

Immunological thought in the mainstream of cancer research

Past divorce, recent remarriage and elective affinities of the future

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Immunological thought is exerting a growing effect in cancer research, correcting a divorce that occurred in the mainstream of the field decades ago just as cancer genetics began to emerge as a dominant movement. Today, with a general consensus on the significance of epigenetics, the inflammatory cancer microenvironment and the immune response in determining cancer pathophysiology, a new synthesis of thought is being spurred by a remarriage with cancer immunology, with great implications for the future of the field. This perspective offers a view on how this synthesis is impacting both the understanding and treatment of cancer using adjuvant immunomodulatory modalities in the context of surgical, radiotherapeutic and chemotherapeutic interventions which are present standards of care. With the revolutions in immunochemotherapy and immunoradiotherapy coming this decade, the next great challenge faced by the field will be how to identify simple, cost effective and broadly applicable solutions that do not rely deeply on personalized characters, in an effort to minimize the daunting complexity and costs of a problem that challenges not only physicians and patients but also health care systems and insurers caring for aging populations in the developed world.

What is Cancer?

For the past three decades, the dominant thought in the mainstream of cancer research has been genetics oriented and cancer cell centric in focus. Building on the historic revolution in molecular genetics, work on cancer genes became the primary mover in modern thinking about cancer as a clinical disease and how to treat it. In the last decade, there has been a broad resurgence of interest in the tissue microenvironment of cancer and in the systemic and host immune factors that influence and may even dominate the development of clinically significant cancers. In particular, there has been a re-flowering of the idea that cancer is a disease of immune insufficiency, in other words, not merely a disease of rogue cells but the body's mismanagement of those rogue cells. This is not a new idea, nor one that ever has been ignored by cancer immunologists, but it is re-emerging nevertheless in the mainstream because of mechanistic advances in understanding

how cancer cells master their tissue microenvironment and host, and how these processes are integrated with oncogenesis and epigenetic alterations in cancer cells. Here I offer a perspective on why this old idea fell from favor in the mainstream, why it has returned, and what is now happening as a result. As a new journal in this exciting area, *Oncoimmunology* is one of the first to seek to capture the implications of the synthesis of thought that is occurring.

There is diverse evidence to show how the cancer cell-centric ideas about cancer can be undermined as a basis to understand the clinical phenomenon. Small occult cancers in the aged appear to present quite frequently, for example, in the case of occult prostate cancers in elderly men. Small benign lesions are found in the lungs of smokers at very high rates that far exceed the incidence of frank lung cancer.¹ With regard to the curious failure of cancer screening programs to affect survival patterns, which recent large studies have shown is the case in several major cancers except colon cancer, one

interpretation may be that the presence of cancer cells cannot fully explain the clinical phenomenon of cancer. Interestingly, in healthy individuals "cured" of cancer the presence of cancer cells can be revealed by organ transplant to recipients receiving immune suppressive therapy, even though the donor was "cured" many years before and remains healthy.² From animal studies, it is quite clear that the cancer penetrance of otherwise powerful oncogenic lesions varies enormously between strains, illustrating the dominant effect that host modifiers exert on restricting oncogenic potency. While these examples do not weaken the significance of cancer cells to cancer, they can be interpreted in such a way as to highlight the weakness of a solely cancer cell-centric focus in understanding the clinical phenomenon of cancer. While this view is not radical, its implications are not fully appreciated, especially among physicians, patients and public health officials who continue to view the presence of cancer cells as synonymous with cancer.

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In revising the mainstream perspective, cancer immunology is taking the field back to the future. The roots of modern cancer research stem from work by the father of cellular pathology, Rudolf Virchow, who in the 1870s popularized the idea that cancer is composed of an unresolved inflammatory immune response involving cells determined much later to be both innate and adaptive in nature. From founding observations of Robert Koch and Louis Pasteur which correlated infections and cancer regressions, in the 1890s Coley attempted to harness this apparent immune response by inoculating his cancer patients with bacterial infections, with some documented successes in metastatic patients now thought to have reflected TLR-mediated immune activation. Paul Ehrlich enunciated in 1909 the hugely influential idea of immune surveillance of cancer cells, which may emerge continuously from the body but are eradicated by the immune system. In the 1950s Burnet and Thomas conceived of

tumor antigens as a basis for immune recognition and surveillance of cancer, a concept developed still further in the 1990s and beyond by Schreiber, Old, Smyth and their colleagues as a phase in their model of immunoediting to describe the long-standing battle between cancer cells and the immune system before frank cancer development is recognized clinically, if ever.³

In contrast, the roots of cancer genetics in the 1910s were much less influential although they would eventually come to dominate the mainstream of cancer research toward the end of the century. Studies by Peyton Rous of oncogenic avian retroviruses initiated what became the oncogene and tumor suppressor gene revolutions of the 1980s, married to pioneering tissue culture advances by Eagle and Dulbecco and mouse transgenic technologies by Mintz and others that made functional analyses feasible. Founding work in cytogenetics marked by the advances of Hungerford and Nowell in the 1960s was

one factor in helping move cancer genetics into the world of cellular oncogenes and suppressor genes in the 1970s, which generated the first sources of the targeted cancer therapeutics to be approved for clinical use in the 1990s.

