Journal of Cellular Biochemistry 101:918–926 (2007)

Immune Cells as Anti-Cancer Therapeutic Targets and Tools

Magnus Johansson,[1] Tingting Tan,[1] Karin E. de Visser,[1,3] and Lisa M. Coussens[1,2]*

[1]Department of Pathology, University of California, San Francisco, 2340 Sutter St., San Francisco, California 94143
[2]Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California 94143
[3]Department of Molecular Biology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

Abstract Chronic inflammation is a contributing factor to overall cancer risk as well as cancer promotion and progression; however, pathways regulating onset of cancer-promoting inflammatory responses are still poorly understood. Clinical data suggest that deficient anti-tumor cell-mediated immunity, in combination with enhanced pro-tumor humoral and/or innate immunity (inflammation), are significant factors influencing malignant outcome. Here, we discuss therapeutic implications from clinical data and experimental studies using de novo immune-competent mouse models of cancer development that together are revealing molecular and cellular mechanisms underlying interactions between immune cells and evolving neoplastic cells that regulate cancer outcome. Understanding the functionally significant links between adaptive and innate immunity that regulate cancer development will open new therapeutic opportunities to manipulate aspects of immunobiology and minimize lethal effects of cancer development. J. Cell. Biochem. 101: 918–926, 2007.

Key words: cancer; immune cells; inflammation; innate; adative

In the past 25 years, a majority of cancer studies have focused on examining functional consequences of activating and/or inactivating mutations in critical genes implicated in cell cycle control. While these studies have been instructive regarding the role of oncogene and tumor suppressor gene functions and signaling pathways regulating cell proliferation and/or cell death, they have largely ignored the fact that in vivo, cancers are heterogeneous multicellular growths whose survival and dissemination is dependent upon reciprocal interactions between genetically modified "initiated" cells and a dynamic microenvironment in which they live. Cancers are composed of multiple cell types, for example, fibroblasts, epithelial cells, innate and adaptive immune cells, cells forming blood and lymphatic vasculature, as well as specialized mesenchymal cell-types unique to each tissue microenvironment. While tissue homeostasis is maintained by collaborative interactions between all of these distinct cell types, cancer development is enhanced when mutant cells harness these collaborative capabilities to favor their own survival. Thus, genomic alterations effecting intrinsic cellular programs, for example, cell cycle check-point control, programmed cell death, differentiation, metabolism and cell adhesion, in combination with somatic or epigenetic alterations effecting extrinsic programs such as immune response, matrix metabolism, tissue oxygenation, and vascular status, underlie human cancer development.

IMMUNE REGULATION OF TISSUE HOMEOSTASIS

The mammalian immune system consists of multiple cell types and mediators that interact with each other and non-immune cells in complex and dynamic networks to ensure protection against foreign pathogens, while

*Correspondence to: Prof. Lisa M. Coussens, Department of Pathology, University of California, San Francisco, 2340 Sutter Street, N-221, San Francisco, CA 94143.
E-mail: coussens@cc.ucsf.edu

Received 15 November 2006; Accepted 16 November 2006
DOI 10.1002/jcb.21230

simultaneously maintaining tolerance towards self-antigens. Based on antigen specificity and timing of activation, the immune system is composed of distinct subsets—adaptive and innate. While cellular composition and antigen specificity of these subsets are distinct, each has developed sophisticated communication networks enabling rapid responses to foreign antigens.

Innate immune cells, for example, dendritic cells (DC), natural killer (NK) cells, macrophages, neutrophils, basophils, eosinophils, and mast cells, are first lines of defense against tissue injury. DCs, macrophages and mast cells, serve as sentinel cells pre-stationed in tissues and monitor their microenvironment continuously for signs of distress. When tissue homeostasis is disturbed, sentinel cells release soluble mediators (cytokines, chemokines, matrix remodeling proteases, reactive oxygen species (ROS), and bioactive mediators, e.g., histamine) that together induce mobilization and infiltration of additional leukocytes into damaged tissue (i.e., inflammation). Macrophages and mast cells also activate vascular and fibroblast responses in order to orchestrate elimination of invading organisms and initiate local tissue regeneration. DCs on the other hand, take up foreign antigens and migrate to lymphoid organs where they present their antigens to adaptive immune cells, thus acting as key players in the interface between innate and adaptive immunity. NK cells also participate in cellular crosstalk between innate and adaptive immune cells via their ability to bidirectionally interact with DCs; certain NK cell subsets eliminate immature DCs, whereas others stimulate DC maturation that then also reciprocally regulate NK cell activation [Raulet, 2004; Degli-Esposti and Smyth, 2005; Hamerman et al., 2005].

