Michael R. Shurin · Viktor Umansky
Anatoli Malyguine *Editors*

The Tumor Immunoenvironment

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ISBN 978-94-007-6216-9 ISBN 978-94-007-6217-6 (eBook)
DOI 10.1007/978-94-007-6217-6
Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2013932859

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

The recent decade brought a tectonic shift in our understanding of the mechanisms regulating tumor development, progression, and metastases. During the majority of the last century, it was widely believed that these processes are governed mainly by genetic alterations in tumor cells. An incredible effort was expended to uncover the molecular mechanisms responsible for genomic instability, tumor cell survival, invasion, metastases, etc. Many transcription factors and signal transduction pathways were implicated in these processes. Not surprisingly, all six of the hallmark capabilities of cancer, suggested by Hanahan and Weinberg in their seminal review in 2000, included traits associated only with tumor cells. However, at the end of the last century, it became increasingly clear that the molecular abnormalities associated with tumor cells could not explain the complexity of the events involved in the regulation of tumor progression. It is now evident that the tumor microenvironment plays a major role in these processes. Epidemiological and experimental data have directly implicated inflammation as one of the major factors responsible for tumor development. The host immune system was shown to play a major role in control of tumor progression. Myeloid cells were demonstrated to be a critical factor in promoting tumor cell invasion and metastases. Tumor development and progression represent intricately connected circuits of intrinsic (associated with tumor cells) and extrinsic (associated with tumor microenvironment) factors. The understanding of tumor biology is impossible without a clear understanding of the role of tumor microenvironment. In 2011, Hanahan and Weinberg revisited those hallmarks of cancer and added the evasion of immune destruction as an emerging new hallmark, and tumor-promoting inflammation as one of the enabling characteristics of cancer. It is evident that, in the near future, tumor microenvironment will occupy an even more prominent role in our understanding of tumor biology.

The cells of the immune system represent, arguably, the most critical element of tumor microenvironment. They are not only responsible for the immune control of tumor progression, but are also involved in tumor cell invasion, conditioning of the metastatic niche, angiogenesis, etc. This book is focused on the analysis of the different components of the immune system, in the regulation of tumor progression.

It presents a unique opportunity for readers to put together the complex and often convoluted relationship between different immune cells and tumors. The editors and contributors effectively presented a logical and comprehensive overview of this complex issue. Readers will find information about the role of inflammation in promoting tumors and the regulation of antitumor immune responses; the analysis of the different immune suppressive mechanisms responsible for tumor escape; the evaluation of abnormalities in different immune cells in cancer including dendritic cells, natural killer cells and T cells, as well as the contribution of regulatory T cells, myeloid-derived suppressor cells, granulocytes, mast cells, and macrophages into tumor progression.

However, this book goes far beyond just a description of the immunological abnormalities in cancer. It presents an overview of therapeutic strategies in targeting both tumor cells and tumor microenvironment. The unique value of this volume is that cancer immune therapy is discussed in the context of the regulation of tumor microenvironment. Finally, this book offers the analysis of the biomarkers of immune responses in cancer, the field that is extremely important for the design and evaluation of numerous immune therapeutic strategies.

I believe this book provides a rare example of the synthetic approach to complex biological problems and is a must read for people interested in the role of the immune system in tumor–stroma interaction.

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Chapter 1
Role of the Immunological Environment in Cancer Initiation, Development and Progression

Anatoli Malyguine, Viktor Umansky and Michael R. Shurin

The last two decades have been characterized by a substantial progress in our understanding of the role of the immune system in tumor progression. We have learned how to manipulate the immune system to generate measurable tumor-specific immune responses. On the other hand, cancer cells induce malfunctions in immunity, as they manage to escape recognition and elimination by immune cells and factors. Chronic inflammation associated with a strong immunosuppression was also found to contribute to tumor initiation, progression and metastatic process. The tumor immunoenvironment represents specific conditions and elements that support cancer cell survival, proliferation and spreading. Understanding the role of the immune system in controlling and supporting tumor initiation, formation, growth and progression has crucial implications for cancer therapy.

