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Immune Surveillance: A Balance Between Pro- and Anti-tumor Immunity

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Summary

Pre-cancerous and malignant cells can induce an immune response which results in destruction of transformed and/or malignant cells, a process known as immune surveillance. However, immune surveillance is not always successful, resulting in “edited” tumors that have escaped immune surveillance. Immunoediting is not simply the absence of anti-tumor immunity, but is due to pro-tumor immunity that blocks anti-tumor adaptive and innate responses, and promotes conditions that favor tumor progression. Several immune pro-tumor effector mechanisms are up-regulated by chronic inflammation, leading to the hypothesis that inflammation promotes carcinogenesis and tumor growth by altering the balance between pro-and anti-tumor immunity, thereby preventing the immune system from rejecting malignant cells, and providing a tumor-friendly environment for progressive disease.

Introduction

The concept that the immune system can be harnessed as a therapeutic agent to treat established tumors (immunotherapy) was first proposed in the early 1900’s by Paul Ehrlich. He suggested that molecules that we now know as antibodies, could deliver toxins directly to cancer cells. Ehrlich’s “magic bullet” strategy was expanded upon in the 1950’s by Burnet and Thomas. They hypothesized that the immune system may also protect against nascent cancers by destroying malignant cells before they developed into detectable tumors, a concept that has become the immune surveillance hypothesis [1,2]. Although enthusiasm for the validity of immunotherapy and immune surveillance waned in the 1970’s, subsequent studies demonstrated that the immune system can protect against tumor onset and be manipulated to reject established tumors. Revival of the immune surveillance hypothesis led to a re-working of the initial concept, to include the concept of “immunoediting.” During immunoediting, the immune system destroys many pre-cancerous and malignant cells; however, some cells escape the immune response and give rise to progressively growing tumors. Immunoediting is thought to continue throughout the life of the tumor so that the phenotype of an established tumor has been directed by the host’s immune response. It has also become apparent that both innate and adaptive immunity have a “dark” side and can promote tumor progression as well as mediate tumor destruction. Not surprisingly, chronic inflammation, which has long been associated with increased tumor risk, is involved in polarizing immunity towards those effectors that facilitate tumor growth. As a result, the immune system has the potential to either promote or

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delay tumor onset and progression, and the effectiveness of immune surveillance and the efficacy of immunotherapy depend on the balance between these diametric opposites (Figure 1). After a brief over-view of the observations supporting the concept of immune surveillance, this article will review the cells that mediate pro-and anti-tumor immunity including a discussion of how inflammation polarizes innate and adaptive immunity towards either a pro-tumor or anti-tumor phenotype.

Immune surveillance and immunoediting

Rejuvenation of the concept that the immune system protects against nascent malignant cells occurred with the demonstration that mice deficient for various components of the adaptive or innate immune systems were more likely to develop some types of tumors, specifically sarcomas as opposed to carcinomas, as compared to immune competent mice, when exposed to carcinogens or transplanted with syngeneic tumor cells. Immune deficiencies included the absence of B cells and αβ or γδ T cells due to deletion of the recombination-activating gene-2 (RAG2) required for immunoglobulin and T cell receptor gene rearrangements, and the absence of interferonγ (IFNγ) or the ability to respond to IFNγ, a key mediator of cellular immunity. Similarly, mice that were knocked-out for perforin, an essential molecule for cell-mediated cytotoxicity used by most effector cells of the innate and adaptive immune systems, or mice deficient for natural killer (NK) or NKT cells, effector cells of the innate immune system, were also more susceptible to spontaneous tumors or had more rapid growth rates of transplanted tumors as compared to wild type or immune competent mice [3,4].

Circumstantial evidence suggests that immune surveillance and immunoediting also occurs in cancer patients. Individuals with hereditary or acquired immunodeficiencies have higher incidences of some types of viral- and carcinogen-associated cancers. Organ transplant patients maintained on immune suppressive drugs are 3–8 fold more likely to develop cancer than normal controls, although tumors are not randomly distributed in all anatomical locations [1, 2]. In contrast, ovarian, colorectal [5], and melanoma patients whose tumors have high levels of tumor-infiltrating lymphocytes have a better prognosis [1,2]. Collectively, experimental studies and the clinical observations in patients indicate that the immune system can foil carcinogenesis and mediate regression of established tumor.