Induction of efficient primary adaptive immune responses requires direct interactions with mature antigen presenting cells and a pro-inflammatory milieu. Adaptive lymphocytes, such as B cells, $CD4^+$ (helper) and $CD8^+$ cytotoxic T lymphocytes (CTL), distinguish themselves from innate leukocytes by expression of somatically generated, diverse antigen-specific receptors, formed through random gene rearrangements, allowing a flexible and broader repertoire of responses as compared to innate immune cells expressing germline-encoded receptors. Distinctive $CD4^+$ T-cell subsets, for example, Th1 or Th2 T helper cells, secrete unique repertoires of cytokines that mediate their responses. Th1 cells produce interleukin (IL)-2 and interferon (IFN)-γ for example, and thereby direct cell-mediated immune (CMI) responses, whereas Th2 cells secrete IL-4 and IL-10 and facilitate local humoral immune (HI) responses. Together, activation of innate and adaptive immune response pathways efficiently removes or eliminates invading pathogens, damaged cells and extracellular matrix (ECM). Once assaulting agents are eliminated, immune cells are critically involved in normalizing cell proliferation and cell death pathways to enable re-epithelialization, new ECM synthesis and re-establishment of tissue homeostasis.

ANTITUMOR ACTIVITIES OF IMMUNE CELLS

The role of the immune system is to protect the body against infectious agents and to facilitate healing process following injury. Therefore, it seems intuitive that immune cells would also play an active role protecting against primary tumor development and/or metastases. Indeed, individuals suffering from various types of immune-deficiency disorders exhibit increased risk for some viral- and/or carcinogen-associated cancers [Zitvogel et al., 2006], thus indicating that absence of anti-viral immunity has effected their relative cancer risk. On the other hand, the relative risk of common epithelial cancers such as breast, prostate, ovarian, and uterine cancer, where cancer etiology is not commonly associated with viral infection or carcinogen exposure, is less than 1.0 in similar cohorts [de Visser et al., 2006], thus indicating a paradoxical regulatory role for the immune system during cancer development where cancer etiology is key.

Lymphocytes and some innate immune cells possess potent anti-cancer activities that can effect growth and/or dissemination of primary tumors. A recent study investigating characteristics of leukocytic infiltrations within colorectal cancers found that $CD3^+$ T cell densities within colorectal cancer biopsies, as opposed to peripheral blood, represented a better predictor of patient survival than current histopathological staging methods [Galon et al., 2006]. Infiltration of NK cells in human gastric or colorectal carcinoma is similarly associated with a favorable prognosis [Coca et al., 1997]. The major anti-cancer function of NK cells likely owes to

their ability to eliminate neoplastic cells with downregulated human leukocyte antigen (HLA) expression before they acquire malignant characteristics. The most compelling evidence for involvement of NK cells in killing human tumor cells in vivo derives from allogeneic bone marrow transplantation, where data indicates their ability to lyse tumor cells ex vivo, presence of NK cells within tumors, increased NK cell function and anti-tumor response in individuals treated with interleukin (IL)-2 and the correlation of decreased NK cell function with tumor progression [Orange and Ballas, 2006].

Based on the idea that a "tumor" can be a recognizable target for the adaptive immune system, several groups have attempted to activate adaptive immune cells in order to elicit anti-tumor immune responses [Dudley and Rosenberg, 2003]. In several experimental murine tumor models, $CD8^+$ T cells were found to be required for antitumor effects [Zitvogel et al., 2006]. Furthermore, that cytotoxic T-cells were able to eliminate only tumor cells expressing their cognate antigen, indicates a specific immune response [Dudley et al., 2003]. Interestingly, treating (by adoptive transfer) animals with tumor-associated B cells has been reported to result in the opposite effect, stimulating tumor invasion and metastasis through antibody–antigen complex-mediated granulocyte and macrophage induction [Barbera-Guillem et al., 1999], and thus highlighting the need to more fully understand all components of adaptive immunity activated during cancer development in tissues.

In order to survive, neoplastic cells must evade cytotoxic T lymphocyte rejection. This can be achieved through subversion of host anti-tumor immune responses. One plausible explanation for how tumor cells escape immune surveillance mechanisms is that neoplastic microenvironments favor polarized chronic pro-tumorigenic inflammatory states as opposed to those representing acute anti-tumor immune responses [Balkwill et al., 2005; Zou, 2005]. Clinical data indicate that the "immune status" of healthy individuals as compared to those harboring malignant tumors is distinct, where in the later population, T lymphocytes are found to be functionally impaired [Finke et al., 1999]. In addition, accumulation of chronically activated granulocytes/suppressor cells and regulatory T cells are found in the circulation, in lymphoid organs and in neoplastic tissues [Curiel et al., 2004; Serafini et al., 2004]. Together, immune states such as these disable tumor-killing $CD8^+$ CTL responses and enable states of immune privilege that foster escape from anti-tumor immunity while simultaneously exploiting activated immune cells that enhance cancer development.

