. During this phase, inflammation seeks to undermine the anti-tumor productivity of T cell immune surveillance.

Ultimately, inflammation prevails, and tumor cells escape immune elimination leading to disease progression. In our description of the Cancer-Inflammation Cycle, our focus is on macrophages as well as macrophage precursors and their involvement in shaping T cell immunosurveillance in cancer. However, the Cancer-Inflammation Cycle is applicable to all innate immune cell subsets that accumulate in tumors and contribute to cancer biology.

The Cancer-Inflammation Cycle (Figure 1) is composed of multiple steps which we present below and describe in greater detail in subsequent sections of this Review. The first step of the Cancer-Inflammation Cycle involves the release of pro-inflammatory factors by tumor and stromal cells with the tumor microenvironment (step 1). These factors accumulate systemically and trigger bone marrow mobilization of monocytes (step 2). Monocytes then circulate through the bloodstream and traffic to (step 3) and infiltrate the tumor bed (step 4). Within the tumor, monocytes differentiate in response to cues from their surrounding microenvironment (step 5). This differentiation process is fundamental to defining the array of monocyte-derived cell phenotypes present within tumors which extend well beyond the classically defined macrophage subsets that have been described as M1 (i.e. tumor-suppressive) or M2 (i.e. tumor-supportive) macrophages [28-31]. For example, macrophage subsets can also be defined spatially within tumors as peri-vascular, stromal, and peri-tumoral. This infantry of monocyte-derived cells then orchestrates multiple tumor-dependent functions (step 6) including angiogenesis, matrix remodeling, immunosuppression, and metastasis which are hallmarks of cancer [13].

The Cancer-Inflammation Cycle coordinates the myeloid compartment in tumor and lymphoid tissues. For instance, bone marrow-derived myeloid cells are the predominant source of tumor-infiltrating myeloid cells and mediate resistance to therapies, including chemotherapy, radiotherapy, and immunotherapy [19, 32]. In mouse models of lung and pancreatic cancer, tissue-resident myeloid cells, such as embryonic-derived macrophages, have also been found to contribute to the myeloid reaction and serve distinct roles from bone marrow-derived cells in orchestrating the tumor microenvironment and supporting tumor development [33, 34]. Whereas some tumor-infiltrating myeloid cells may be retained indefinitely within tumors, others (e.g. dendritic cells) may ultimately exit tumors to enter draining lymph nodes for presentation of antigen [35]. In doing so, the Cancer-Inflammation Cycle converges with the Cancer-Immunity Cycle [36] which defines key processes fundamental to the productivity of T cell immunosurveillance in cancer. Specifically, the Cancer-Inflammation Cycle regulates the priming and effector phases of the Cancer-Immunity Cycle by directing the immunoregulatory functions of myeloid cells in lymph nodes and tumor, respectively. For instance, myeloid cells are fundamental in the priming of tumor-specific T cells and regulate the effector activity of T cells in tumors [37]. Thus, the Cancer-Inflammation Cycle details steps for maintaining the inflammatory reaction in cancer which is also a fundamental determinant of T cell immunosurveillance. In addition, it portrays a conceptual model that may be used to understand and potentially disrupt or even redirect inflammation in cancer.

Cancer inflammation is a major regulator of productive T cell immunity. Most commonly, inflammation is viewed as an obstacle to T cell immunosurveillance. However, the pliability of myeloid cells renders them vulnerable to re-education and as a result, to shifting their

phenotype from immunosuppressive to immunostimulatory [14]. To this end, triggering a potent T cell immune response against cancer may lead to a reshaping of the infiltrating myeloid cell reaction which then becomes essential, rather than an obstacle, to the success of immunotherapy. Thus, the Cancer-Inflammation and Cancer-Immunity Cycles are interdependent and together may be viewed as containing the necessary elements for generating both pro- and anti-tumor inflammation. A major challenge is how to remove or redirect inhibitory elements of the inflammatory reaction that restrain the potential of productive T cell immunosurveillance without interfering with components necessary for a successful immune response.

3. Inflammation as a determinant of immune escape in cancer.

The capacity to evade immune recognition is characteristic of cancer [13] and is facilitated, at least in part, by chronic inflammation [19]. Tumor cells exploit four hallmarks of immune escape defined by decreased antigenicity, reduced immunogenicity, formation of an immunosuppressive microenvironment, and impairment of immune capacity, which refers to the ability of the immune system to produce anti-tumor activity [38]. Inflammation contributes to each of these hallmarks which we discuss below. For example, inflammation shapes tumor cell antigenicity, or the presence of antigens capable of eliciting an immune response. Tumors which lack sufficient antigenicity may appear invisible to the immune system. However, antigenicity can be toggled and in this regard, it can be enhanced by myeloid cell-derived reactive chemical entities (e.g. reactive oxygen species) which display mutagenic potential and trigger genome-wide DNA mutations in mice [39]. Similarly, in patients, chronic inflammation in the setting of *Helicobacter Pylori* infection has been shown to associate with distinct genetic alterations in the gastric epithelium [40]. This process appears mediated by upregulation of activation-induced cytidine deaminase (AID), a DNA-mutator enzyme [40]. Further, TNF-induced AID expression has been linked to genetic mutations in human colonic epithelial cells [41]. Thus, inflammation may be a determinant of mutational load in human cancer. In mouse models of lymphoma, sarcoma, and breast cancer, IFN-γ exposure has also been associated with DNA damage [42]. Overall, increased mutational burden in tumor cells supports the emergence of mutated neoantigens which may be recognized by the immune system as non-self [43-46]. However, inflammatory mediators (e.g. TNF-α) can also reduce the immunogenicity of tumor cells, such as by increasing PD-L1 expression [47]. In mouse models of melanoma and colorectal cancer, overexpression of PD-L1 on tumor cells is sufficient to promote immune evasion by immunogenic tumors [48]. In addition, mouse models show that IL-6 produced by inflammatory cells induces STAT3 signaling in tumor cells and their paracrine release of immunosuppressive molecules (e.g. VEGF, IL-10) which then impair cancer immunosurveillance [49]. Thus, inflammation is not only a determinate of tumor cell antigenicity but can coordinate the release of inflammatory mediators which reduce tumor cell immunogenicity, or the capacity to trigger a productive adaptive immune response.