$CD4^+$ and $CD8^+$ T lymphocytes

$CD4^+$ and $CD8^+$ T cells are the principal helper and effector cells, respectively, of adaptive cellular immunity, and many immunotherapy strategies are aimed at activating these cells to promote tumor cell destruction and long-term immune memory against recurrence of primary disease or outgrowth of metastases. Type 1 $CD4^+$ T cells (Th1) facilitate tissue destruction and tumor rejection by providing help to cytotoxic $CD8^+$ T cells, while Type 2 $CD4^+$ T cells T (Th2) facilitate antibody production by B cells and polarize immunity away from a beneficial cell-mediated anti-tumor response (Figure 2). $CD4^+$ T regulatory cells (T regs), which are naturally occurring or antigen-induced, promote tumor immunity by blocking the activation of $CD8^+$ cytotoxic T cells. Although additional studies are needed to fully characterize the mechanism(s) by which $CD4^+$ T regs block $CD8^+$ T cell activation, T reg expression of cytotoxic T lymphocyte antigen 4 (CTLA4), an inhibitory signal for T cells, may be involved [6]. As for many pro-tumor mediators, inflammation enhances T reg function since prostaglandin E2 (PGE2) causes differentiation of T regs and increases their immune suppressive activity [7,8]. In addition to their inhibiting $CD8^+$ T cell activation, $CD4^+$ T regs block killing by natural killer cells [9], and thereby down-regulate both adaptive and innate anti-tumor immunity. Although most T regs are $CD4^+$, $CD8^+$ T regs induced by plasmacytoid DC have been identified in ovarian cancer patients [10].

Recently identified $CD4^+$ Th17 cells [11,12], may also promote tumor progression. Th17 cells are induced by IL-23, a cytokine closely related to IL-12 and whose receptor shares the IL-12Rβ1 with IL-12 [13]. Upon activation by IL-23, Th17 cells produce IL-17 which exacerbates inflammation by inducing IL-6, TNFα, G-CSF, and other acute phase proteins [14]. IL-23 itself, has been shown to reduce $CD8^+$ T cell infiltration into tumors, thereby promoting tumor growth [13,15] (Figure 2). Earlier experiments using IL-17-transfected tumor cells were inconclusive as to whether IL-17 promoted tumor growth or tumor rejection [16, 17]. This ambiguity may be explained by a recent study showing that Th17-induced IL-6 blocks $CD4^+$ T regs [18]. Additional experiments are clearly necessary to clarify the roles of IL-23, Th17 cells, IL-17, and regulatory T cells in tumor progression.

B lymphocytes

Tumor-reactive monoclonal antibodies can have significant anti-tumor efficacy when passively administered to cancer patients. In contrast, most cancer vaccines or other therapies that are aimed at inducing tumor-reactive antibodies are largely ineffective in promoting tumor rejection, although there are exceptions [19]. More recent experiments indicate that activated B cells and their soluble products, presumably antibodies, can also facilitate carcinogenesis. Using a transgenic mouse model in which the human keratin 14 promoter drives expression of early region genes of human papilomavirus 16, B cells were shown to promote a chronic inflammatory microenvironment that recruits innate immune cells and factors to the tumor site, thus establishing a stromal environment that supports de novo carcinogenesis. Thus, humoral immunity can enhance malignant transformation by activating the innate immune system [20,21].

Macrophages

Macrophages are part of the innate immune system and play important roles in all aspects of immunity. They are an exceptionally heterogeneous population of cells. Similar to $CD4^+$ T cells, macrophages can contribute to tumor destruction or facilitate tumor growth and metastasis, depending on their phenotype (Figure 3).