Chronically activated innate immune cells can indirectly contribute to cancer development via suppression of anti-tumor adaptive immune responses, allowing tumor escape from immune surveillance. A subset of innate immune cells, for example, myeloid suppressor GR^+CD11b^+ cells, accumulate in peripheral blood of cancer patients [Almand et al., 2001; Serafini et al., 2004], as well as in tumors and lymphoid organs [Gabrilovich et al., 2001; Serafini et al., 2004; Zou, 2005]. Myeloid suppressor cells are known to induce T lymphocyte dysfunction by direct cell–cell contact and by production of immunosuppressive mediators, and thus actively inhibit anti-tumor adaptive immunity [Gabrilovich et al., 2001; Serafini et al., 2004]. Myeloid suppressor cells can also directly promote tumor growth by contributing to tumor-associated angiogenesis [Yang et al., 2004]. In addition, malignant lesions attract regulatory T cells that can suppress effector functions of cytotoxic T cells [Zou, 2005]. Classic regulatory T cells are $CD4^+CD25^+FOXP3^+$, however, different subtypes may also exist. Initial investigations have revealed that in vivo depletion of regulatory T cells using antibodies against CD25 enhanced anti-tumor T cell responses and induced regression of experimental tumors [Onizuka et al., 1999; Shimizu et al., 1999]. In an elegant study by Curiel et al. [2004], it was revealed that tumor-derived macrophages from patients with ovarian cancer produce CL22, a chemokine that mediates trafficking of regulatory T cells to tumors. These regulatory T cells in ovarian cancer patients suppressed tumor-specific T cell immunity, and their presence correlated with reduced survival. Thus, in the vicinity of a growing neoplasm, the balance between innate and adaptive immunity is often disturbed in favor of cancer progression. Taken together, the accumulated data from human and animal studies support the existence of an immune response involving $CD8^+$ T cells, T_H1 cells and NK cells that protect against tumor development and progression—a system that can be suppressed locally by myeloid suppressor cells and regulatory T cells.

PROTUMOR ACTIVITIES OF IMMUNE CELLS

The association of immune cells and cancer has been known for over a century [Balkwill and Mantovani, 2001]. Initially, it was believed that leukocytic infiltrates in and around developing neoplasms represented an attempt of the host to eradicate neoplastic cells, as described above. However, clinical and experimental data now indicate that chronic presence and activation of some innate immune cell types, for example, neutrophils, macrophages, and mast cells, exerts a promoting role during cancer development [Coussens and Werb, 2002; Balkwill et al., 2005; de Visser et al., 2006]. Malignant tissues containing infiltrates of macrophages (human breast carcinoma) and mast cells (human lung adenocarcinoma and melanoma), for example, correlate with an unfavorable clinical prognosis [Leek et al., 1996, 1999; Imada et al., 2000; Ribatti et al., 2003]. In experimental murine models of organ-specific cancer development, genetic elimination of mast cells or macrophages minimizes squamous carcinogenesis [Coussens et al., 2001; Giraudo et al., 2004], whereas elimination of macrophages during mammary carcinogenesis limits late-stage cancer progression and pulmonary metastasis formation [Lin et al., 2001]. Other cells of the myeloid lineage also have been reported to contribute to tumor development [Sparmann and Bar-Sagi, 2004]. NK cells can play a role in protection against experimental tumor growth, in part by producing mediators with anti-angiogenic properties [Smyth et al., 2001; Hayakawa et al., 2002]. Together, these studies have induced a paradigm shift regarding the role of immune cells during malignant progression. Whereas the historical viewpoint was that host immunity is protective with regards to cancer, it is now clear that certain subsets of chronically activated innate immune cells promote growth and/or facilitate survival of neoplastic cells.

In support of these experimental findings are population-based studies reporting that chronic inflammatory conditions predispose humans to certain cancers, most notably patients with chronic *Helicobacter pylori* infection exhibit a 75% increased risk for gastric cancer, the second most common type of cancer globally [Ernst and Gold, 2000; Kuper et al., 2000]. Consistent with this are experimental findings demonstrating that development of colon cancer in transforming growth factor beta-1 (TGFβ1)-deficient mice is essentially eliminated by maintaining mice in germ-free environments [Engle et al., 2002]. Other clinical examples where chronic inflammation has an associated increased cancer risk are inflammatory bowel syndrome with colon cancer [Shacter and Weitzman, 2002], chronic pancreatitis with pancreatic adenocarcinoma [Farrow and Evers, 2002], and hepatitis with hepatocellular carcinoma [Shacter and Weitzman, 2002]. Population-based studies examining long-term usage of anti-inflammatory therapeutics, for example, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and cycloygenase-2 (COX-2) inhibitors, support the conclusion that chronic inflammation enhances cancer risk [Peek et al., 2005; Ulrich et al., 2006]. However, it must also be appreciated that all organ systems are not identical and as such, there are also data indicating an increased risk of pancreatic cancer and Non-Hodgkin's lymphoma amongst long-term salicylic acid users [Cerhan et al., 2003; Schernhammer et al., 2004].