Tumor cells must ultimately circumvent immune pressure arising from acquisition of antigens that provoke dissimilarity from self. Darwinian selection imposed by the immune system enforces the emergence of tumor cells with reduced antigenicity, reduced immunogenicity, or both [26, 38]. However, tumor cells also establish a microenvironment,

of inflammatory cells and other stromal cells that restrain the productivity of T cell immunosurveillance. These inflammatory cells deplete vital nutrients (e.g. tryptophan and arginine) necessary for T cell effector activity [50], while also facilitating the production of immunosuppressive elements (e.g. adenosine) that impair anti-tumor T cell biology [51]. In doing so, the stromal microenvironment that surrounds tumor cells assumes a hostile phenotype that fosters immune dysfunction rather than activation. Chronic systemic inflammation in the setting of cancer may also impair the functional capacity, or fitness, of the immune system. To this end, a clinical study in patients with advanced adenoma of the colon showed that increased mobilization of myeloid cells from the bone marrow associates with decreased responsiveness to a MUC1 vaccine [52]. Indeed, myeloid cells can directly impinge upon adaptive immunity via multiple mechanisms, including depletion of key amino acids (e.g. tryptophan and arginine) that are critical for T cell function [53], and production of immunosuppressive molecules, such as reactive oxygen species and nitric oxide which impair T cell activity [54]. In addition, chronic inflammation impairs the generation of memory T cell responses [55], which might be important for preventing disease relapse. Thus, local and systemic inflammation in cancer may influence the quality of immune cells and in doing so, may impact the success of immunotherapy.

4. The Inflammostat

During cancer development, inflammation is detected not only locally within a developing tumor, but also systemically. Collectively, local and systemic inflammatory responses form an inflammostat that contributes to the capacity of tumor cells to evade immune recognition and elimination. Within the blood, systemic inflammation associates with increases in inflammatory markers, such as neutrophils, monocyte subsets, C-reactive protein (CRP), IL-6, and serum amyloid A (SAA). These markers correlate with poor prognosis but may also impinge on treatment outcomes. For example, multiple meta-analyses show that an elevated neutrophil-to-lymphocyte ratio (NLR) associates with poor survival in patients treated with chemotherapy, independent of tumor histology [56-58]. In addition, an elevated NLR in patients with melanoma and NSCLC is associated with poor outcomes to immune checkpoint blockade therapy and correlates with reduced overall survival for patients with renal cell carcinoma treated with high-dose IL-2 [59-63]. Similarly, accumulation within the blood of $CD11b^{+}$ myeloid cells lacking HLA-DR correlates with decreased responsiveness to vaccines in patients [52]. CRP, which is primarily synthesized in the liver in response to IL-6, also associates with reduced survival in patients with melanoma treated with immune checkpoint blockade therapy [16, 64, 65]. However, these markers are not only prognostic but may also directly impair immune fitness. In support of this, CRP can inhibit T cell proliferation by disrupting calcium-dependent T cell signaling [65-67] and promote the expansion of myeloid cells with suppressive properties [68]. Similarly, SAA is an acute phase reactant produced primarily in the liver by hepatocytes and has been found to be a potent stimulator of myeloid cells leading to release of cytokines and chemokines, including IL-6, CXCL1, and G-CSF, which may then reinforce the systemic inflammatory reaction [69-71]. Taken together, the inflammostat, comprised of both systemic and local inflammation, is not only prognostic of poor outcomes in cancer but also a determinant of immunobiology.

The inflammostat is defined by the contexture of the inflammatory response to cancer and includes the type, polarity, and density of inflammatory immune cells (Figure 2). The parameters establishing this contexture consist of macrophages, immature myeloid cells, and dendritic cells as well as other innate immune cells (e.g. mast cells, eosinophils) that are detected locally within tumors and systemically in the blood. These cellular parameters associate with a polarity that defines their functional connotation and thus, their capacity to either support or inhibit productive T cell immunosurveillance in cancer. In the blood, systemic inflammation correlates with alterations in liver-specific acute phase reactants including increased CRP and SAA as well as a decrease in blood albumin levels [14]. Inflammatory mediators (e.g. G-CSF, CCL2, IL-8) released in response to cancer development trigger increased bone marrow mobilization of some myeloid cell subsets and interrupt the mobilization of others. For example, bone marrow mobilization of $CD15^+$ neutrophils and $CD14^+$ monocytes lacking HLA-DR accumulate in the blood of both mice and humans with systemic inflammation [52, 72, 73]. In contrast, bone marrow production of conventional dendritic cell subsets may be diminished, as seen in mice as well as patients with breast and pancreatic cancer [74]. Within tumors, myeloid cell accumulation is influenced by chemokine signatures established within the tumor microenvironment. To this end, chemokines lure circulating myeloid cells to gather within tumors where they then regulate T cell entry or exclusion. For example, $CD103^+$ dendritic cells that infiltrate tumors can support T cell recruitment and activity via interferon-dependent release of CXCL9/10 [75]. In the MC38 colorectal cancer model, CXCL9 production by $CD103^+$ dendritic cells was found to be critical for anti-tumor activity mediated by $CXCR3^+$ T cells in the setting of PD1 blockade [76]. In contrast, increased macrophage accumulation in tumors most often portends a poor prognosis and commonly displays an inverse relationship with T cell infiltration in mouse and human cancers [77, 78]. To this end, macrophages expressing scavenger receptors (e.g. CD206 and CD163) are recognized for their capacity to orchestrate immunosuppression [79, 80]. However, the cellular phenotype of macrophages ultimately governs their behavior. For instance, myeloid cells can be induced by interferons to activate the STAT1 signaling pathway and in doing so, increase their expression of MHC and co-stimulatory molecules (e.g. CD86) that are critical for supporting T cell activation and effector activity [81, 82]. However, these signals also enhance the production of immunoregulatory molecules, such as PDL1 and IDO, which subsequently aim to dampen an ongoing immune response [83, 84]. Thus, the inflammostat is dynamic and not only defined by inflammatory cells and their mediators but also by their functional phenotype, or polarity.

The importance of inflammation in cancer is increasingly appreciated. Preclinical models have established inflammation as a generalized mechanism of resistance to chemotherapy, radiotherapy, and immunotherapy. Despite this, strategies to merely disrupt or redirect elements of the inflammatory response have produced little clinical benefit for patients with advanced malignancies. In contrast, intervening on inflammation as an approach to prevent cancer development or its recurrence has produced promising outcomes. For example, exploratory results from a randomised, double-blind, placebo-controlled trial showed that blockade of IL-1β associated with decreased lung cancer incidence and mortality in patients with atherosclerosis and prior myocardial infarction [85]. Similarly, anti-inflammatory

medications including aspirin, which irreversibly inactivates the cyclooxygenase (COX) enzyme, and celecoxib, a selective COX-2 inhibitor, have shown activity in reducing the risk of cancer for select patient populations in multiple prospective studies [14].Consistent with this, preclinical models of pancreatic cancer show that mere expression of oncogenic Kras is insufficient to promote cancer development in the absence of inflammation [86, 87]. Similarly, in mouse models of multiple myeloma, cancer progression is dependent on inflammatory mediators, specifically IL-18, that drive the generation of myeloid-derived suppressor cells to obstruct T cell immunosurveillance [88]. Together, these findings suggest that the inflammostat may assume distinct roles depending on the stage of cancer development. During the earliest stages of cancer conception, the inflammostat underpins tumor cell potential. However, in later stages of cancer, the inflammostat is a facilitator of cancer progression.