Macrophages that are “classically activated” by IFNγ and bacterial lipopolysaccharides destroy tumor cells through their production of nitric oxide and type 1 cytokines and chemokines. These macrophages also function as antigen presenting cells to activate cytotoxic $CD8^+$ T [22]. In contrast, macrophages activated through the “alternative” pathway with IL-4, IL-13 and/or TGFβ promote tumor progression by enhancing angiogenesis and producing type 2 cytokines and chemokines [23]). Because of the similarities in cytokine profiles, Mills coined the terminology “M1/M2” after the Th1/Th2 paradigm for classically-activated and alternatively-activated macrophages, respectively [24]. This jargon was further developed by Mantovani and colleagues, although they are careful to point out that macrophages are a continuum of phenotypes with M1 and M2 being the polarized extremes [25,26].

Most progressively growing tumors are infiltrated by large numbers of macrophages. These tumor-associated macrophages (TAMS) are a key component of the tumor stroma and are essential for the angiogenesis and matrix remodeling that supports progressively growing neoplasms. Using a spontaneous mouse mammary tumor model, the transition from pre-malignant to malignant phenotype was associated with increased blood vessel formation, and that the elimination of TAMS blocked the neoangiogenesis, while early infiltration of TAMS enhanced angiogenesis [27]. Metastasis is also enhanced by TAMS when they promote the intravasation of tumor cells into local blood vessels, as graphically shown by intravital multiphoton imaging of live mammary tumors in situ [28]. As shown in human ovarian cancer, TAMS also promote tumor progression by blocking the activation of tumor-specific T cells by their expression of B7-H4, a negative regulator of T cell activation [29]

Since TAMS promote tumor progression, they are often called M2 macrophages. Gene profiling of TAMS and alternatively-activated peritoneal macrophages (M2) has confirmed that TAMS and M2 macrophages express many of the same molecules; however, TAMS also express some IFN-inducible genes that are characteristic of M1 macrophages, indicating that they are intermediate in the continuum of macrophage phenotypes [30,31].

Natural killer (NK) cells

NK cells are components of the innate immune system that interact with adaptive immunity through their production of cytokines that modulate dendritic cell (DC) and cytotoxic T cell maturation. They are well recognized for their ability to directly lyse MHC class I-deficient tumor cells through the engagement of their activating receptors and lack of engagement of their inhibitory receptors. However, a subset of NK cells are also cytotoxic for activated $CD8^+$ T cells [32] and DC [33], and thereby can reduce CD8-mediated anti-tumor immunity. In addition, NK cells have been shown to inhibit DC-mediated antigen presentation through a non-cytotoxic mechanism [34], and elimination of NK cells increases activation of tumor-specific $CD8^+$ T cells following immunization [35].

NKT cells

NKT cells, which express both NK and TCR, bridge the innate and adaptive immune systems. They are usually $CD4^+$ and respond to lipid and glycolipid antigens as presented by non-classical MHC class I CD1d molecules. Until recently there was confusion as to whether NKT cells promote tumor rejection or enhance immune surveillance. NKT cells prevent the spread of B16 melanoma metastases and promote immune surveillance in mice treated with the carcinogen 3-methyl-cholanthrene. However, CD1d knockout mice, which lack CD1d-restricted NKT cells, reject recurrent fibrosarcomas and are resistant to the 4T1 mammary carcinoma. These apparently conflicting findings were resolved when it was found that type I NKT cells, which express the invariant Vα14Jα18 TCR Vβ chain, mediate tumor rejection, while type II NKT cells, which express a non-Vα14Jα18 TCR Vβ chain, promote tumor growth [36].

Myeloid-derived suppressor cells (MDSC)

MDSC are a morphologically and functionally heterogenous population of cells of myeloid origin that are elevated in almost all patients and experimental mice with cancer [37]. They suppress both innate and adaptive anti-tumor immunity by inhibiting $CD8^+$ and $CD4^+$ T cells, NK and NKT cells, and by blocking DC maturation [38–41]. MDSC suppress T cells through their production of arginase and/or reactive oxygen species (ROS); however, there is variability in which mediator(s) is used depending on the tumor model [38,42,43]. MDSC heterogeneity is further demonstrated by the requirement for CD80 expression for suppression by some MDSC [44] and the absence of CD80 on other MDSC [45,46]. Likewise, the IL-4Rα is required for the IL-13-induced activation of some MDSC [47]; however, equally suppressive MDSC have been isolated from IL-4R-deficient and wild type mice [40]. Suppression requires MDSC to T cell contact, and for suppression of $CD8^+$ T cells, MDSC nitrate tyrosines of the $CD8^+$ T cells' TCRs, thereby rendering the T cells incapable of activation by peptide-MHC I complexes of antigen presenting cells [48].