Cancer represents more than 200 different diseases and is a major public health problem in the United States and other parts of the world. Some of the earliest evidence of cancer is found among fossilized bone tumors, human mummies in ancient Egypt, and ancient manuscripts. The oldest description of cancer called the Edwin Smith Papyrus was discovered in Egypt and dates back to about 3000 BC. It describes 8 cases of tumors or ulcers of the breast that were treated by

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M. R. Shurin et al. (eds.), *The Tumor Immunoenvironment*,
DOI: 10.1007/978-94-007-6217-6_1,

cauterization (www.Cancer.gov). Hippocrates named the disease "karkinos" (the Greek name for crab) to describe tumors.

At the present time, one in eight deaths worldwide is due to cancer. Cancer causes more deaths than AIDS, tuberculosis, and malaria combined and is the leading cause of death in developed countries and the second leading cause of death in developing countries (following heart diseases) (ACS 2012). According to estimates from the International Agency for Research on Cancer (IARC), there were 12.7 million new cancer cases in 2008 (the most recent year of available data) in the world (Ferlay et al.2008). The total cancer deaths estimate in 2008 was 7.6 million (about 21,000 cancer deaths a day). By 2030, worldwide 21.4 million new cancer cases and 13.2 million cancer deaths expected due to the growth and aging of the population, as well as reductions in childhood mortality and deaths from infectious diseases in developing countries (ACS 2012).

Although the ability of the immune system to effectively respond to tumor growth is now recognized, its role in controlling tumor initiation, expansion, and progression is a matter of long-term controversy. Understanding how the immune system affects cancer development and progression has been one of the most challenging questions in immunology.

Cancer biotherapy began around 1768 when Dr. G. White reported "the wonderful method of curing cancers by means of toads" (Goldsmith 1774; Hoption Cann et al. 2002). He described a woman from Hungerford, England, who treated patients with breast cancer (*In many cultures, animals such as guinea pigs or pigeons are applied to diseased parts of the body*). The method required that a toad be applied to the breast lesion until its death. One patient treated by this unorthodox method had a regression of her metastatic lesions following the "*toad cure*". It is possible that the skin of the toad contains some poisonous substances that might adversely affect cancer cells. Since the dead toad was affixed to the breast lesion for several weeks, it also provided an excellent breeding ground for local infections. Although, surgeon to the Duke of Kent injected himself with malignant tissue as a prophylaxis against development of cancer in 1777 and doctor to Louis XVII inoculated himself with breast cancer in hope of reversing a soft-tissue sarcoma in 1808, the principle that the immune system can recognize and respond to neoplastic cells was first proposed in the 19th century.

In 1890s, William Coley, a surgeon from Memorial Sloan Kettering Cancer Institute in New York, reported that using heat-killed endotoxin-containing bacteria (a combination of *Streptococcus pyogenes* and *Serratia marcescens*) resulted in a cure rate of 10 % in soft-tissue sarcoma patients (Coley 1891). A key aspect that Coley found to be necessary for tumor regression was the induction of a mild to moderate fever. At present, the only conventional treatment analogous to Coley's technique is bacillus Calmette-Guerin (BCG) treatment of bladder cancer. Yet unlike Coley's approach, BCG therapy uses a live bacterium (Rakoff-Nahoum and Medzhitov 2009).

The concept that the immune system surveys the body and prevents the outgrowth of carcinomas that would otherwise occur with high frequency was first suggested by Ehrlich (1909). With the better understanding of the mechanisms of

immune response, Frank Macfarlane Burnett in 1957 proposed his cancer immunosurveillance theory which underpins the current belief that tumors can be recognized and eliminated by the immune system and proposed that tumor-specific neo-antigens were capable of eliciting a protective immunity (Burnet 1957a, b). Lewis Thomas speculated that complex and long-lived organisms should possess mechanisms capable of protecting against tumors (Thomas 1959).