5. Blockade of the initiators of the cancer inflammation cycle

The Cancer-Inflammation Cycle defines multiple distinct steps that may be therapeutically targeted (Figure 3). For example, signaling pathways that coordinate the initiation of the cycle offer potential targets for therapy. One such target is focal adhesion kinase (FAK), a non-receptor tyrosine kinase family member that is activated in tumor cells [89-91]. FAK regulates secretion of multiple soluble factors involved in macrophage recruitment and polarization, granulocyte recruitment, and matrix remodeling [89, 90]. Tumor-derived chemokines, such as CCL2 and CXCL1, which lure macrophages and neutrophils, respectively, into the tumor microenvironment represent a second class of targets for intervening on cancer inflammation [72, 78, 92-98]. A third class of targets includes genomic drivers of cancer, such as oncogenic Kras, which trigger tumor cells to release soluble factors, including ICAM-1 and GM-CSF, which then attract macrophages early during tumor development to facilitate tumor growth, metastasis, and T cell exclusion [22, 99, 100]. In a mouse model of lung cancer, Myc was also shown to cooperate with oncogenic Kras activation to support inflammation and simultaneously, to drive immunosuppression by facilitating tumor cell release of CCL9 and IL23. Whereas IL23 coordinated exclusion of adaptive immunity, CCL9 attracted macrophages to tumors in a manner that required sustained Myc activation [101]. To this end, Myc deactivation was found to reverse inflammation as well as immunosuppression and correlated with tumor regression. Thus, strategies to intervene on oncogene-driven signaling pathways or on downstream molecules may hold promise for reprogramming the immunological state of tumors.

Tumors can adapt swiftly to changes in their surrounding microenvironment. For example, tumor cells respond to cytotoxic stress (e.g. radiation and chemotherapy) by increasing their release of myeloid chemoattractants (e.g. CCL2 and CSF1) which then support neovascularization and elaboration of immunosuppression within tumors [94, 102]. However, disruption of a single chemokine signaling pathway can also invoke compensatory mechanisms that sustain pro-tumorigenic inflammation, immunosuppression and foster therapeutic resistance. For example, blocking the recruitment of either $CXCR2^{+}$ neutrophils or $CCR2^{+}$ monocytes is sufficient in a mouse model of pancreatic cancer to trigger a reciprocal increase in the alternative cell population [95]. This compensatory response to

disruption of the inflammatory reaction thwarts the efficacy of chemotherapy but can be circumvented by dual targeting of both the CCR2 and CXCR2 signaling pathways. Similarly, mouse models have revealed that inhibition of CSF1R as a strategy to deplete tumor-associated macrophages arouses cancer-associated fibroblasts which release chemoattractants to facilitate the recruitment of $CXCR2^{+}$ neutrophils [103]. Together, these findings illustrate the significance of redundancy mechanisms that coordinate the myeloid reaction in cancer. However, while blockade of inflammatory elements trigger compensatory mechanisms, withdrawal of chemokine blockade has been found in a mouse breast cancer model to accelerate cancer progression as a result of a rebound in myeloid cell recruitment [104]. This finding raises important concerns with the translation of strategies aimed at long-term disruption of myeloid cell trafficking in cancer. One approach to circumventing this issue may be to incorporate chemokine blockade administered temporally with cytotoxic- and immune-based therapies to transiently disrupt the recruitment of myeloid cell subsets that act to inhibit treatment efficacy. Nonetheless, these preclinical studies suggest that the cancer inflammostat is hardwired with resilience and as a result, it may not be sufficient to disrupt a single mechanism underpinning the initiation and recruitment of inflammation but rather require a coordinated attack on multiple mechanisms and steps within the Cancer-Inflammation Cycle.

6. Myeloid-dependent orchestration of immune suppression in cancer

Tumor-infiltrating myeloid cells undergo differentiation to establish extraordinary diversity that is detected transcriptionally as well as spatially within tumors. However, the precise mechanisms by which this infantry of myeloid cells cooperates to direct biology within tumors is still not completely understood. Despite this, it is clear that myeloid cells are influential in defining the immunological state of the tumor microenvironment. To this end, tumor-infiltrating macrophages deplete essential amino acids necessary for T cell effector function. For instance, indoleamine 2,3 dioxygenase (IDO), produced by macrophages, catabolizes tryptophan (Trp) to kynurenine (Kyn). In mouse models of cancer, IDO regulates immune tolerance by depleting tryptophan levels needed for T cell activity and by producing tryptophan metabolites, such as kynurenine, that support immunosuppression [105-107]. Increased IDO activity in patients with cancer is marked by a decrease in the serum Trp/Kyn ratio and associates with a poor prognosis [105, 108]. Similarly, neutrophils express and release arginase into their surrounding microenvironment to deplete arginine levels [50]. Arginine is an important amino acid involved in cellular proliferation, protein synthesis, metabolite production (e.g. polyamines and nitric oxide), and T cell biology. Increased arginase expression is a classic mechanism of T cell suppression mediated by myeloid cells [54, 109-111]. In cancer patients, plasma levels of arginine are commonly decreased [112]. Notably, decreased arginine concentrations directly affect T cell metabolism and in doing so, impair T cell survival and their anti-tumor activity [113]. Taken together, myeloid cells shape the metabolic state of the host as well as the tumor microenvironment with implications for the efficacy of T cell immunosurveillance in cancer.

Although myeloid cells residing within tumors are fundamental to defining the immunological state of the tumor microenvironment, macrophages residing outside of tumors also regulate immunosurveillance in cancer [114]. To this end, depletion of

extratumoral macrophages in secondary lymphoid organs may be sufficient to facilitate the infiltration of T cells into spontaneously-arising tumors. Moreover, T cell-dependent anti-tumor efficacy achieved with chemotherapy and a CD40 agonist was found to be dependent on elimination of extratumoral macrophages [114]. It is noteworthy, though, that this same immunotherapy approach, in which chemotherapy is combined with a CD40 agonist, was effective at facilitating T cell infiltration into implanted tumors without a requirement for elimination of extratumoral macrophages [114]. This observation implies that extratumoral macrophages are co-opted during spontaneous cancer development and that mechanisms of immune resistance may differ depending on the tumor model investigated. Nonetheless, elements of inflammation occurring outside of tumors may be critical in defining T cell immunosurveillance in cancer.