In addition to inhibiting anti-tumor immunity by blocking T cell activation, MDSC also induce $CD4^+$ T regs through an IL-10 and IFNγ-dependent process that is ROS-independent [49]. They also polarize immunity towards a tumor-promoting type 2 phenotype by secreting high levels of IL-10 and shutting down macrophage production of the Type 1 cytokine, IL-12. Macrophages in turn, up-regulate MDSC production of IL-10 further favoring tumor progression [50].

MDSC are similar to other immune system cells in that chronic inflammation heightens their pro-tumor activity. IL-1β and IL-6 increase the accumulation and suppressive activity of MDSC [46,51,52], while reductions in these cytokines reduce MDSC levels [52]. PGE2 is one of the inflammatory inducers of MDSC, since co-cultures of c-kit$^+$ mouse bone marrow stem cells with PGE2 produce immune suppressive Gr1$^+$CD11b$^+$ MDSC [53], and cyclooxygenase-2 (COX-2) produced by human lung cancer cells up-regulates arginase expression in human MDSC [54].

Conclusions

The immune system has the capacity to either block tumor development and deter established tumors, or to promote carcinogenesis, tumor progression, and metastasis. Which of these conditions prevails depends on the balance between the pro- and anti-tumor mediators of both innate and adaptive immunity. Presumably, there are unifying mechanisms that orchestrate immunity towards tumor promotion vs. tumor destruction. Since many of the tumor-promoting elements of the immune system are induced by, or themselves cause, inflammation, chronic inflammation may be a key process that polarizes immunity towards a tumor-promoting phenotype [55]. Accordingly, chronic inflammation would produce an immune suppressive, tumor-friendly environment that would negate immune surveillance and be permissive for carcinogenesis. As tumor growth progressed and tumors themselves produced pro-inflammatory molecules, innate and adaptive immunity would be further polarized towards a tumor-promoting phenotype, creating an ideal environment for further tumor growth and metastasis (Figure 4). Chronic inflammation has long been associated with increased risk of tumor onset and progression, and is known to enhance angiogenesis and tissue remodeling, and promote protein and DNA damage through oxidative stress, processes that are integral to tumor progression [55–57]. By polarizing immunity towards a tumor-promoting phenotype, inflammation not only promotes the genetic and histological changes that facilitate carcinogenesis, but it also deters immune surveillance, thereby functioning as both an initiator and a protector for neoplastic cells.