The Divorce

One notable event that occurred in the 1970s as the cancer genetics revolution was developing was the creation of an immunodeficient strain of mice, in particular the nude mouse, the study and use of which in cancer research I believe ultimately had a major negative impact in dampening mainstream interest in cancer immunology (Fig. 1). Nude mice made possible the creation of human tumor xenograft models from which many chemotherapeutic agents were subsequently developed. However, nude mice were also reported to lack any change in the rate of spontaneous cancers which arise naturally. At the

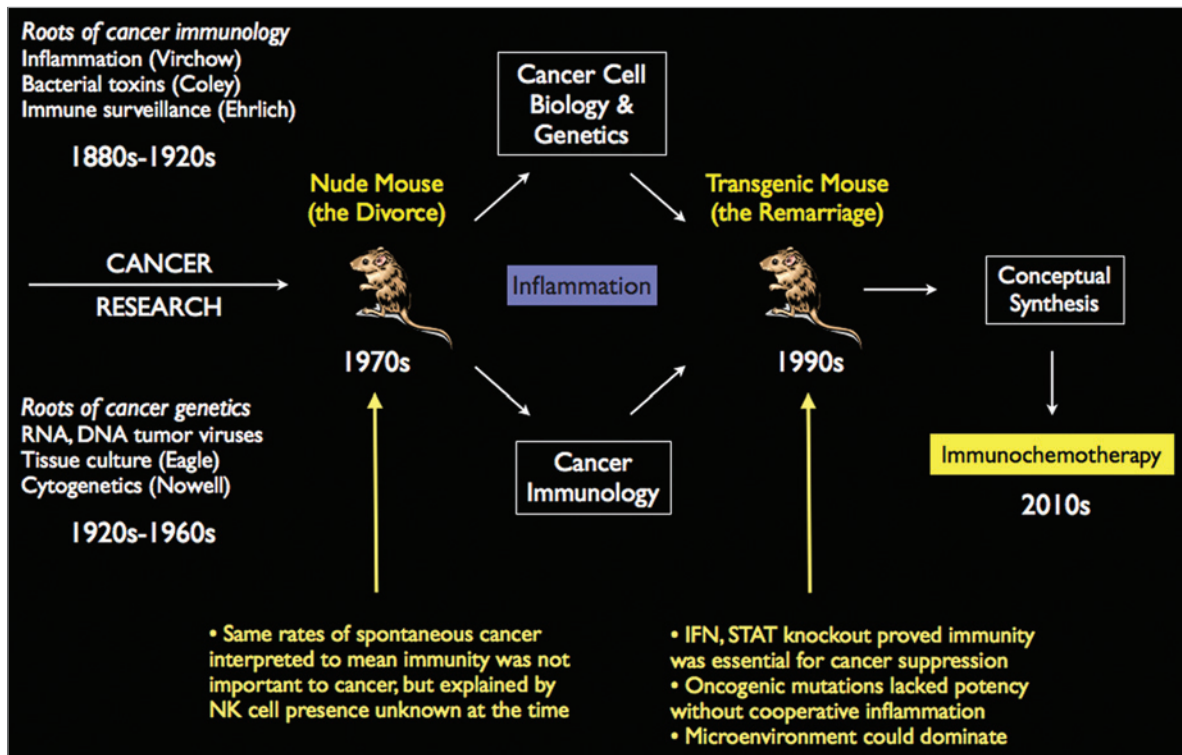


Figure 1. Perspective on the historical impact of immunological thought in cancer research. A key event in changing the impact of immunological thought on cancer research may have been the generation of nude mice as an immunocompromised animal system for tumor formation and treatment studies. In permitting human tumor xenograft models to be developed, the nude mouse had a huge influence on the identification of cytotoxic chemotherapeutic drugs for solid tumors. Nude mice have similar rates of spontaneous cancer, which was interpreted as a sign that the immune system was unimportant to cancer formation or control, but the presence of natural killer (NK) cells that exert powerful anticancer effects in nude mice was not appreciated until much later. Later studies in transgenic models corrected this view, but the “divorce” that had occurred to weaken the mainstream perspective on cancer immunology was not healed for decades, as genetics and cell biology became major drivers in what became a mainly “cancer cell centric” field until the 2000s.