Tumor-infiltrating macrophages can regulate immunosurveillance in cancer by intermingling with T cells in the stromal microenvironment that surrounds tumor cells. In this regard, macrophages form long-lived interactions with T cells and in doing so, can sequester T cells away from tumor cells [77]. Within tumors, macrophages upregulate immunoregulatory molecules, such as PD-L1, which protects them during antigen presentation from T cell-mediated killing [115], but also imparts them with the capacity to restrain both T cell proliferation and release of cytokines [116, 117]. Although IFN-γ is a major mechanism for upregulation of PD-L1 on myeloid cells, PD-L1 expression can be triggered by multiple mechanisms. For example, hypoxia can upregulate PD-L1 on myeloid cells in multiple mouse models of cancer [117]. Tumor cells can also instruct myeloid cells to upregulate PD-L1 in a COX2/PGE2 dependent manner [116]. However, the capacity of myeloid cells to inhibit T cells in a cell-contact dependent manner extends beyond PD-L1. Macrophages and other antigen presenting cells can express other checkpoint molecules, such as B7S1, which affect T cell differentiation in tumors and limit their expansion and cytolytic activity [118]. Signaling proteins, such as PI3Kγ and BTK, also engender tumor-infiltrating macrophages in mouse models of breast and pancreatic cancer with a transcriptional program that supports T cell suppression [119, 120].

Within tumors, myeloid cells actively remodel the extracellular matrix as if attempting to repair a wound. In this process, they respond to signals, such as ATP, which can be released by dying tumor cells [121]. Myeloid cells use P2 adrenergic receptors (e.g. P2X7) to sense extracellular ATP (eATP), which acts as a Danger-Associated Molecular Pattern (DAMP) to trigger inflammation [122, 123]. For example, eATP acts as a chemoattractant for circulating neutrophils [124-128]. During inflammation, eATP also undergoes phosphohydrolysis by ectonucleotidases. Specifically, eATP is degraded to AMP by CD39 and then hydrolyzed by CD73 to adenosine and inorganic phosphate [51]. CD39 is expressed by an array of tumor-infiltrating leukocytes, including regulatory T cells, effector T cells, and myeloid cells. Notably, CD39 is upregulated on activated T cells; is suggested to mark tumor-reactive effector T cells within tumors; but is also associated with reduced T cell polyfunctionality [45, 129-131]. In contrast, CD39 expression on myeloid cells correlates with their capacity to suppress T cell functions [132]. Similarly, while CD73 is expressed on macrophages, multiple cell subsets can express CD73 including tumor cells, regulatory T cells, lymphocytes, and dendritic cells [133]. Together, CD39 and CD73 are important factors regulating adenosine production.

Whereas adenosine supports wound healing in non-malignant settings [134, 135], production of adenosine in cancer is associated with immunosuppression [51]. The suppressive activity of adenosine is ascribed to activation of adenosine A2A receptors (A2AR) which elicit the expansion of regulatory T cells but also impair the cytotoxic, proliferative and cytokine release potential of effector T cells [51]. Myeloid cells also express A2ARs and respond to adenosine by restraining anti-tumor T cell activity [136]. In a mouse model of colon adenocarcinoma, CD39 antibodies were used to inhibit eATP conversion to adenosine and in doing so, were found to augment eATP-P2-mediated proinflammatory responses [137]. In this study, blockade of CD39 enzymatic activity triggered intra-tumoral macrophage depletion and NALP3 inflammasome activity leading to generation of IL-1β and IL-18. Altering the inflammatory reaction in tumors with CD39 blockade also enhanced T cell proliferation and effector function as well as reversed anti-PD1 resistance. Combining antibodies that block both CD39 and CD73 to disrupt their sequential activity for producing adenosine has also been explored using peripheral blood mononuclear cells isolated from breast cancer patients [138]. In this model system, addition of ATP suppressed human T cell proliferation in response to CD3-CD28 stimulation. This suppression was more effectively reversed with combined antibody blockade of both CD39 and CD73 compared to either alone. These data support a role for CD39 as a pivotal regulator in balancing the pro-inflammatory effects of eATP with CD73-dependent production of adenosine which favors immunosuppression. Overall, it is evident that tumor-infiltrating myeloid cells convey a variety of regulatory strategies capable of supporting tumor cell evasion of T cell immunosurveillance.

7. Toggling the phenotype of the inflammatory reaction in tumors

Although cancer inflammation is most commonly skewed toward promoting tumor growth and inhibiting immune activation, the inherent pliability of myeloid cells raises the possibility that inflammation may be redirected to have anti-tumor and immunostimulatory properties. As such, the Cancer-Inflammation Cycle may also be viewed as a model for devising strategies capable of harnessing the therapeutic potential of the inflammatory response to cancer.

The phenotype of myeloid cells is defined by an array of signals received from the surrounding microenvironment. For example, CSF-1, IL-4, IL-13, and IL-10 are cytokines that contribute to the development of myeloid cells displaying immunosuppressive features. In contrast, IFN-γ and acute Toll-Like Receptor (TLR) stimulation (e.g. LPS) have long been associated with instructing myeloid cells with anti-tumor properties [28, 139]. In cancer, inflammatory monocytes are recruited to tumors and are most commonly viewed as myeloid-derived suppressor cells [73]. However, in mouse models of pancreatic cancer, this same myeloid cell subset can be engendered with anti-tumor and anti-stromal properties in response to systemic activation of the CD40 signaling pathway [140-142]. In this regard, CD40 stimulation triggers the release of IFN-γ which induces inflammatory monocytes with anti-tumor properties and instructs them to facilitate the release of matrix metalloproteinases within tumors that then transiently resolve elements of the stromal matrix. This anti-stromal response sensitizes tumor cells to cytotoxic chemotherapy. Similarly, partial activation of CD11b, an integrin involved in the recruitment of myeloid cells to sites of inflammation, can

redirect myeloid cells with immunostimulatory properties capable of fostering productive T cell immunosurveillance in a mouse model of pancreatic cancer [143]. Inhibition of class IIa histone deacetylase (HDAC) also stimulates the recruitment and differentiation of macrophages that are highly phagocytic and in doing so, sensitizes mouse breast tumors to chemotherapy and immune checkpoint blockade [144]. Thus, the myeloid response to cancer may be harnessed for therapeutic benefit, both by re-education of existing tumor-associated myeloid cells towards an anti-tumor phenotype and by *de novo* recruitment of myeloid cells with anti-tumor properties.