Innate immune cells directly potentiate cancer risk through the diversity of bioactive mediators they secrete and/or deliver to neoplastic tissue microenvironments. Leukocytes are variably loaded with chemokines, cytokines, cytotoxic mediators including ROS, serine-, cysteine-, and metallo-proteases, membrane-perforating agents, and soluble mediators of cell killing, such as tumor necrosis factor-alpha (TNF-α), interleukins and interferons [Tlsty and Coussens, 2006]. Individually, all of these molecules are known mediators of acute inflammation and evoke innate immune cell recruitment and/or activation, tissue remodeling and angiogenesis, and together, create an organ microenvironment favoring cell proliferation, genomic instability, and expansion of cell populations into ectopic tissue microenvironments, that is, malignant conversion and cancer development. Thus, clinical and experimental data largely indicate a promoting role for innate immune cells during neoplastic progression and suggest that elucidating the mechanisms by which inflammatory cells participate in carcinogenesis may eventually facilitate development of novel anti-cancer therapeutic agents.

Based on the inter-relationship between adaptive and innate immunity in tissue homeostasis and disease [Hoebe et al., 2004], we investigated whether activation of adaptive

immune responses was a critical regulator of chronic inflammation-associated with epithelial cancer development. To achieve this, we generated HPV16-expressing transgenic mice prone to squamous carcinoma development [Coussens et al., 1996], that were genetically deficient (−/−) for recombinase acitivating gene (RAG)-1 and thus lacking all mature B and T lymphocytes [de Visser et al., 2005]. HPV16/RAG-$1^{-/-}$ mice exhibited a markedly decreased infiltration of innate immune cells into premalignant skin that was associated with reduced local levels of tissue remodeling proteases activities and vascular endothelial growth factor (VEGF), lack of activation of angiogenesis, reduced epithelial proliferation, and retention of terminal differentiation in oncogene-positive keratinocytes. Thus, skin of HPV16/RAG-$1^{-/-}$ mice failed to progress beyond a hyperplastic phenotype, resulting in only 6.4% of HPV16/RAG-$1^{-/-}$ mice developing invasive squamous cell carcinomas of the skin as compared to ~50% in control HPV16 mice [de Visser et al., 2005]. Significantly, transfer of B lymphocytes or serum isolated from HPV16 mice, but not naïve wildtype mice, into HPV16/RAG-$1^{-/-}$ mice was sufficient to restore characteristics of premalignant progression, for example, chronic inflammation and infiltration of neoplastic skin by mast cells and neutrophils, development of angiogenic vasculature, epithelial hyperproliferation, and loss of keratinocyte terminal differentiation [de Visser et al., 2005]. Thus, soluble mediators derived from B lymphocytes enhance epithelial carcinogenesis in HPV16 mice by initiating a cascade of chronic inflammation in the premalignant microenvironment.

These experimental data are supported by clinical data revealing presence of antibodies, specific for tumor antigens, in serum of patients with squamous cell carcinoma of the head and neck whose presence were found to correlate to tumor progression and clinical course [Vlock et al., 1992]. Interestingly, an early case study reported that nonspecific removal of serum IgG from a patient with metastatic colon carcinoma correlated with an improvement in the general condition of the patient and decreased tumor size [Bansal et al., 1978]. More recent studies have demonstrated that proportions of T_H1 cells, identified by intracelluar production of interferon (IFN)γ or IL-2 is markedly reduced in peripheral blood of patients with bladder or colorectal cancer, whereas proportions of T_H2 cells producing IL-4, IL-6, and/or IL-10 is significantly elevated, as compared to otherwise healthy patient populations [Kanazawa et al., 2005; Agarwal et al., 2006]. Taken together, the accumulated data from human and experimental animal studies support the existence of a protumor immune response involving B cells, T_H2 cells and activated innate immune cells that favors neoplastic development and emergence of invasive carcinomas.

