Cancer Immunologists and Cancer Biologists: Why We Didn’t Talk Then but Need to Now

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Abstract

What is cancer? Cancer is a disease initiated by a series of cumulative genetic and epigenetic changes that occur in a normal cell. However, in addition to the malignant cell itself, cancer is a disease of microenvironment and immunity. Although genetic and epigenetic alterations drive cellular transformation, genomic plasticity, and evolution, it has become increasingly apparent that multiple signals delivered within the tumor microenvironment by modifier genes, stromal and endothelial cells, and immune cells are critical factors in determining the progression versus dormancy or destruction of an initiated lesion and also whether metastasis may occur. With regard to the important roles of immune cells in cancer, a chasm exists between immunologists and biologists: although sharing a common disease interest, there is little history for workers to draw on based on shared perspectives or understanding. How did this disconnect arise? Here, we look at how these workers became separated in the past and address why it has now become critical to spur greater cross-fertilization. In particular, we highlight three ideas that we believe are important for discussion and debate. The first idea is that therapeutic strategies that fail to harness the immune system will always be defeated by tumor resistance, due to the large "genomic space" that genetically plastic tumor cells can readily access to evolve resistance mechanisms. Because all therapies drive tumor progression by imposing a selection for resistant cells, harnessing the adaptivity of the immune system will be indispensable to ultimately stanching the deadly adaptability of the tumor cell. The second idea is that using molecular targeted agents to reverse tumoral immune suppression may offer a powerful method to leverage the efficacy of most if not all therapeutic agents. We suggest that the mechanisms that support evolution of a "smoldering" inflammatory environment in cancer overlap with those that support evolution of tumoral immune escape. If true, relieving immune suppression will switch the inflammatory state from supportive to destructive for the tumor. The third idea is that by ablating immunosuppression mechanisms, cytotoxic chemotherapy might synergize with, rather than antagonize, active immunotherapy. Provocative preclinical studies in this area prompt clinical attention. We believe that increased efforts to intermingle the perspectives and work of cancer immunologists with cancer biologists and pharmacologists will be needed to realize the National Cancer Institute’s goal of managing cancer in the clinic by 2015. [Cancer Res 2007;67(8):3500–4]

Historical Segregation of Cancer Immunology from Cancer Genetics and Cell Biology

"I can’t understand why people are frightened of new ideas. I’m frightened of the old ones." (attributed to the composer John Cage, 1912-1992)

Starting about 1980, investigations in cancer genetics and cell biology began to assume the prominence in cancer research that they now hold today. Hatched initially from studies of avian and mammalian tumor viruses, the field of cancer genetics has been the dominant contributor to our understanding of the biological pathways involved in tumor development, identifying many specific targets for therapeutic intervention in cancer cells. With the discovery of oncogenes, the once radical idea that cancer was a disease of normal cellular genes gone wrong now became established as the dominant idea in the field. Importantly, this new concept began to strongly influence how to develop new cancer drugs, that being to attack the products of these altered genes. At the same time, these developments in the field outpaced concepts of cancer as a systemic disease involving perturbations in the immune system. Now, after decades of mutual skepticism, a historically important consensus among cancer researchers is emerging about the causality of chronic inflammation and altered immunity in driving malignant development and progression. Ironically, this synthesis is having the effect of making the "new" genetic ideas of the past two decades about cancer seem naïve and outdated. In particular, it is becoming apparent that the tumor cell–centric focus championed by cancer genetics is unlikely to give a full understanding of clinical disease, in the absence of knowing about the systemic and localized tissue conditions that surround and control the growth and activity of the tumor cell. Perhaps contributing to some consternation about the conceptual weight of the "new" ideas since the 1980s, few of the molecular therapeutics developed from them have had much major clinical effect (the Bcr-Abl kinase inhibitor Gleevec being perhaps the most notable exception to the rule for a cancer driven essentially by a single oncogenic pathway).