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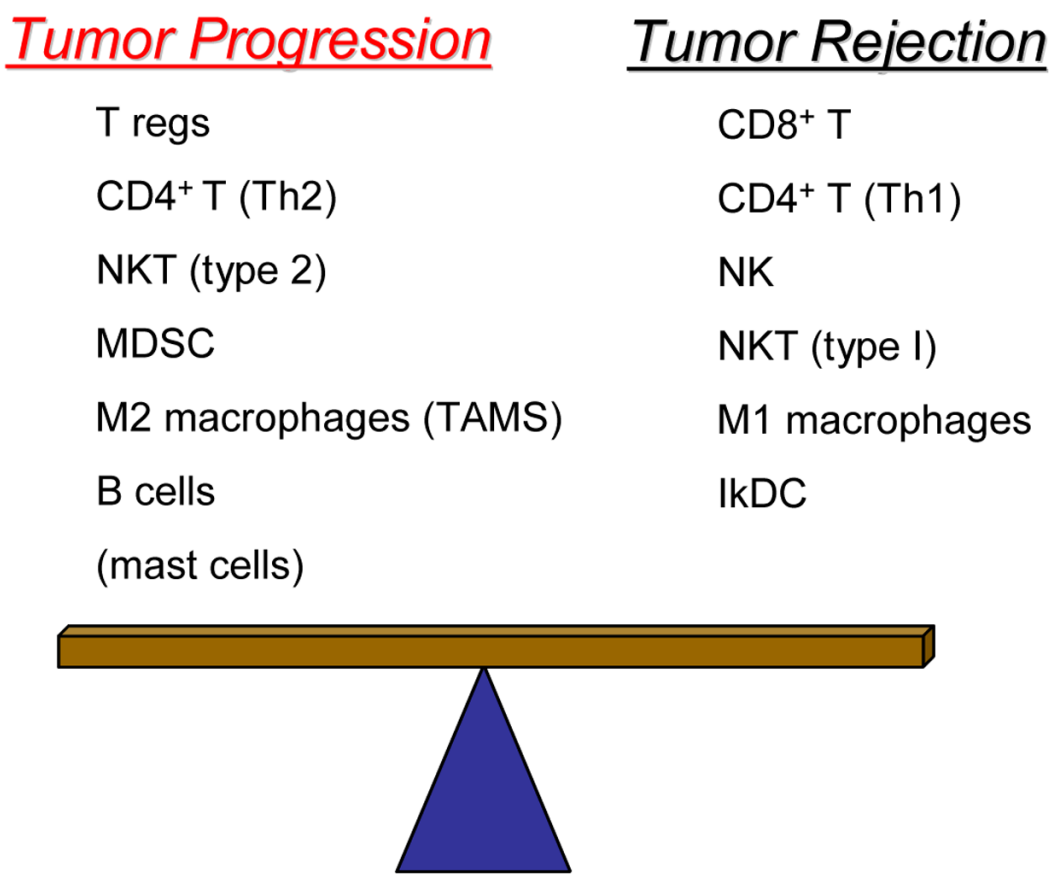

Figure 1.
Tumor immunity is a balance between immune mediators that promote tumor progression vs. mediators that promote tumor rejection. $CD4^+$ T regulatory cells, Type 2 $CD4^+$ T cells, Type 2 natural killer T cells, myeloid-derived suppressor cells, M2 or tumor-associated macrophages, B cells, and possibly mast cells promote tumor progression, while $CD8^+$ T lymphocytes, type 1 $CD4^+$ T lymphocytes, natural killer, type 1 natural killer T cells, M1 macrophages, and immune killer dendritic cells promote tumor destruction.