BALANCING PRO- AND ANTI-TUMOR IMMUNITY TO EFFECT CLINICAL OUTCOME

The Hegelian (or Fichtean) dialectic [Williams, 1992] is often presented in a threefold manner where a thesis is initially provided that gives rise to a reaction, followed by an antithesis, which contradicts the thesis. The conflict is later resolved by formation of a synthesis that reconciles their common truths and forms a new proposition. Perhaps the time has come to coagulate published disparate theories on the role of the immune system in cancer. Thus, there is compelling evidence for the thesis that the immune system protects the organism from tumor development, as well as for its antithesis, that the immune system promotes cancer progression. This paradoxical role during cancer development may seem contradictory; however, the conflict is resolved by altering the way in which the immune systems role is viewed.

During the last decade, insights have been gained regarding mechanisms underlying the dynamic interplay between immune cells and tumor progression. The accumulated data indicates that the outcome of an immune response toward a tumor is largely determined by the type of immune response elicited. A tumor-directed immune response involving cytolytic $CD8^+$ T cells, T_H1 cells, and NK cells appears to protect against tumor development and progression. If, on the other hand, the immune response involves B cells and activation of humoral immunity, and infiltration of T_H2 cells innate inflammatory cells into an organ harboring initiated cells, the likely outcome is promotion of tumor development and progression (Fig. 1). This balance between a protective cytotoxic response and a harmful humoral or T_H2 response can be regulated systemically by the general immune status of the individual, as well as locally by myeloid suppressor cells and

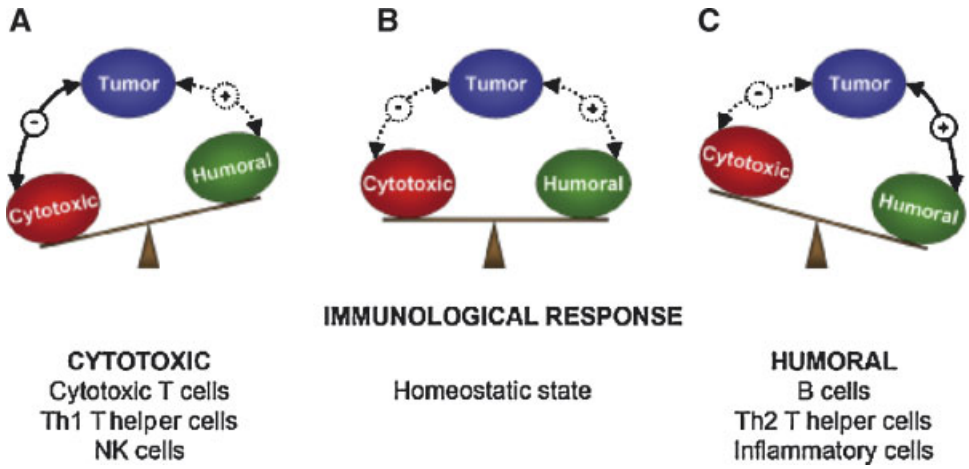

Fig. 1. Schematic overview of dynamic interactions between tumor cells and the host immune system. **A**: Balance in favor of a cytotoxic response, leading to tumor regression, (**B**) tumor evasion of an immunological response, (**C**) balance in favor of a humoral/innate response, stimulating tumor progression. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

regulatory T cells, and thus presents clinicians with attractive targets for anti-cancer immune-based therapies.

HOPES FOR THE FUTURE

Bolstering effective cytotoxic T cell responses, in combination with neutralizing harmful pro-tumor humoral and innate immunity would seem to represent a powerful anti-cancer therapeutic approach. The promise of such an approach recently became apparent in a study by Morgan et al. [2006]. The authors isolated autologous T cells from patients with metastatic melanoma, transfected the cells with a retrovirus encoding a tumor-recognizing T cell receptor, expanded them ex vivo followed by reinfusion into lymphodepleted patients following treatement with IL-2 to stimulate T cell reactivity. Two of 15 patients exhibited durable tumor regression—a promising result demonstrating that bolstering anti-tumor immunity can be an effective clinical tool. However, the low success rate may indicate that achieving robust rejection of solid tumors is limited, perhaps by prominent humoral and/or innate immune mechanisms, even with high numbers of circulating tumor-specific cytotoxic T cells.

Regarding the significance of enhanced humoral immune responses in individuals with cancer, recent data from our laboratory indicates that peripheral B cell activation, in combination with delivery of humoral immune factors to local neoplastic microenvironments, favors carcinoma development [de Visser et al., 2005]. However, the identity of the B cell-derived soluble factor(s) present in serum represent the critical mediators for pro-tumor immunity remains to be determined. Since neoplastic progression in HPV16 mice is characterized by deposition of antibodies in stroma underlying neoplastic epidermis [de Visser et al., 2005] and given the central role of immunoglobulins (Ig) and immune-complexes in regulating several chronic inflammatory diseases [de Visser et al., 2006], we hypothesize that Igs may represent the functional link between peripheral B lymphocyte activation and cancer progression. Continuous presence of antibodies can elicit chronic inflammation via activation of the complement cascade and subsequent cross-linking of complement receptors on resident innate immune cells [Benoist and Mathis, 2002] Alternatively, Igs can induce pro-tumor immune responses following their cross-linking with Fc receptors expressed on innate immune cells [Hogarth, 2002]. Further elucidation of the intrinsic immune cell signaling pathways regulated by enhanced humoral immunity in HPV6 mice may shed light on these mechanisms and reveal potent anti-tumor targets for therapeutic intervention.