Over the past 25 years, as a result of historical and scientific divisions, there has been limited communication, understanding, and collaboration among tumor immunologists, molecular geneticists, and cell biologists working in the field. For the latter groups, a major disconnect was the perception that the immune system did not seem to be very important to tumor development in laboratory animals, produced by experiments in nude mice in the 1960s that were argued to weaken the concept of tumoral growth.
immunosurveillance. The bias of cancer cell biologists and geneticists against a major role for immune dysfunction in cancer was exaggerated, on one hand, by powerful demonstrations of the effects of oncogenes and tumor suppressor genes in animals and, on the other hand, by the resulting narrow focus on tumor cell-centric concepts of cancer encouraged by these demonstrations. In recent years, a wider appreciation of the role of cancer modifier genes in dictating tumor development in different strains of animals has emerged, but this concept has not yet widely penetrated the field. In any case, whereas genetic and cell biological studies of cancer became prominent, biological studies of the role of microenvironment and immune function tended to lag and to offer limited molecular insights into how an inflammatory microenvironment and immune cells could either control or promote cancer. Although advances in recent years have led to a wider appreciation of these processes in licensing cancer cell proliferation, survival, and metastasis, the historical reach of the old biases against these areas tend to cause intellectual segregation and separation of different camps of investigators.

Selection against Therapy: The Chief Challenge of Cancer

Clearly, the goal of cancer therapy is to kill residual tumors that cannot be excised surgically. However, the inherent nature of the cancer cell limits the full effectiveness of therapies that have been developed, or that arguably can be developed. Being of host origin, cancer cells share features of the host that make effective treatment difficult, due to side effects that limit the therapeutic window. Moreover, the plastic nature of tumors makes them remarkably resilient in rebounding from clinical regimens of radiotherapy and chemotherapy that are traditionally used. For example, even when the vast majority of cancer cells are killed by a cytotoxic chemotherapeutic drug, a small number of residual cells that are resistant to the agent can be sufficient to seed the regrowth of a tumor. Making matters worse, the regrown tumor may no longer respond to the previously successful therapy, due to the capacity of tumor cells to evolve resistance under selective pressures applied by cytotoxic agents. Indeed, the concept of selection is central to understanding this disease: development and progression is driven by selection for cells that can survive conditions that would normally be lethal. Resistance to virtually any lethal pressure can be selected by evolution in a cancer cell population because of its genetic plasticity, a key characteristic of cancer cells. As shown in the treatment of other diseases caused by a highly mutable entity (e.g., HIV), successful targeting of tumor cells will require the application of multiple agents that target different survival mechanisms. However, compared with HIV, the genetic space available for the evolution of a cancer cell is far larger, due to the far greater size of the cancer cell genome. Thus, effective eradication of tumors has been, and may continue to prove to be, quite challenging, even using multiple targeted agents in combination, because of the diversity of options that the cancer genome can realize to evolve mechanisms of survival in response to the selection pressures these agents apply.

Two general solutions to this apparently dismal situation may be to redirect the focus of attack from the tumor cell itself to the environment that sustains its growth and survival or to engage the immune system in a way that allows it to eradicate tumor cells like an infection. The former strategy is essentially passive in nature insofar as cancer cells are killed by an indirect route. For example, by depriving tumors of a blood supply antiangiogenic therapies can indirectly kill cancer cells. Resistance to such therapies should be difficult to evolve, as the argument goes, because stromal cells in the tumor environment are not genetically plastic. However, due to their passive nature, such therapies are still prone to circumvention through tumor cell evolution (e.g., vascular mimicry in the case of antiangiogenesis therapies; ref. 1). In contrast, active strategies to engage or “awaken” active immunity in the cancer patient has many appeals, the chief of which is its capacity to “dodge and weave” with tumor evolution and heterogeneity. In this regard, the immune system may be particularly well suited to clear the small numbers of residual tumor cells, particularly dormant cells or cancer stem cells that may be poorly eradicated by radiotherapy and chemotherapy, helping to lengthen remission periods. Indeed, even treatments that did not cure cancer but rather converted it to a long-term subclinical or at least manageable condition, by analogy to HIV infections, would represent a resounding success. Therefore, one key question becomes how a tumor can outrun an activated immune system, given that precisely this event has occurred during tumorigenesis, so that the balance might be tipped back in favor of the immune system.

In terms of therapeutic responses, it is becoming clear that tumors actively subvert the immune system, and that active immunotherapy is probably defeated as a result of the activation of a variety of immune suppression mechanisms in the tumor and microenvironment. Thus, in order for immunotherapy to “push the gas” of immune activation, it will likely be necessary to “get off the brakes” of immunosuppression. Some cancer immunologists are using the term “immune checkpoints” to refer to the negative-acting suppression pathways that prevent activation the immune system (e.g., by vaccines). Cancer geneticists may recognize these ideas, just now gaining ground in cancer immunology, as analogous to concepts developed in the 1990s with regard to checkpoint controls on cell growth and how oncogenes can only “push the gas” of neoplastic cell proliferation when the “brakes” imposed by tumor suppressor genes are relieved. The war on cancer has only just begun on several fronts, but by combining genetics, chemotherapy, and immunotherapy, we believe it may be possible shortly to open an all-out attack on cancer.