These initial observations and hypotheses were confirmed in numerous experimental models demonstrating that the immune system can identify and destroy cancerous cells in a process termed cancer immunosurveillance, which functions as an important defense mechanism against cancer. Numerous reports of increased incidence and aggressiveness of a variety of cancers in immunodeficient patients or in patients receiving immunosuppressive therapy have further supported the hypothesis that the immune system plays a critical role in controlling the generation of malignant tumors. For instance, a systematic review of studies evaluating the incidence of cancer in both organ recipients and people with HIV/AIDS compared with the general population suggests that the weakening of the immune system may result in the increase of new cases of cancer in immunocompromised populations (Cobucci et al. 2012). The ability of immune cells to recognize and destroy cancerous cells has been directly documented both in vitro and in vivo, suggesting the role of cellular mechanisms in tumor immunosurveillance. Cytokines such as interleukin-2 are now established agents for the treatment of tumors. The description of a wide variety of human cancer antigens that are expressed on multiple cancer types, including many common epithelial cancers, presents new opportunities for the development of cancer immunotherapies (Vanneman and Dranoff 2012). Thus, data obtained from various studies in animal tumor models and in cancer patients offer ample evidence that several innate and adaptive immune cell types, specific effector molecules and definite pathways can collectively function as tumor-suppressor mechanisms (Vesely et al. 2011).

There are a large number of examples of how the immune system is able to recognize tumor antigens and eliminate or control tumor cell growth and spreading. As a result, we have learned how to manipulate the immune system to generate measurable tumor-specific immune responses (Rosenberg 2012). Unfortunately, the results of the numerous cancer vaccine clinical trials were mostly disappointing, and although immunotherapy of cancer is still being considered as an attractive therapeutic approach, its impact on clinical practice, with the exception of several antibodies, cytokines and dendritic cell (DC) vaccines, is very limited (Prestwich et al. 2008). Moreover, clinical studies demonstrated that the therapy-induced tumor-specific immune responses do not always correlate with clinical responses regardless of the generation of tumor-specific cytotoxic lymphocytes recognizing and efficiently killing tumor cells ex vivo, showing that somehow the anti-tumor immunity is often ineffective (Shurin et al. 2010). It is also obvious that though theoretically the immune reaction is responsible for controlling nascent cancer through immunosurveillance, tumors are able to escape this control and develop into clinical cancer.

Immune responses against cancer, including those induced by vaccination, depend on a balance between functional activity of various subsets of effector and suppressor T cells. While suppressor cells represent an important mechanism by which the immune system regulates specific immune responses, expansion of these cells in cancer patients interferes with the antitumor immunity and responses to therapy. In an immunocompetent cancer patient, the immune system may suppress effector cell attack against tumor antigens, especially in the tumor microenvironment. The suppressive compartment of the immune system includes several heterogeneous subsets of immune cells, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), alternatively activated (M2) or regulatory subsets of tumor-associated macrophages (TAMs), protumorigenic neutrophils (N2), tolerogenic or regulatory tumor-associated DCs (regDCs), regulatory B cells and possibly specific subsets of natural killer T (NKT) cells (Byrne et al. 2011; Montero et al. 2012; Shurin et al. 2011; Allavena and Mantovani 2012; Gregory and Houghton 2011).

Immune escape is the result of tumor-induced changes in cancer cells themselves, as well as the surrounding stromal tissues and the immune system. Cancers have been found to utilize diverse mechanisms to avoid, suppress and polarize both innate and adaptive anti-tumor immune responses. There is a significant number of identified mechanisms leading to immune unresponsiveness associated with the immunosuppressive tumor microenvironment.

Down-regulation of antigen processing and presentation by malignant cells, altered expression of certain chemokines and cytokines, induction of apoptosis in immune cells and suppression of immune cell function have been implicated in tumor escape from immune recognition and elimination (Coley 1891; Condamine and Gabrilovich 2011; Goldsmith 1774; Gregory and Houghton 2011). Importantly, both adaptive and innate responses might be dysfunctional in the tumor microenvironment. For instance, several identified tumor-derived factors have been reported to block the generation of DCs and their ability to uptake, process and present tumor antigens to T cells (Shurin et al. 2006). Furthermore, up-regulation of the immunosuppressive cell surface glycoprotein CD200 on acute myeloid leukemia (AML) cells specifically compromises NK cell anti-tumor responses. Patients with high CD200 expression on their AML cells exhibited a reduced frequency of activated NK cells and a lowered lytic activity and IFN-γ response against autologous CD200-expressing leukemic cells (Coles et al. 2011; Lion et al. 2012).