Clinical studies also lend support for the concept of B lymphocyte-mediated promotion of cancer development. Many studies have described increased levels of (auto) antibodies in serum or tumors of cancer patients (reviewed in: [de Visser et al., 2005]. Moreover, presence of autoantibodies in serum of breast cancer patients at time of diagnosis correlates with

poor prognosis [Wasserman et al., 1975]. In combination with our data indicating that B lymphocytes exert their pro-tumor effects early during premalignant progression, together suggests that therapies neutralizing B lymphocytes or their downstream effector pathways may represent promising therapeutic targets. Elimination of B lymphocytes by treatment with rituximab, a monoclonal antibody directed against CD20 present on B cells, has now successfully been applied in a variety of autoimmune disorders with relatively few side-effects [Kazkaz and Isenberg, 2004] as well as some hematologic malignancies, where long-term usage appears to be well-tolerated [Hainsworth et al., 2003]. While promising, the efficacy of rituximab, or other reagents neutralizing B cells, remains untested for solid tumors.

Established tumors represent formidable opponents that harbor inherent potential for developing diverse drug resistances. Aside from investing in earlier screening approaches to detect and eradicate premalignant disease, our best hope for minimizing lethal effects of cancer are to develop combinatorial treatment strategies where intrinsic pathways regulating neoplastic cell survival are targeted, in combination with therapies effecting extrinsic pathways that neutralize pro-tumor immunity, bolster anti-tumor immunity and limit or normalize angiogenic blood vessels. Our belief is that a broader understanding of the role of the immune system in tumor development will facilitate development of novel anti-cancer treatment strategies.

ACKNOWLEDGMENTS

The authors acknowledge all individuals who contributed to research discussed here but not referenced due to size restrictions. The authors were supported by NIH grants CA72006, CA94168, CA098075, Sandler Program in Basic Sciences, National Technology Center for Networks and Pathways (U54 RR020843), a Department of Defense Breast Cancer Research Program Era of Hope Scholar Award (BC051640), a M-P2 postdoctoral grant from the Swedish Research Council (MJ) and the Dutch Cancer Society (KEdV)

REFERENCES

Agarwal A, Verma S, Burra U, Murthy NS, Mohanty NK, Saxena S. 2006. Flow cytometric analysis of Th1 and Th2 cytokines in PBMCs as a parameter of immunological dysfunction in patients of superficial transitional cell carcinoma of bladder. Cancer Immunol Immunother 55: 734–743.

Almand B, Clark JI, Nikitina E, van Beynen J, English NR, Knight SC, Carbone DP, Gabrilovich DI. 2001. Increased production of immature myeloid cells in cancer patients: A mechanism of immunosuppression in cancer. J Immunol 166:678–689.

Balkwill F, Mantovani A. 2001. Inflammation and cancer: Back to Virchow? Lancet 357:539–545.

Balkwill F, Charles KA, Mantovani A. 2005. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell 7:211–217.

Bansal SC, Bansal BR, Thomas HL, Siegel PD, Rhoads JE Jr, Cooper DR, Terman DS, Mark R. 1978. Ex vivo removal of serum IgG in a patient with colon carcinoma: Some biochemical, immunological and histological observations. Cancer 42:1–18.

Barbera-Guillem E, May KF Jr, Nyhus JK, Nelson MB. 1999. Promotion of tumor invasion by cooperation of granulocytes and macrophages activated by anti-tumor antibodies. Neoplasia 1:453–460.

Benoist C, Mathis D. 2002. Mast cells in autoimmune disease. Nature 420:875–878.

Cerhan JR, Anderson KE, Janney CA, Vachon CM, Witzig TE, Habermann TM. 2003. Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-Hodgkin lymphoma. Int J Cancer 106: 784–788.

Coca S, Perez-Piqueras J, Martinez D, Colmenarejo A, Saez MA, Vallejo C, Martos JA, Moreno M. 1997. The prognostic significance of intratumoral natural killer cells in patients with colorectal carcinoma. Cancer 79: 2320–2328.

Coussens LM, Werb Z. 2002. Inflammation and cancer. Nature 420:860–867.