Steps toward Conversations between the Camps

“I am not interested in the old or the new. What I am interested in is the old in the new.” (attributed to the art critic John Ruskin, 1819-1900)

The earliest histopathological descriptions of cancer in the 1800s noted the surfeit of inflammatory cells present. Arising from this root, tumor immunology represents one of the oldest disciplines in cancer research. Historically, this field has struggled to gain a full understanding of the precise relationships among inflammation, immunity, and cancer and to resolve frustrations in developing principles to broadly improve the diagnosis, prognosis, and treatment of malignancy. With the emergence of cancer genetics and the tumor cell-centric concepts of disease as major conceptual drivers in the late 20th century, roles for tumor stromal cells and immunity in cancer became marginalized or simply ignored by most investigators in the field. Indeed, old skepticism about whether immunity was important or not in cancer have persisted until quite recently, as illustrated by the omission of immune escape as a critical trait of cancer noted in prominent reviews in
the field (2). However, since the turn of the 21st century, perspectives have once again undergone a radical shift, with an increasing number of investigators becoming intensely interested in how tumor development is shaped by the stromal-immune microenvironment and local inflammatory processes.

A first step. Two new central concepts that are important to all cancer researchers today are microenvironmental control and immunoediting. Stromal cells in the solid tumor microenvironment nourish and often outnumber the tumor cells themselves: Endothelial cells, fibroblasts, inflammatory cells, and T regulatory immune cells are all generally abundant. In this setting, it is possible to consider tumor cells as a chronic infection that underlies the “smoldering” inflammatory conditions that can drive malignant progression (3). The “master-slave” relationship ultimately imposed by the tumor cell on its stromal microenvironment represents its defeat in terms of managing the “infection,” insofar as the extracellular cues normally provided in tissues pose a powerful barrier to the persistence, growth, and movement of transformed cells.

Immunoediting proposes to outline the battle in the microenvironment between the immune system and the tumor cell “infection.” Conceptually, immunoediting can be viewed as a veneer that overlays the genetic model of cancer (4), which, as is widely known, is characterized by accumulating oncogene and tumor suppressor mutations that drive neoplastic cell transformation, genomic plasticity, and evolution. Immunoediting starts with the immune recognition and destruction of transformed cells that have acquired genetic damage. This stage of immune surveillance is similar to that expressed in the 20th century initially by Ehrich and later by Burnett and Lewis. Presenting tumor antigens to the immune system also creates a mechanism to select for the evolution of cell populations that can limit or elude destruction, leading to immune equilibrium or immune escape. Thus, the three stages of immunoediting lead to control, stasis, or outgrowth of a tumor. By shaping the response of a tumor to the immune system, immunoediting can drive tumor evolution and progression. One implication of the immunoediting model is that the cell-intrinsic traits of cancer (immortalization, growth deregulation, apoptotic resistance, and tumor suppressor inactivation) may lead to the development of subclinical or occult lesions that are not clinically significant until the immune-shaped and cell-extrinsic traits (invasion, angiogenesis, metastasis, and immune escape) have been evolved by the tumor. In light of this model, how oncogenes and tumor suppressor genes affect inflammation and immune responses to the tumor represents an increasingly important area for investigation, at present poorly developed. In the last several years, historically descriptive knowledge about the stromal and immune components of the tumor environment has gradually given way to molecular and mechanistic understanding, with key “nodal” components of stromal and immune support rapidly coming to light in the manner that oncogenes and tumor suppressor genes did in the late 1980s and early 1990s.