The fate of tumor-infiltrating myeloid cells is ultimately defined by the tumor microenvironment. As such, maintaining an anti-tumor shift in the phenotype of cancer inflammation is challenged by the inevitable tendency to revert to a pro-tumor state. For example, lactic acid produced by tumor cells as a by-product of glycolysis supports a pro-tumor phenotype in macrophages [145]. Similarly, macrophages are lured into hypoxic regions in tumors in response to hypoxia-induced Semaphorin 3A (Sema3A) and as a result, acquire a pro-tumor phenotype. Disrupting the Sema3A/Neuropilin-1 signaling axis in mouse models of cancer prevents macrophage recruitment to hypoxic regions and supports T cell-dependent anti-tumor immunity [146]. The importance of instructing and maintaining cancer inflammation with an anti-tumor phenotype is accentuated by its requisite role in T cell-dependent tumor immunity.

For example, macrophages responding to cytokines (e.g. IFN-γ and GM-CSF) released by tumor-infiltrating T cells trigger endogenous immunity and eliminate tumor cells in models of ovarian cancer [147]. This finding reveals an interdependent relationship between cancer inflammation and adaptive immunity. Whereas cancer inflammation can suppress T cell immunosurveillance, T cells can engender cancer inflammation with anti-tumor functions and in doing so, inflammation may then nurture a productive Cancer-Immunity Cycle. Thus, establishing productive T cell immunosurveillance may be a tipping point for successfully toggling and maintaining the inflammostat in a position supportive of immune-mediated elimination of cancer.

The anti-tumor potential of myeloid cells is determined by a balance of inhibitory and stimulatory signals. For macrophages, this balance is critical to defining their capacity to phagocytose tumor cells and mediate anti-tumor activity. As such, tumor cells evade clearance by macrophages by overexpressing cell surface proteins, including CD47, CD24, and β2M [148-150], which act as ‘don’t eat me’ signals and inhibit the phagocytic machinery of macrophages. Disrupting these signals with monoclonal antibodies has shown therapeutic promise in models of human solid cancers as well as in patients with Non-Hodgkin’s Lymphoma [151, 152]. However, merely blocking inhibitory signals without provision of activation stimuli may not be sufficient for persuading macrophages to attack tumor cells [153]. Moreover, the metabolic state of macrophages may be fundamental to engaging their appetite for eliminating tumor cells [153]. To this end, TLR9 agonists can rewire macrophages with a metabolic state that shunts tricarboxylic acid cycle intermediates for *de novo* lipid biosynthesis that is necessary for their phagocytosis of tumor cells [153]. This process also imparts macrophages with antitumor potential capable of overcoming inhibitory signals mediated by CD47 on tumor cells. Thus, toggling the phenotype of

macrophages is a promising approach for converting the inflammatory reaction from a therapeutic obstacle to a clinical opportunity.

8. Combined targeting of the Cancer-Immunity and Cancer-Inflammation Cycles

Inflammation is a major determinant of anti-tumor immunity and acts as a rheostat to finetune T cell immunosurveillance. However, mere targeting of the Cancer-Inflammation Cycle has yet to reproducibly demonstrate clinical benefit in patients with advanced cancer. Given the interconnection between cancer inflammation and T cell immunosurveillance, preclinical and clinical studies are investigating the benefit of combining strategies that intervene on inflammation and concurrently, potentiate effector T cell activity while overcoming mechanisms of T cell exhaustion. To do this, three major approaches are being studied in which immune checkpoint inhibitors are combined with therapies that (i) disrupt cytokine and chemokine signals (e.g. FAK, CSF1R, CXCR2), (ii) activate myeloid cells to bridge innate and adaptive immunity (e.g. CD40, TLR9), and (iii) inhibit inflammatory elements involved in metabolic dysregulation (e.g. IDO, arginase, adenosine).

It has become increasingly clear that multiple tumor intrinsic mechanisms of cancer inflammation converge to regulate T cell immunosurveillance. Derailing these signaling pathways may shift the immunological state of tumors from immune-resistant to -sensitive. For example, one approach is to inhibit signals that promote the recruitment of immunosuppressive myeloid cells to tumors. FAK activity in tumor cells facilitates the release of multiple chemoattractants involved in establishing myeloid-dependent immunosuppression in tumors [89-91]. Blockade of FAK signaling in models of pancreatic cancer impairs myeloid cell recruitment and in doing so, unveils the efficacy of immune checkpoint blockade [91]. In patients, defactinib, an oral ATP-competitive FAK inhibitor is being tested in combination with anti-PD1 therapy for the treatment of advanced cancer. Preliminary results show safety of this combination and suggest potential clinical activity [154].

Whereas FAK inhibition aims to impair the release of a range of chemoattractants that orchestrate immunosuppression in cancer, an alternative approach is to intervene selectively on distinct soluble factors that foster cancer inflammation. For example, tumor and host cells produce CSF1 which signals through CSF1R to regulate macrophage phenotype and to mediate macrophage homing and survival. In patients with advanced cancer, CSF1R inhibition is tolerable and demonstrates biological activity as seen by elimination of tumor-associated macrophages. However, with the exception of tenosynovial giant cell tumors [155-157]. CSF1R-directed therapies have not produced clinical activity as monotherapy in patients. In mice, anti-CSF1R therapy triggers a compensatory accumulation of neutrophils within tumors, which support tumor growth. The chemokine C-X-C motif receptor 2 (CXCR2) mediates neutrophil homing via interaction with multiple chemokines, including CXCL1, CXCL5, and CXCL8. In mouse models of sarcoma and pancreatic cancer, inhibition of CXCR2 in combination with anti-PD1 therapy reduces metastases and improves the efficacy of anti-PD1 immunotherapy [96, 158]. Further, anti-CSF1R therapy

combines with CXCR2 inhibition to unleash the capacity of anti-PD1 checkpoint inhibition to trigger T cell-dependent immunity in mouse models of cancer [103]. Ongoing clinical studies are evaluating CSF1R blockade as well as CXCR1/2 inhibition in combination with checkpoint inhibitor therapy for the treatment of solid and hematologic malignancies (NCT02777710, NCT03927105, NCT03697564, NCT02880371, NCT03502330, NCT03238027, NCT02526017, NCT02829723, NCT03161431).