Coussens LM, Hanahan D, Arbeit JM. 1996. Genetic predisposition and parameters of malignant progression in K14- HPV16 transgenic mice. Am J Path 149:1899–1917.

Coussens LM, Shapiro SD, Soloway PD, Werb Z. 2001. Models for gain-of-function and loss-of-function of MMPs. Transgenic and gene targeted mice. Methods Mol Biol 151:149–179.

Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, Evdemon-Hogan M, Conejo-Garcia JR, Zhang L, Burow M, Zhu Y, Wei S, Kryczek I, Daniel B, Gordon A, Myers L, Lackner A, Disis ML, Knutson KL, Chen L, Zou W. 2004. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 10:942–949.

de Visser KE, Korets LV, Coussens LM. 2005. De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell 7:411–423.

de Visser KE, Eichten A, Coussens LM. 2006. Paradoxical roles of the immune system during cancer development. Nature Reviews Cancer 6:24–37.

Degli-Esposti MA, Smyth MJ. 2005. Close encounters of different kinds: Dendritic cells and NK cells take centre stage. Nat Rev Immunol 5:112–124.

Dudley ME, Rosenberg SA. 2003. Adoptive-cell-transfer therapy for the treatment of patients with cancer. Nat Rev Cancer 3:666–675.

Dudley ME, Wunderlich JR, Shelton TE, Even J, Rosenberg SA. 2003. Generation of tumor-infiltrating lymphocyte cultures for use in adoptive transfer therapy for melanoma patients. J Immunother 26:332–342.

Engle SJ, Ormsby I, Pawlowski S, Boivin GP, Croft J, Balish E, Doetschman T. 2002. Elimination of colon cancer in germ-free transforming growth factor beta 1-deficient mice. Cancer Res 62:6362–6366.

Ernst PB, Gold BD. 2000. The disease spectrum of Helicobacter pylori: The immunopathogenesis of gastroduodenal ulcer and gastric cancer. Annu Rev Microbiol 54:615–640.

Farrow B, Evers BM. 2002. Inflammation and the development of pancreatic cancer. Surg Oncol 10:153–169.

Finke J, Ferrone S, Frey A, Mufson A, Ochoa A. 1999. Where have all the T cells gone? Mechanisms of immune evasion by tumors. Immunol Today 20:158–160.

Gabrilovich DI, Velders MP, Sotomayor EM, Kast WM. 2001. Mechanism of immune dysfunction in cancer mediated by immature Gr-1+ myeloid cells. J Immunol 166:5398–5406.

Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pages C, Tosolini M, Camus M, Berger A, Wind P, Zinzindohoue F, Bruneval P, Cugnenc PH, Trajanoski Z, Fridman WH, Pages F. 2006. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 313:1960–1964.

Giraudo E, Inoue M, Hanahan D. 2004. An amino-bisphosphonate targets MMP-9-expressing macrophages and angiogenesis to impair cervical carcinogenesis. J Clin Invest 114:623–633.

Hainsworth JD, Litchy S, Barton JH, Houston GA, Hermann RC, Bradof JE, Greco FA. 2003. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: A phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 21:1746–1751.

Hamerman JA, Ogasawara K, Lanier LL. 2005. NK cells in innate immunity. Curr Opin Immunol 17:29–35.

Hayakawa Y, Takeda K, Yagita H, Smyth MJ, Van Kaer L, Okumura K, Saiki I. 2002. IFN-gamma-mediated inhibition of tumor angiogenesis by natural killer T-cell ligand, alpha-galactosylceramide. Blood 100:1728–1733.

Hoebe K, Janssen E, Beutler B. 2004. The interface between innate and adaptive immunity. Nat Immunol 5:971–974.

Hogarth PM. 2002. Fc receptors are major mediators of antibody based inflammation in autoimmunity. Curr Opin Immunol 14:798–802.

Imada A, Shijubo N, Kojima H, Abe S. 2000. Mast cells correlate with angiogenesis and poor outcome in stage I lung adenocarcinoma. Eur Respir J 15:1087–1093.

Kanazawa M, Yoshihara K, Abe H, Iwadate M, Watanabe K, Suzuki S, Endoh Y, Takita K, Sekikawa K, Takenoshita S, Ogata T, Ohto H. 2005. Effects of PSK on T and dendritic cells differentiation in gastric or colorectal cancer patients. Anticancer Res 25:443–449.

Kazkaz H, Isenberg D. 2004. Anti B cell therapy (rituximab) in the treatment of autoimmune diseases. Curr Opin Pharmacol 4:398–402.

Kuper H, Adami HO, Trichopoulos D. 2000. Infections as a major preventable cause of human cancer. J Intern Med 248:171–183.