Tumor-redirected differentiation and functional polarization of immune cells results in accumulation of specific immune cell subsets with pro-tumorigenic potential, which support tumor development, growth and progression through different mechanisms. Thus, the immune system plays a dual role in cancer. It can not only suppress tumor growth by destroying cancer cells or inhibiting their outgrowth but also promote tumor progression either by selecting tumor cells that can survive in an immunocompetent host or by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth (Gregory and Houghton 2011). For instance, antigen-specific Tregs primarily target DCs and inhibit DC

functions including the expression of costimulatory molecules and the presentation of antigen early during the generation of the immune response. The end result is a complete inhibition of both the expansion and differentiation of T effector cells. Polyclonal Tregs also act on DCs, but at a later phase, and fail to inhibit expansion of T effector cells, but appear to modulate cell differentiation and trafficking (Shevach 2011). MDSCs represent a heterogeneous cell population composed mainly of myeloid progenitor cells that do not differentiate into mature macrophages, DCs or granulocytes. The tumor microenvironment effects the composition of cancer-induced MDSCs through the release of various tumor-derived factors, including cyclooxygenase 2, prostaglandins, granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage CSF (M-CSF), IL-6, IL-10, vascular endothelial growth factor (VEGF), stem-cell factor, IL-3, FMS-related tyrosine kinase 3 (FLT3), and cell-expressed molecules (such as Notch). MDSCs are characterized by combinations of different surface markers and can be divided into two major subsets: granulocytic PMN- and monocytic MO-MDSCs (Hussain and Harris 2007; Ismail and Shurin (2012) Jain 2005).

MDSCs also exert their direct immunosuppressive function on antigen-specific T cell responses but also on mitogen-activated T lymphocytes, therefore bypassing the antigen dependency (Solito et al. 2011). In addition to being potent suppressors of T cell function, recent studies have demonstrated the ability of MDSCs to modulate activity of NK and myeloid cells and have implicated MDSCs in the induction of Tregs (Condamine and Gabrilovich 2011). Regulatory DCs in cancer may directly and indirectly maintain antigen-specific and non-specific T cell unresponsiveness by controlling T cell polarization, MDSC and Treg differentiation and activity, and affecting specific microenvironmental conditions in premalignant niches (Ma et al. 2012). Tumor-associated macrophages (TAMs) are also significant for fostering tumor progression. Up to 50 % of a malignant tumor mass can be composed of TAMs. While classical macrophages (M1) uptake antigens and play an important role in control of infections, TAMs can be reprogrammed in the tumor microenvironment in M2 cells as a result of tumor-driven 'alternative' activation (Daurkin et al. 2011). M2 are able to inhibit functions of immune cells and promote tumor survival, progression, angiogenesis and metastasis by releasing IL-10, PGE2, NO, high amounts of TGF-β or reactive oxygen species (ROS) (Whiteside 2010; Talmadge 2011). TAMs also contribute to immune evasion via induction of tolerogenic forkhead box P3 ($FOXP3^+$) and IL-10—secreting T cells as well as via upregulation of inhibitory receptor cytotoxic T lymphocyte antigen 4 (CTLA-4) expression in effector T cells (Daurkin et al. 2011).

Although neutrophils are traditionally considered in the context of their antibacterial functions, it is becoming increasingly clear that tumor-associated neutrophiles (TANs) play an important role in cancer biology (Fridlender and Albelda 2012). Many cancers are capable of recruiting neutrophiles to sites of tumorigenesis where they enhance tumor growth (Houghton 2010). N2 neutrophiles can inhibit effector T cell functions by the secretion of stored arginase 1 (ARG1) that degrades extracellular arginine, a factor needed for the proper activity of T cells (Fridlender and Albelda 2012). Additionally, products secreted from TANs, such

as ROS and proteinases, have defined and specific roles in regulating tumor cell proliferation, angiogenesis, and metastasis (Gregory and Houghton 2011). Neutrophiles can also have a significant impact on the tumor microenvironment via produced cytokines and chemokines, which influence inflammatory cell recruitment and activation (Sansone and Bromberg 2011).