Myeloid cells are central to the development of productive T cell immunosurveillance in cancer. Acting as a bridge to alert the adaptive immune system of non-self, myeloid cells process and present antigens to prime and activate antigen-specific T cells. Classically, this process is mediated by dendritic cells which much be “licensed” with T cell stimulatory capacity [159-162]. In this regard, stimulation of CD40 expressed on dendritic cells triggers their cross-presentation of antigens and subsequent priming of T cells. Agonistic CD40 monoclonal antibodies can substitute for CD40L, the natural ligand of CD40 which is expressed on activated T cells [163-165]. In patients, CD40 antibodies have produced modest activity as monotherapy with some responses reported in patients with melanoma [166, 167]. However, mere stimulation of the CD40 pathway produces no clinical benefit for most patients and similarly, shows limited activity in many mouse models of cancer [167]. However, CD40 is fundamental to the efficacy of T cell immunotherapy, where anti-tumor activity mediated by tumor-specific T cells is reliant on CD40 and CD40L [168]. For these reasons, CD40 agonists are now being studied for their capacity to sensitize tumors to immune checkpoint blockade. For example, CD40 agonism can induce APCs to secrete IL-12 which decreases PD1 expression on tumor-infiltrating T cells and in doing so, conditions murine tumors for enhanced responsiveness to anti-CTLA4 and anti-PD1 therapy [169]. In addition, preclinical models show that CD40 agonists can enhance the therapeutic potential of tumors responsive to dual immune checkpoint blockade with anti-PD1 and anti-CTLA4 [170]. Together, these preclinical data suggest a role for CD40 agonists in settings where checkpoint blockade produces anti-tumor activity but does not achieve complete remission. However, for pancreatic tumors where neither CD40 agonism or dual checkpoint inhibitor blockade produces significant activity, the combination in preclinical models is also ineffective. This treatment resistance, though, may be overcome by depleting extra-tumoral macrophages [114] or by genetic ablation of CXCL1 release by tumor cells [92]. In patients with advanced pancreatic cancer, CD40 agonists have been combined with anti-PD1 therapy and found to be safe [171]. However, in this study, chemotherapy was also included making it unclear whether tumor responses seen in patients were produced by chemotherapy or the combination.

Whereas CD40 agonists have mainly been used as a strategy to trigger systemic immune activation, TLR agonists have been administered intratumorally to invoke chemokine and antigen release and to enhance T cell infiltration locally [172, 173]. TLRs recognize conserved microbial molecules, so-called pathogen-associated molecular patterns (PAMPs). In mice, intratumoral injection of a TLR7 agonist shifts the intratumoral macrophage population from immunosuppressive to immunostimulatory [174]. Similarly, TLR9, which is activated by microbial DNA, has garnered interest for its potential to enhance the activity of anti-PD1 treatment in patients with advanced melanoma [175]. A CpG-oligodeoxynucleotide (CMP-001) designed to activate TLR9 via intratumoral injection has

also been studied in combination with anti-PD1 therapy for the treatment of patients with PD-1 refractory advanced melanoma. Of 68 patients treated in the phase I setting, the objective response rate was 22% and produced increases in CXCL10, PDL1 and tumor-infiltrating CD8 T cells [176]. Thus, strategies to redirect the local inflammatory response in cancer may sensitize tumors to T cell-directed immunotherapy.

Cancer inflammation is sustained by multiple signals which may be disrupted therapeutically. One such example is interleukin-6, a prototypical inflammatory cytokine that plays a central role in the acute phase response. IL-6 activates STAT3 locally in tumor and stromal cells as well as systemically, such as in hepatocytes which respond to IL-6 by elaborating the production of CRP and SAA [177], [178]. Broadly, IL-6 has pleiotropic capacity and impacts multiple biological processes including inflammation, bone homeostasis, metabolism and T cell differentiation [179, 180]. In the context of cancer, IL-6 can be produced by both tumor and host cells. Additionally, IL-6 can be detected in the peripheral blood of patients and is associated with poor outcomes when elevated [181-185]. In pre-clinical models, IL-6 blockade in combination with anti-PD-L1 therapy elicits productive anti-tumor immunity and effectively controls tumor growth [186, 187]. An early phase clinical trial investigating the combination of anti-IL-6 therapy and checkpoint inhibition for the treatment of melanoma is ongoing (NCT03999749).

Cancer inflammation produces derangements in metabolism which can impair the functional fitness of the immune system. In this regard, IDO is a key enzyme involved in tryptophan metabolism. Reduced tryptophan levels and increased tryptophan metabolites combine to alter T cell and dendritic cell function, and in doing so, inhibit productive anti-tumor immunosurveillance [107]. In tumors inflamed with T cell infiltrates, IDO is often increased due to IFN-γ produced by tumor-infiltrating lymphocytes [107]. In preclinical models of cancer, IDO inhibition combines to enhance the efficacy of immune checkpoint blockade [188]. In patients with melanoma, IDO inhibition has been combined with anti-PD1 therapy but unexpectedly was found not to significantly improve outcomes compared to anti-PD1 therapy alone [189, 190]. However, recent biomarker analyses suggest that IDO inhibition may need to be considered for select patient populations. For instance, a decreasing Trp/Kyn ratio after treatment with anti-PD1 therapy has been found to associate with worse overall survival in patients with melanoma and renal cell carcinoma [108]. This finding highlights the potential relevance of metabolic aberrations in governing the efficacy of cancer immunotherapy. To this end, extracellular metabolites represent a distinct class of immunosuppressive molecules. For example, adenosine produced from eATP released within tumors in the setting of hypoxia and cell death can inhibit T cell immunosurveillance. Adenosine engages with A2AR, including A2a and A2b adenosine receptors, on immune cells producing diverse immunoregulatory effects [51, 191]. In mouse models of cancer, acquired resistance to anti-PD-L1 therapy is associated with upregulation of CD38. CD38 contributes to accumulation of adenosine in tumors and in doing so, inhibits CD8 T cell function and the efficacy of anti-PDL1 immunotherapy [192]. Blockade of CD38 reversed this biology and sensitized tumors to anti-PDL1 therapy. Alternative strategies to disrupt the adenosine pathway include targeting CD73 and A2AR. In mice, inhibition of A2AR synergizes with anti-PD1 therapy to delay tumor outgrowth, reduce metastasis, and improve survival [193-195]. Similarly, treatment with anti-CD73 to block adenosine production

combines with anti-PD1 therapy in multiple mouse models of cancer to produce T cell dependent anti-tumor activity [196]. Together, these studies form the basis for ongoing clinical trials investigating the CD39-CD73-adenosine signaling pathway as monotherapy and in combination with immune checkpoint blockade [197].

9. Concluding Remarks

The immune system is characterized by remarkable diversity and specificity that combine to create an exceptional therapeutic opportunity for distinguishing cancer from normal tissue. Harnessing the immune system for therapy is now standard of care for many cancers. However, while immunotherapy can produce exceptional responses in some patients including durable complete remissions, the majority of patients still do not respond. Multiple mechanisms may shape immune-resistance in cancer, but inflammation has emerged as a fundamental determinant. Inflammation acts as a rheostat, which we have termed the inflammostat, to finetune T cell-dependent immunosurveillance. This inflammostat is defined by the degree and phenotype of local and systemic inflammatory responses associated with cancer. Once triggered, inflammation is self-propagating and reinforced in a vicious cycle. By understanding the biology that drives inflammation in cancer, inflammatory-related biomarkers (Figure 2) may allow for mapping out the Cancer-Inflammation Cycle for individual patients. Functional determinants associated with liver inflammation, bone marrow mobilization, immune cell activation, myeloid cell chemotaxis, inflammatory molecules, and metabolism have been identified that associate with treatment and survival outcomes. Many of these determinants can be detected readily with blood sampling and may provide an opportunity for non-invasive and efficient evaluation of the inflammatory status of a patient. Inclusion of peripheral markers of inflammation in future clinical trials is needed to robustly define the utility of these markers and associations with tumor biology. Ultimately, profiling the inflammostat may enable tailoring specific therapeutic approaches for intervening on cancer inflammation with the goal to unleash productive T cell immunosurveillance and produce durable complete remissions for cancer patients.