Leek RD, Lewis CE, Whitehouse R, Greenall M, Clarke J, Harris AL. 1996. Association of macrophage infiltration with angiogenesis and prognosis in invasive breast carcinoma. Cancer Res 56:4625–4629.

Leek RD, Landers RJ, Harris AL, Lewis CE. 1999. Necrosis correlates with high vascular density and focal macrophage infiltration in invasive carcinoma of the breast. Br J Cancer 79:991–995.

Lin EY, Nguyen AV, Russell RG, Pollard JW. 2001. Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. J Exp Med 193:727–740.

Morgan RA, Dudley ME, Wunderlich JR, Hughes MS, Yang JC, Sherry RM, Royal RE, Topalian SL, Kammula US, Restifo NP, Zheng Z, Nahvi A, de Vries CR, Rogers-Freezer LJ, Mavroukakis SA, Rosenberg SA. 2006. Cancer regression in patients after transfer of genetically engineered lymphocytes. Science 314:126–129.

Onizuka S, Tawara I, Shimizu J, Sakaguchi S, Fujita T, Nakayama E. 1999. Tumor rejection by in vivo administration of anti-CD25 (interleukin-2 receptor alpha) monoclonal antibody. Cancer Res 59:3128–3133.

Orange JS, Ballas ZK. 2006. Natural killer cells in human health and disease. Clin Immunol 118:1–10.

Peek RM Jr, Mohla S, DuBois RN. 2005. Inflammation in the genesis and perpetuation of cancer: Summary and recommendations from a national cancer institute-sponsored meeting. Cancer Res 65:8583–8586.

Raulet DH. 2004. Interplay of natural killer cells and their receptors with the adaptive immune response. Nature immunology 5:1038–1114.

Ribatti D, Ennas MG, Vacca A, Ferreli F, Nico B, Orru S, Sirigu P. 2003. Tumor vascularity and tryptase-positive mast cells correlate with a poor prognosis in melanoma. Eur J Clin Invest 33:420–425.

Schernhammer ES, Kang JH, Chan AT, Michaud DS, Skinner HG, Giovannucci E, Colditz GA, Fuchs CS. 2004. A prospective study of aspirin use and the risk of pancreatic cancer in women. J Natl Cancer Inst 96:22–28.

Serafini P, De Santo C, Marigo I, Cingarlini S, Dolcetti L, Gallina G, Zanovello P, Bronte V. 2004. Derangement of immune responses by myeloid suppressor cells. Cancer Immunol Immunother 53:64–72.

Shacter E, Weitzman SA. 2002. Chronic inflammation and cancer. Oncology 16:217–226.

Shimizu J, Yamazaki S, Sakaguchi S. 1999. Induction of tumor immunity by removing $CD25^{+}CD4^{+}$ T cells: A common basis between tumor immunity and autoimmunity. J Immunol 163:5211–5218.

Smyth MJ, Crowe NY, Godfrey DI. 2001. NK cells and NKT cells collaborate in host protection from methylcholanthrene-induced fibrosarcoma. Int Immunol 13:459–463.

Sparmann A, Bar-Sagi D. 2004. Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. Cancer Cell 6:447–458.

Tlsty TD, Coussens LM. 2006. Tumor stroma and regulation of cancer developemnt. Annual Rev Pathol: Mechan of Disease 1:119–150.

Ulrich CM, Bigler J, Potter JD. 2006. Non-steroidal anti-inflammatory drugs for cancer prevention: Promise, perils and pharmacogenetics. Nat Rev Cancer 6:130–140.

Vlock DR, Arnold B, Humpierres J, Schwartz DR, Baker SR, Krause CJ, Swanson N, Carey TE. 1992. Serial

studies of autologous antibody reactivity to squamous cell carcinoma of the head and neck. Cancer Immunol Immunother 34:329–336.

Wasserman J, Glas U, Blomgren H. 1975. Autoantibodies in patients with carcinoma of the breast. Correlation with prognosis. Clin Exp Immunol 19:417–422.

Williams RR. 1992. Recognition: Fichte and Hegel on the Other. New York: SUNY Press.

Yang L, Debusk LM, Fukuda K, Fingleton B, Green-Jarvis B, Shyr Y, Matrisian LM, Carbone DP, Lin PC. 2004. Expansion of myeloid immune suppressor Gr^+CD11b^+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell 6:409–421.

Zitvogel L, Tesniere A, Kroemer G. 2006. Cancer despite immunosurveillance: Immunoselection and immunosubversion. Nat Rev Immunol 6:715–727.

Zou W. 2005. Immunosuppressive networks in the tumour environment and their therapeutic relevance. Nat Rev Cancer 5:263–274.