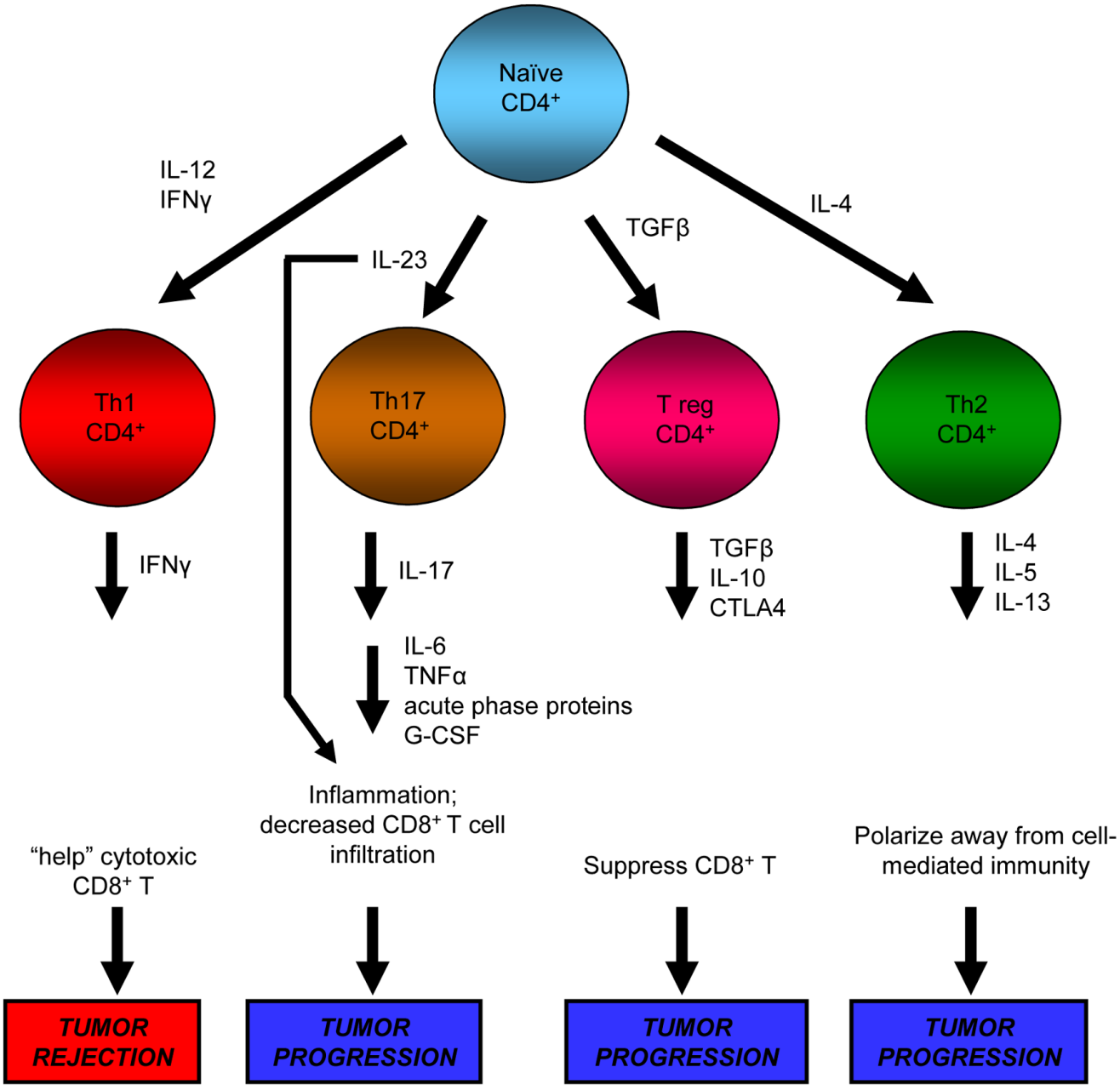

Figure 2.

$CD4^+$ T lymphocytes are induced by cytokines to produce cytokines that either promote tumor progression or mediate tumor elimination. Type 1 $CD4^+$ T cells are induced by IL-12 and IFNγ to produce IFNγ which promotes the differentiation and expansion of $CD8^+$ T cells that are cytotoxic for tumor cells. In contrast, IL-4 polarizes $CD4^+$ T cells towards a type 2 phenotype that produces IL-4, IL-5, and IL-13 which help B cells produce antibodies, thereby directing immunity away from a tumor-rejecting type 1 response. Under the influence of transforming growth factor β, $CD4^+$ T cells develop into T regs that actively block tumor immunity by suppressing tumoricidal $CD8^+$ T cells. Recently identified Th17 cells are induced by IL-23 to produce IL-17, which in turn induces cytokines and chemokines that promote inflammation. The resulting inflammatory mediators may contribute to tumor progression by

up-regulating immune suppressive cells of the adaptive and innate immune systems (see figure 4)