A pathophysiological association between inflammation and cancer has already been proposed in the 19th century, when in 1863 Rudolf Virchow noted leucocytes in neoplastic tissues and made a connection between inflammation and cancer (Virchow 1863). He suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. Later, numerous laboratory and population-based studies suggested that certain malignancies arise at tissues severely damaged by chronic inflammation (Jochems and Schlom 2011). For example, cancers of stomach, liver, gallbladder, prostate, and pancreas are causally linked to gastric inflammation, chronic hepatitis, cholecystitis, inflammatory atrophy of the prostate, and chronic pancreatitis, respectively (Aggarwal et al. 2009). Colitis, a condition characterized by persistent colonic mucosal inflammation, often progresses to colorectal cancer; inflammatory bowel disease increases the risk of colorectal cancer by 10-fold and the management of colitis with anti-inflammatory therapy reduces this risk (Kundu and Surh 2012). Although approximately 25 % of all cancers have a proven etiologic background of chronic inflammation and/or infection (Mantovani et al. 2008; Montero et al. 2012), 90–95 % of neoplasia are linked to obesity, tobacco smoke, environmental pollutants, radiation and chronic infections, which all have in common a chronic inflammatory state (Grivennikov et al. 2010).

The role of inflammation in tumorigenesis is now accepted, and it is likely that an inflammatory microenvironment is an important cofactor for the development of all tumors, including those in which a direct causal relationship with inflammation is not yet confirmed (Chow et al. 2012). In the case of infection, host cells synthesize and release a number of antimicrobial factors, which include reactive oxygen species (ROS) and nitrogen intermediates (RNI), cytokines and chemokines, which recruit and activate protective effector cells such as macrophages, neutrophils, mast cells and DCs. If infection still persists, negative condition develops as a result of the continuous attack of infected tissues by immune cells and may promote cancer growth (Ismail and Shurin 2012).

Some of the mechanisms of tumor promotion by an inflammatory microenvironment are an increase of mutation rates and proliferation of mutated cells. Activated inflammatory cells provide ROS and RNI which induce DNA damage and genomic instability (Grivennikov et al. 2010; Lowe and Storkus 2011). Also inflammatory cells may promote ROS accumulation in neighboring epithelial cells as a result of production of cytokines as TNF-α. Furthermore, DNA damage can lead to inflammation and in turn promote tumorigenesis (Grivennikov et al. 2010). The production of pro-inflammatory cytokines and chemokines (IL-6, IL-8, IL-1β, CCL2, CCL20) may be activated through signal pathways of several oncoproteins such as Ras, Myc and RET (Mantovani et al. 2008). Production of tumor promoting cytokines that activate transcription factors, such as NF-κB, STAT3 and

AP-1, in pre-malignant cells, induce genes that stimulate cell proliferation and survival (Grivennikov et al. 2010).

Since intensive tumor growth requires additional blood supply, at some point the tumor becomes oxygen and nutrition deficient. As a result of tumor hypoxia and necrosis, the pro-inflammatory mediators are released enabling neoangiogenesis in tumor microenvironment (Vakkila and Lotze 2004). Important role in this process is played by *RAS, MYC* and *RET* oncogene family members. They activate a transcriptional program resulting in transformation of the tumor microenvironment through the recruitment of inflammatory cells and production of inflammation- and tumor-promoting chemokines and cytokines, metalloproteinases or adhesion molecules (Soucek et al. 2007; Sparmann and Bar-Sagi 2004). In addition, mutations in Von Hippel-Lindau tumor suppressor (VHL), transforming growth factor-β (TGF-β), and phosphatase and tensin homologue (PTEN), may activate transcription factors involved in inflammation and vascularization, particularly NF-κB, hypoxia inducible factor 1α (HIF-1α), and STAT3 (Mantovani et al. 2008).