A second step. It is perhaps no surprise that there has been a recent explosion in our mechanistic understanding of historically descriptive stromal and immune-based principles, because the same molecular and proteomic technologies pushing the genetic field forward at an exponential pace has also pushed the field of immunology into the 21st century at supersonic speed. For example, it was not until the early 1990s that technologies became available to rapidly identify gene products within a tumor cell that are the targets of both B and T immune cells. Before the emergence of this information, it was largely believed that tumor antigens, if they existed at all, were probably gene products with unique alterations that were present only in a patient’s own tumor. However, during the past 15 years, molecular cloning and gene expression technologies have falsified this concept. Instead, the majority of tumor antigens identified so far are not mutated, but rather differentially expressed or upregulated gene products. These findings are important because they strongly support the feasibility of developing generalizable immune-based therapies that can target cancers within groups of patients. As a second example, recent molecular advances have initiated a whole subfield of tumor immunology that is focused on identifying the “immune checkpoint” signals that can suppress most if not all immune responses. Based on seminal work done by a number of investigators, we now appreciate the important role played by costimulatory molecules and their ligands in activating or down-regulating T cells, not only within the tumor microenvironment but also systemically. These findings have already led to the development of biological agents that either suppress (in the case of autoimmune diseases) or activate (in the case of cancer) immune responses targeted at a particular disease type. Thus, we are at a critical crossroads, one that is strongly pointing toward the merger of multiple scientific disciplines.

Immunochemotherapy: Using Molecular Targeted Therapy toDefeat Specific Mechanisms of Immune ToleranceandRemodel the Immune Microenvironment

The translation of modern concepts of cancer into molecular targeted therapies represents a significant new development in strategies to treat cancer (5). However, the main challenge faced by this development is the inherent plasticity of the cancer cell in evolving drug resistance. Thus, one way to exploit molecular targeted concepts may be to apply them against less plastic targets in the supportive microenvironment of the tumor rather than targets within the tumor cell itself. Recently, a variety of critical targets that mediate tumor immunosuppression have come to light (6), many of which are enzymes that are amenable to small-molecule targeting (7), such as indoleamine 2,3-dioxygenase (IDO) and arginase that seem to be critical for the action of dendritic and myeloid suppressor cells in cancer, respectively. Additionally, cell surface receptors that are amenable to targeting by monoclonal antibody tactics have emerged, such as the programmed death-1 receptor on T cells (8, 9) or the interleukin-9 receptor on mast cells, the latter of which have been implicated recently as essential mediators of T regulatory cell tolerance (10). Some existing therapeutics may be valuable in correcting tumoral immune tolerance. For example, through its ability to inhibit the tyrosine kinase activity of c-Kit, which is essential for supporting mast cell activity, Gleevec might disrupt mast cell-dependent control of T regulatory cells that support tumoral immune tolerance.

Molecular targeting of the same immunosuppression principles might also be valuable for cancer prevention or blocking progression of early-stage lesions. One notion is that these immunosuppression principles underlie the development of “smoldering inflammation,” which plays a critical role in driving the development and progression of many tumors. In other words, “smoldering inflammation” associated with cancer development may be molecularly distinct from normal inflammatory processes (that would eradicate cancer cells) on the basis of aberrant...
activation of immune escape molecules such as IDO, arginase, etc. in inflammatory cells. A key prediction of this model is that mice that are genetically deficient in molecules that support immune escape should also be cancer resistant. Reprogramming "smoldering inflammatory" environments with Toll-like receptor (TLR) ligands such as bacterial CpG oligonucleotides might be enhanced further by using inhibitors of IDO or arginase (e.g., NO aspirins; refs. 11, 12), since their up-regulation by TLR signaling (13) may blunt the desired immune microenvironmental reprogramming effect of a TLR ligand.

Imunochemotherapy: Using Classic Chemotherapy to Defeat Immune Suppression and Leverage the Efficacy of Active Immunotherapy

During recent years, a number of preclinical studies have provided both descriptive data and mechanisms supporting the combination of a number of traditional cytotoxic agents with cancer vaccines (14). For example, a number of studies more than 20 years ago suggested that the chemotherapeutic agent cyclophosphamide, when given before a cancer vaccine, inhibited what was then a hypothesized immunosuppressor cell to allow a more effective activation of antitumor immunity. However, it was not until the late 1990s when Sakaguchi et al. identified and isolated regulatory T cells that it became clear that these suppressor cells exist. Importantly, this finding allowed a number of investigators to show the mechanisms by which low doses of cyclophosphamide given before a cancer vaccine will indeed enhance the antitumor immune response. It now seems that cyclophosphamide inhibits only those cells that are cycling at the time of administration of the agent. T regulatory cells seem to dominate among cycling blood cells in an untreated cancer patient and are the major cells that are inhibited by this agent. In addition, inhibition of T regulatory cells seems to allow the recruitment of higher-avidity cancer-specific T cells to the antitumor immune response in animal models. If this is proven to be true in cancer patients, this will shift the paradigm for activating anticancer immunity since it has long been thought that only lower-avidity T cells are available for activation in cancer patients in whom multiple mechanisms of immune tolerance exist.