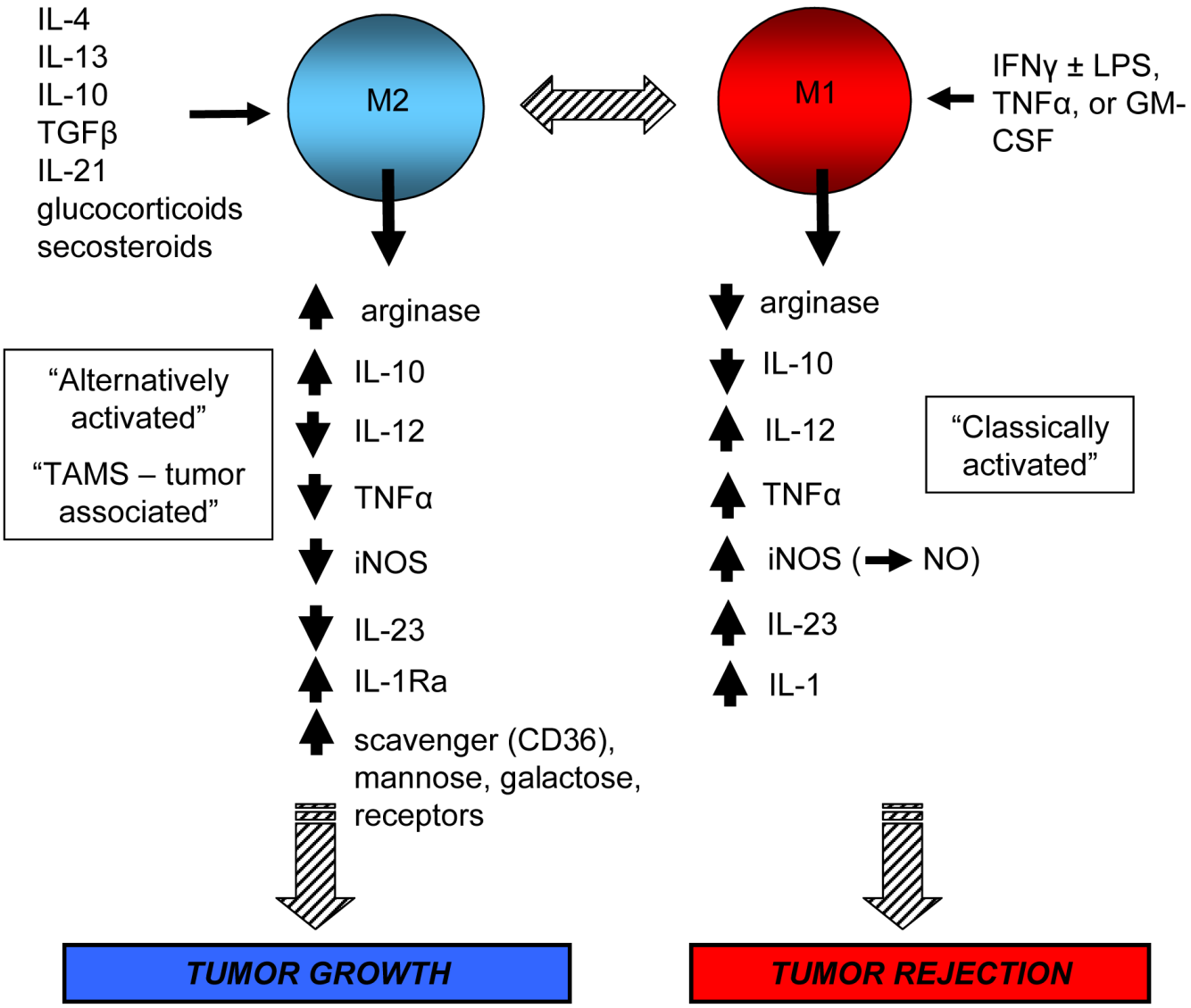

Figure 3.

Macrophages are differentially activated by different cytokines or other factors and become either tumor-promoting or tumoricidal. Classically-activated or M1 macrophages produce high levels of type 1 cytokines that promote a tumor-rejecting type 1 response as well as factors such as inducible nitric oxide synthase which are cytotoxic for tumor cells, and low levels of type 2 cytokines. In contrast, alternatively-activated or M2 macrophages produce high levels of cytokines that polarize immunity towards a tumor-promoting type 2 response, and low levels of cytokines that promote a tumor-destructive type 1 response. Some of the molecules produced by M2 macrophages attract additional pro-inflammatory mediators to the tumor site, thereby amplifying the inflammatory microenvironment.