Current studies show that NF-κB plays a fundamental role in the formation and development of malignant tissue caused by inflammation. As an ubiquitous central transcription factor, NF-κB plays a role both in the transformation of tissue cells to cancer cells, and in the regulation of the immune cell activity (Pikarsky et al. 2004; Karin 2006). The stimulation of immune cells by inflammatory cytokines such as interferon, TNF-α or IL-1β also leads ultimately to the activation of NF-κB and thereby to nonspecific inflammatory reactions. In tumor cells, the continued activation of NF-κB leads to the increased expression of genes which encode inflammation-promoting cytokines, adhesion molecules, angiogenic factors, etc. (Karin 2006). Furthermore, through the increased expression of anti-apoptotic genes such as *BCL2*, NF-κB activation promotes the survival of cancer cells (Van Waes 2007). There are emerging indications of an interaction between the NF-κB and HIF-1α systems (Rius et al. 2008).

New blood vessels growing in tumor site are often functionally impaired, leading to an increased interstitial fluid pressure, hypoxia and low pH within the tumor microenvironment (TME) that negatively influence lymphocyte homing, extravasation and function (Pardoll and Drake 2012; Schafer and Werner 2008). As Virchow already described over a 100 years ago, in terms of tissue morphology, tumor tissue resembles a chronically infected non-healing wound (Schafer and Werner 2008). Cancer cell hypoxic signals induce the expression and release of VEGF and PDGF promoting a local chronic inflammation, which supports tumor growth and progression (Rini 2009). Tumor cell hypoxia can also enable the migration of inflammatory cells, such as TAMs into tumor, which boost angiogenesis further by secreting such factors as VEGF (Allen and Louise Jones 2011; Finger and Giaccia 2010).

Therefore, all these events limit immune reactions (i.e., a immunosurveillance) mediated by immune effector cells like CD8 and NK cells that protect the host against premalignant and cancer cells. It is reasonable to assume that chronic inflammation helps the creation of an early primary tumor lesion that is less sensitive to type 1 immune response, allowing the tumor progression and metastatic spread.

Over 90 % of cancer patients die not from a primary lesion but from metastases to organs such as the brain, liver, lung and bones (Shurin et al. 2011). Metastatic process requires close interaction of cancer cells, stromal elements, and immune and inflammatory cells. The process of metastasis starts from epithelial-mesenchymal transition that permits cancer cells to enter blood and lymphatic vessels. Structural alterations in the extracellular matrix (EM) of the tumor microenvironment, which allow invasion and metastasis, are carried out mostly by stromal-derived matrix metalloproteinases (MMP), which degrade EM substrates like collagen. Moreover, TAMs and neutrophils are also important producers of matrix MMP within the TME (Lowe and Storkus 2011; Solinas et al. 2010; Kalluri and Weinberg 2009). IL-1, TNF-α and IL-6 promote MMP expression, invasiveness, and metastasis via NF-κB and STAT3 (Yu et al. 2007). EM expression of integrins and other cell surface receptors also increase tumor cells migratory capacity. In addition, inflammatory infiltrates such as TAMs, MDSCs, and cancer-associated fibroblasts could provide significant levels of TGF-β, an important regulator of the epithelial-mesenchymal transition and metastasis (Yang and Weinberg 2008).

Once metastatic cells enter the circulation, they need to survive in suspension. The survival of these cells is affected by inflammatory mediators released by immune cells activated by cancer- or pathogen-derived stimuli (Luo et al. 2004; Kim et al. 2009) and depends on activation of NF-κB. A variety of cytokines, including TNF-α and IL-6, can also promote circulating cancer cell survival (Nguyen et al. 2009) and some of these cytokines can physically link cancer cells to TAMs, allowing them to travel together (Condeelis and Pollard 2006). Circulating cancer cells may overcome immunosurveillance by interaction with platelets or macrophages which results in protection of cancer cells from NK mediated killing (Palumbo et al. 2007). Interestingly, tumor cells co-cultivated with macrophages develop an increasingly metastatic phenotype, comparable with that induced by the activation of the NF-κB pathway or TNF-α activation (Wyckoff et al. 2007). The migration of metastasis initiating cells is directed by chemokine gradients via CXCR4, CCR4, CCR7, CCR9 and CCR10 (Bonecchi et al. 2009). To colonize distant sites/organs, cancer cells becoming trapped in capillary beds resulting in integrin-dependent attachment to endothelium (Chaffer and Weinberg 2011). Several proinflammatory cytokines that are elevated in the circulation of cancer patients up regulate expression of adhesion molecules on the endothelium or in target organs and facilitate metastatic cell attachment (Mantovani et al. 2008). The homing is followed by extravasation into the tissue, and quick adaptation of malignant cells to a foreign environment by interaction with immune, inflammatory, and stromal cells (Polyak and Weinberg 2009). A state of chronic inflammation may provide a hospitable environment to incoming cancer cells by preventing apoptosis and inducing epigenetic and mutational effects that would favor cancer progression within the distal tissue location. In addition, the various factors secreted by locally recruited inflammatory cells, such as TAMs, could provide the protumorigenic effect (Sansone and Bromberg 2011; Lowe and Storkus 2011).