The taxanes are a second example of cytotoxic agents that show enhanced immune activation (15) that, given in sequence, can promote the activity of a cancer vaccine. The cytotoxic properties of taxanes are known to act directly on cancer cells by stabilizing microtubule formation and thereby inhibiting cell division. However, taxanes may also signal on antigen-presenting cells such as dendritic cells through TLR-4, a critical signaling pathway in the innate immune response that mediates initial recognition of bacterial infection. Signaling through TLR-4 may enhance antigen processing and presentation to T cells. These examples highlight two important issues. First, cytotoxic chemotherapeutics likely trigger an anticancer response via multiple mechanisms including immune-based mechanisms. These mechanisms obviously will be missed by preclinical models lacking immune components, such as traditional xenograft models. Second, there is a specific dose range and sequence when given with other immune-based agents, such as vaccines, which may optimize the synergistic effects of the two forms of cancer-directed immune-based therapy.

Preclinical studies have also shown that the combination of immune checkpoint (suppression) inhibitors with vaccines will enhance a given vaccine’s antitumor activity. Clinical trials based on these studies employing vaccines in sequence with agents that modulate one or more mechanisms of immune tolerance are already showing clinical promise. It is clear that the most effective therapy will require a combined approach, incorporating the best targeted interventions for modulating systemic and local mechanisms of immune tolerance. Preclinical models have already revealed the synergy between immunotherapy and other targeted therapeutics, such as inhibitors of cytotoxic T lymphocyte–associated antigen 4, vascular endothelial growth factor receptor, and epidermal growth factor receptor family signaling. These combinations are already under clinical development. Employing the newer gene and protein discovery techniques has resulted in the rapid identification of other targets of immunoregulation. This information will likely translate into additional therapeutic interventions for augmenting antitumor immune responses in patients with cancer.

Closing

Recently, the former Director of the U.S. National Cancer Institute issued a challenge to cancer researchers to develop new strategies that can successfully manage cancer in the clinic by 2015. We believe that the concepts of microenvironment and immunoediting, each of which intimately involve cells of the innate and adaptive immune systems, will be crucial in developing tactics to more effectively prevent and treat cancer. We expect that rapid advances that are increasing the resolution of noninvasive imaging technologies used in the clinic may reveal that subclinical (occult) cancers occur much more commonly than expected, and that clinical cancer represents a fraction of lesions that have escaped immune control. From this perspective, clinical disease is less about the processes that led to the initiated lesion but more about the microenvironment and immune context that controls (or does not control) the lesion. Combination treatment will remain state-of-the-art, but more accurate molecular definition of clinical cancer is needed to reveal more effective therapeutic regimes. Combinations of cytotoxic chemotherapy and molecular targeted therapeutics have gotten and are getting a great deal of attention, but recent advances and newer concepts warrant more focus on agents that can target key "nodal" points in the stromal microenvironment, particularly immunomodulatory agents that may relieve immune suppression. Greater attention to combinations of cytotoxic chemotherapy, biology that inhibit down-regulatory immune checkpoints, and active immunotherapy is warranted. Recent advances in defining molecular mechanisms of immunosuppression, particularly involving myeloid suppressor cells and T regulatory cells, offer attractive points of focus and the opportunity for broad synergy with traditional and targeted drugs to de-repress antigen immunity. In the present culture, cancer immunologists tend to be oriented to biological therapies and to have limited knowledge of cancer pharmacology or genetics. Conversely, cancer geneticists and pharmacologists tend to be oriented toward small-molecule therapies and to have less understanding about cancer immunology or immune-based therapies (other than passive therapies; e.g., antibodies). Overall, we believe greater interactions between these two relatively disparate and segregated groups will be intellectually and clinically rewarding and will provide a powerful new kind of stimulus to realize the goal of managing cancer by 2015. Toward this end, it is critical to support forums and think...
tanks that bring these two groups together to share data and concepts and to develop new ways for genetics, chemotherapy, and immunotherapy to provide an all-out attack on cancer.

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