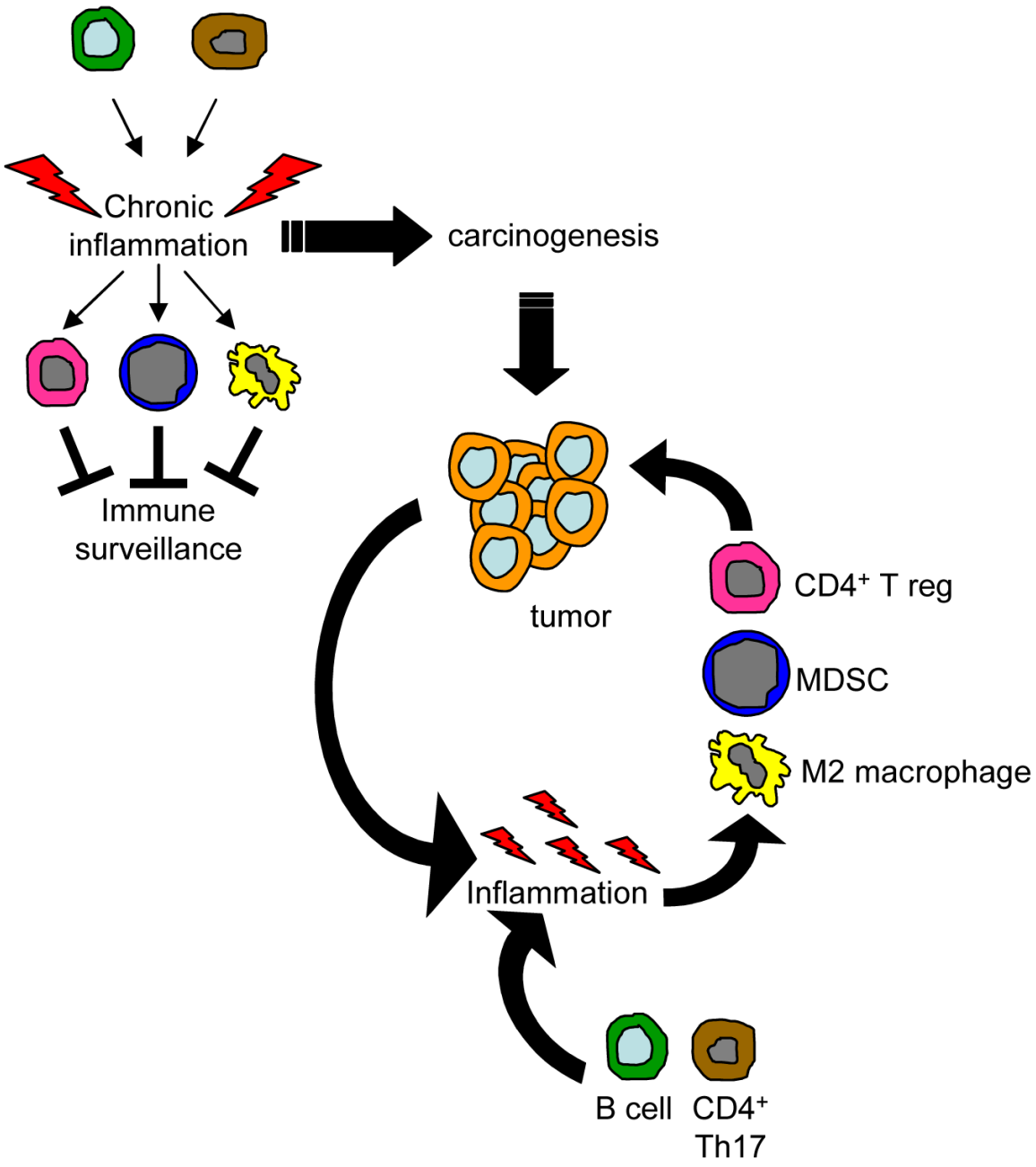

Figure 4.

Inflammation may regulate the balance between pro- and anti-tumor immunity by inducing the development of immune mediators that promote carcinogenesis and tumor progression. Activated B cells or possibly $CD4^+$ Th17 cells can contribute to an existing state of chronic inflammation or de facto induce inflammation which results in the increase and activation of M2 macrophages, $CD4^+$ T regulatory cells, and myeloid-derived suppressor cells. These immune suppressive cells then block immune surveillance, preventing the host's immune system from rejecting pre-malignant cells. In the presence of established tumor, the inflammatory environment is maintained by B cell-secreted factors and possibly $CD4^+$ Th17 cells, and by additional factors produced by the tumor cells and by host cells attracted to the

tumor site. This increased inflammation induces the accumulation and activation of additional M2 macrophages and myeloid and T suppressor cells which fuel tumor progression.