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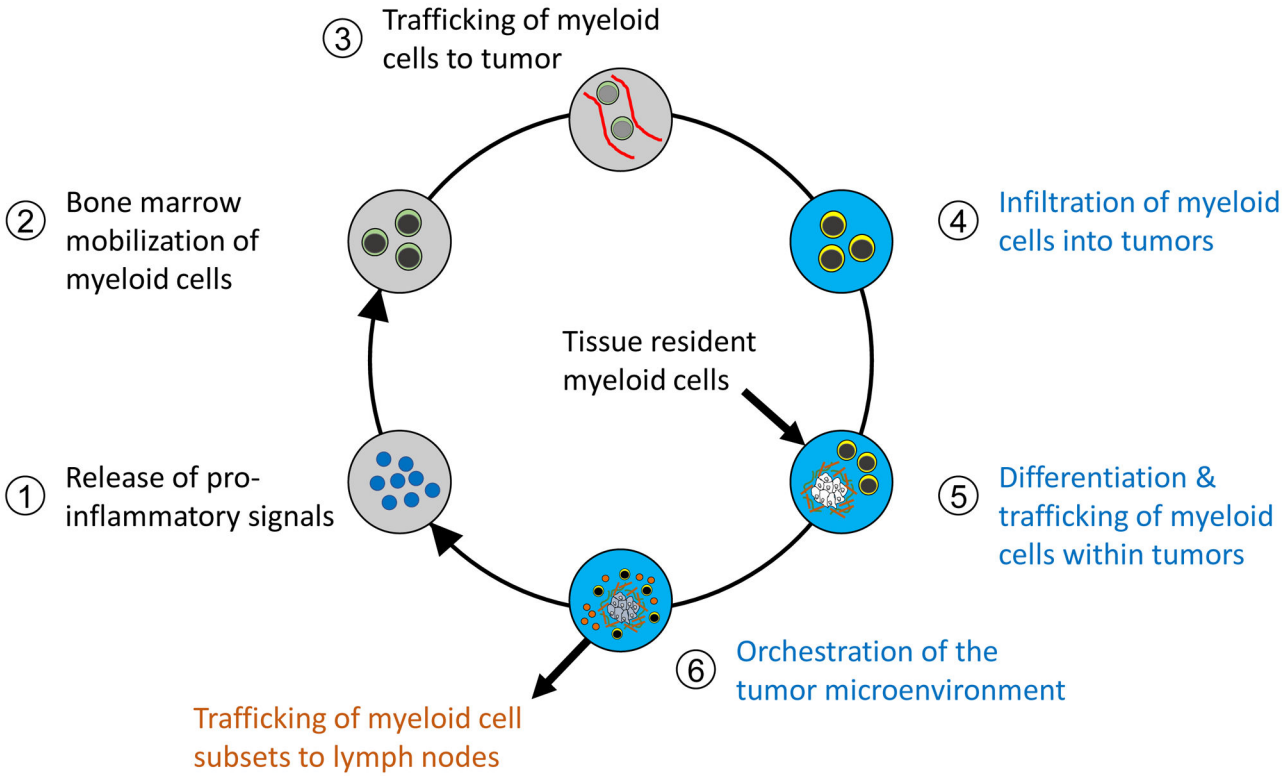

Figure 1. The Cancer-Inflammation Cycle.

Cancer inflammation is a cyclic process that is initiated at disease conception. The cycle is dynamic and evolves with cancer progression. This cycle can be divided into six major steps, starting with the release of pro-inflammatory signals that elaborate the mobilization (from bone marrow or adjacent tissues), recruitment, and differentiation of myeloid cells. Tumor-infiltrating myeloid cells then orchestrate a microenvironment that is supportive of cancer growth, metastasis, immune evasion, and therapeutic resistance. Each step is described above, with the anatomic location of each immunologic event given including processes occurring extra-tumoral (grey), intra-tumoral (blue), and within draining lymph nodes (orange).

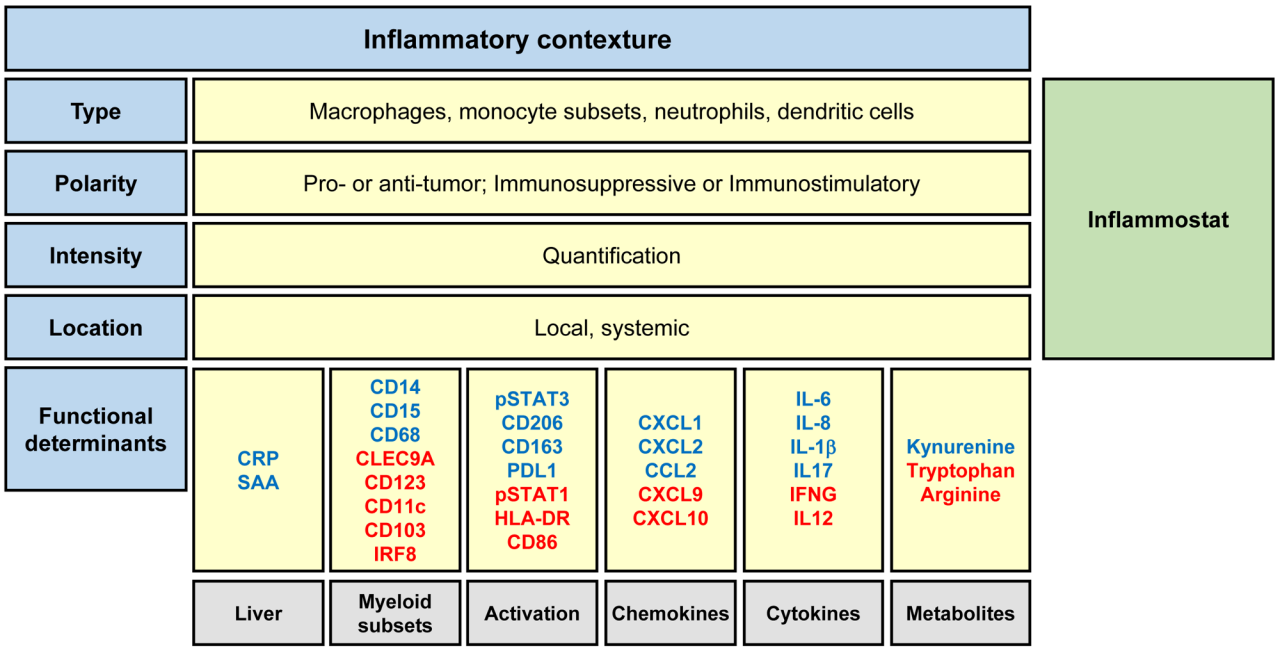

Figure 2. Graphical representation of the Inflammatory Contexture and Inflammostat.