In summary, we now appreciate that the immune system, in addition to tumor-suppressive function by eliminating nascent transformed tumor cells, can also facilitate tumor initiation and progression by providing a complimentary TME through the maintenance of chronic inflammatory state in the tumor mass and by inducing polarized immunosuppressive regulatory cells. However, the distinctions between tumor-promoting inflammation and tumor-suppressive immunity are still not clear due to the dual role of some cytokines and other molecules in the immune system. Recently it was shown that interaction between tumor cells and DCs, but not monocytes, leads to rapid induction of the genomic mutator activation-induced cytidine deaminase (AID) and AID-dependent DNA double-strand breaks (DSBs) in tumor cell lines and primary tumor cells (Koduru et al. 2012). AID-mediated genomic damage led to altered tumorigenicity and indolent behavior of tumor cells in vivo. These data show a novel pathway for the capacity of immune cells to regulate genomic integrity (Koduru et al. 2012).

Understanding the role of the immune system in controlling and supporting tumor initiation, formation, growth and progression has crucial implications for cancer therapy since immunomodulatory interventions aimed at early pathogenic events may no longer be efficient when these pathways have altered due to a different effects of the immune response (Schreiber et al. 2011). Therefore, it is critical to recognize why and how the cancer-associated immune activities evolve over time, so that time-dependent therapies may be rationally implemented for an improved clinical outcome. These new insights in evolving interactions of different cell subsets in the tumor immunoenvironment are constantly improving the design and efficacy of modern cancer immunotherapy protocols, as reviewed elsewhere (Whiteside 2010; Wyckoff et al. 2007; Yang and Weinberg 2008; Yu et al. 2007). Deciphering the interaction between immune cells, malignant cells, stromal elements and treatment modalities will therefore guide the future combination of immunotherapy with conventional therapies to achieve optimal antitumor effects in cancer patients.

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Part I
Tumor Microenvironment and Immunoenvironment

Chapter 2
The Metastatic Microenvironment

Shelly Maman and Isaac P. Witz

Abstract Metastasis is the major killer of cancer patients. Although increased understanding of the metastatic process was achieved in recent years, the mechanisms underlying the progression of cancer cells to form site-specific metastasis are still awaiting complete elucidation. The current consensus is that circulating tumor cells disseminate into future metastatic sites and that these disseminated tumor cells form micrometastasis in these sites. The micrometastases remain in a state of dormancy in these sites until "awakened" to progress towards overt metastases. Whereas the evidence implicating chemokine–chemokine receptor interactions as the mechanism responsible for the targeted migration of tumor cells to future metastatic sites is quite strong, the mechanisms that maintain dormancy of disseminated tumor cells and the mechanisms that awaken these dormant micrometastases, driving their progression towards frank metastasis, are still obscure. It is clear, however, that the metastatic microenvironment plays a major role in these events. Three topics are discussed in this review: Mechanisms that are involved in the targeted migration of tumor cells to future metastatic sites; Specific molecular signatures expressed by metastases and micrometastases and interactions between metastatic and micrometastatic cells with the metastatic microenvironment. In reviewing these topics we focused on studies performed in our lab with neuroblatoma lung and melanoma brain metastasis.

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M. R. Shurin et al. (eds.), *The Tumor Immunoenvironment*,
DOI: 10.1007/978-94-007-6217-6_2,