The inflammatory contexture is defined as the type, polarity, intensity, and location of cancer inflammation. Parameters comprising the inflammatory contexture include myeloid cell subsets detected within the blood and tumor (type), the functional phenotype of myeloid cells (polarity), and the intensity of the inflammatory response (intensity) determined by cell density within tumors and the magnitude of inflammatory factors present within the bloodstream (location). The immunostat, a rheostat of the inflammatory reaction, is derived from the magnitude and polarity of the inflammatory contexture and serves as a fundamental regulator of immunosurveillance. A high inflammostat signifies an immunological state that is unlikely to respond to therapies that seek to solely engage T cell immunosurveillance by derailing immune checkpoints (e.g. CTLA4 and PD1/PDL1). The functional orientation of the inflammatory contexture is characterized by proteins and their activation status (e.g. phosphorylation) that predict the phenotype of inflammatory cells (e.g. immunostimulatory or immunosuppressive) and that associate with responses to immunotherapy. Shown are a select set of proposed determinants and their association with immune suppression (blue) or stimulation (red). Abbreviations: CRP, c-reactive protein; CXCL/CCL, chemokine motif ligands; IFNG, interferon gamma; IRF8, interferon regulatory factor 8; IL, interleukin; PDL1, programmed death-ligand 1; SAA, serum amyloid A; STAT, signal transducer and activator of transcription.

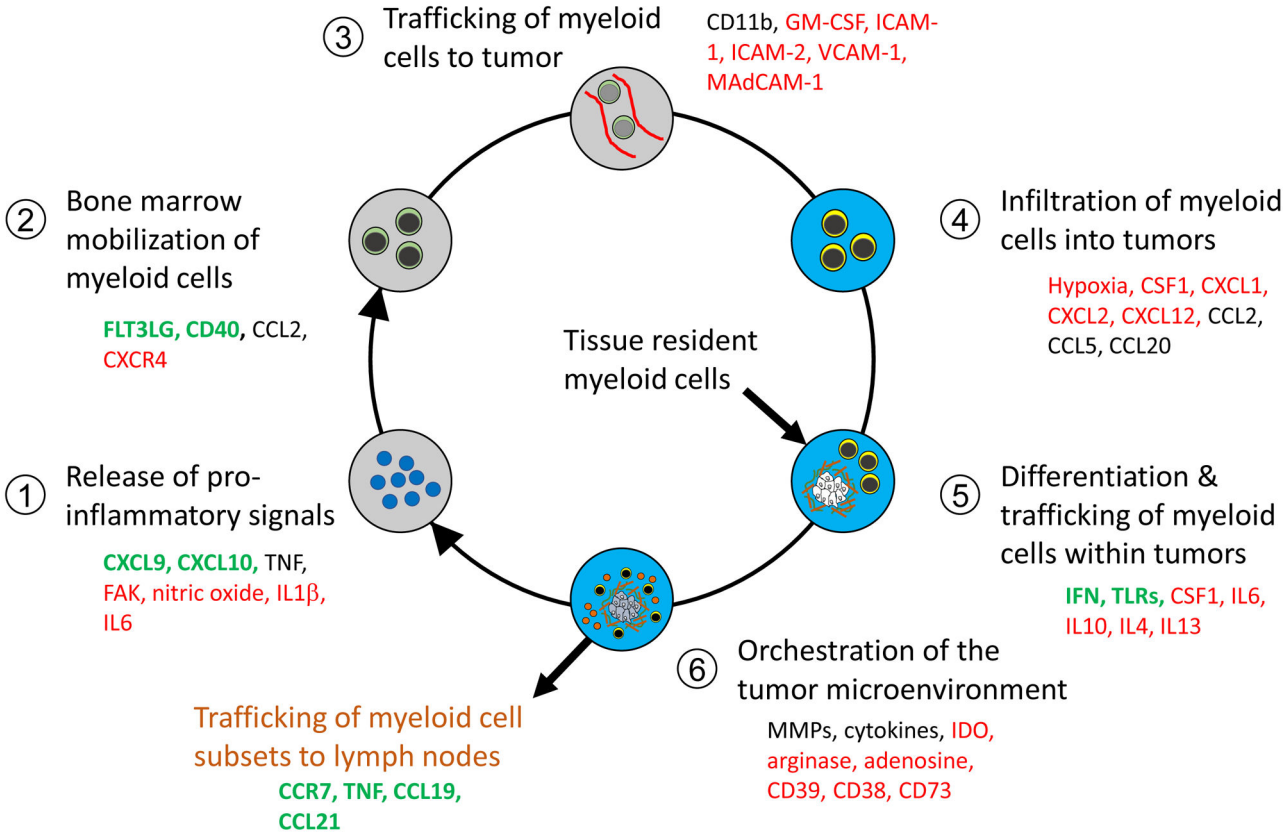

Figure 3. Regulatory factors that shape the Cancer-Inflammation Cycle.

Each step of the Cancer-Inflammation Cycle is coordinated by an array of factors. Factors shown in green may stimulate anti-tumor immunity, whereas factors shown in red engage an inflammatory response that more commonly suppresses anti-tumor immunity. Factors that are in black may support either the stimulation or suppression of anti-tumor immunity. Together, these factors contribute to the inflammatory contexture of cancer and establish an inflammatory rheostat (“inflammostat”). In addition, these factors identify potential therapeutic targets that may be derailed to disrupt the Cancer-Inflammation Cycle as a strategy to disengage the pro-tumorigenic potential of inflammation and redirect the inflammatory response with immunostimulatory properties. Abbreviations: CSF1, colony stimulating factor 1; IL, interleukin; CXCL/CCL, chemokine motif ligands; FAK, focal adhesion kinase; FLT3Lg, Fms related tyrosine kinase 3 ligand; ICAM, intracellular adhesion molecule; IDO, indoleamine 2,3-dioxgenase; IFN, interferon; MAdCAM-1, mucosal addressin cell adhesion molecule 1; MMP, matrix metalloproteinase; TLR, toll like receptor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.