time, this finding was interpreted to mean that the immune system was unimportant to understanding cancer, since eliminating immunity did not correlate with any increased tumorigenesis. One source of this misinterpretation may have been the lack of knowledge that nude mice retained natural killer (NK) cells capable of controlling cancers. In any case, I believe that the highly influential effect of nude mice on cancer biology and pharmacology studies combined with the misinterpretation of the spontaneous cancer data were important in putting cancer immunology in a poor light among the mainstream of cancer researchers, who became even more intently focused on cancer cells with the genetics revolution. Working as a graduate student on Myc in the 1980s, I recall the strong biases voiced among most molecular and cellular biologists against immunology as a significant aspect of cancer, and these biases were reinforced that decade by the many dramatic cell transformation experiments which could be interpreted as evidence for disease sufficiency. The divorce of cancer immunology from the mainstream that started in the 1970s and deepened in the 1980s separated a whole generation of cancer researchers from the concepts and language of an important discipline in the field, isolating it. Unfortunately, it was not until transgenic mouse experiments starting in the 1990s that livened interest in the cancer microenvironment, pointing increasingly to inflammation and immune insufficiency as critical elements to license the action of oncogenes, tumor suppressor genes and epigenetic changes that act in cancer cells.

The Remarriage

Among the preclinical studies that re-established the immune system as a causative factor in cancer, those from Schreiber and colleagues demonstrating a higher incidence of solid tumors in immunocompetent mice lacking interferon signaling elements may have been the most seminal.⁴ While not noted at the time, in retrospect this work offered a definitive refutation of the earlier nude mice experiments that immunity was correlative rather than causative in cancer. In parallel, as cancer biologists and geneticists widely applied

transgenic mouse technologies to study many oncogenes and suppressor genes, it became increasingly apparent to these workers in the mainstream that inflammatory processes and immune responses were crucial. Further demonstrations from founding work by Bissell and Werb in the 1990s which focused solely on microenvironment extended the concept that changes at this level were fully sufficient to engender cancer. Through such studies based on the whole organism, a remarriage of the mainstream with concepts long appreciated in cancer immunology was essentially achieved by the end of the 2000s, repairing the conceptual damage done by the biases and misinterpretation of solely cancer cell-centric and nude mouse studies.

The synthesis of oncogenesis and immunoediting as a unified model has more robust explanative and predictive power than the non-unified models for understanding cancer (Fig. 2). Oncogenesis provides a source of neoantigens that initiates immunoediting, but also the plasticity to maintain the immune selection that provides forward feedback for cancer evolution. Immunoediting can be viewed as a veneer to oncogenesis which drives the evolution of plasticity, feeding the continuing cycle of parry and thrust with cancer cells.³ Both processes inform perspectives on inflammation, which serves as the landscape upon which the battle of cancer and immune cells in the microenvironment occur. Indeed, cancer-associated inflammation and immune escape can be seen to be genetically synonymous.⁵ Thus, reprogramming inflammation to change the landscape of the battle will exert the same outcome as blocking immune escape: iterations of immune escape mechanisms “flavor” the inflammatory processes of the microenvironment, converting it from antagonistic to supportive for cancer progression. In summary, if immune escape is inflammatory reprogramming, and immune escape is the pivotal event in defining the phenomenon of clinical cancer, then effective therapies would be those achieved only by a successful reprogramming of inflammation (which is the same as blocking immune escape).

Considering Coley’s project to reprogram the inflammatory milieu of a cancer

patient, it is intriguing to consider what he might have achieved by inoculating protists (parasites) instead of bacteria, since protists undergo far more antigenic variation like cancers than bacteria do. As geneticists have defined the extreme diversity of cancer cells in a single patient,⁶ they reinforce some early ideas that the immune response to tumor antigens fuels the selective pressures responsible for escaping immunity but perhaps also therapy. As we learn more of the inflammatory “flavor” of a productive cancer microenvironment, it may be interesting to determine whether the adjuvant signals engendered by protist infection are more akin to effective cancer therapies than those engendered by bacterial infections. In any case, modifiers acting in the host and microenvironment that “flavor” the immune response may become increasingly critical in determining whether tumors initiated by mutations ultimately achieve any clinically significant state, as well as what the prospects for effective therapy are.

The Future

The new conceptual synthesis is now propelling elective affinities of modalities as new therapeutic principles in a tripartite strategy of immunochemotherapy (Fig. 3). Vaccines long studied by cancer immunologists despite historical disappointments will benefit greatly from combination with agents that correct immune escape, degrade immune tolerance and reprogram inflammation. In the 1990s, cancer geneticists realized that oncogenes were impotent until tumor suppressor genes were lost. In the 2000s, mechanistic advances made it possible for immunologists to realize that immune stimulation was ineffectual until tumoral immune suppression could be relieved. Some of the character of traditional chemotherapy and radiotherapy has long been recognized as immunogenic, but only recently have the mechanisms underlying these effects begun to be understood sufficiently to exploit correctly. Cytotoxic chemotherapy was generally recognized as damaging to the immune system, such that its combination with immunotherapy was viewed as nonsensical, but this has now changing quickly based in part on the recognition of mechanisms of chemotherapy that

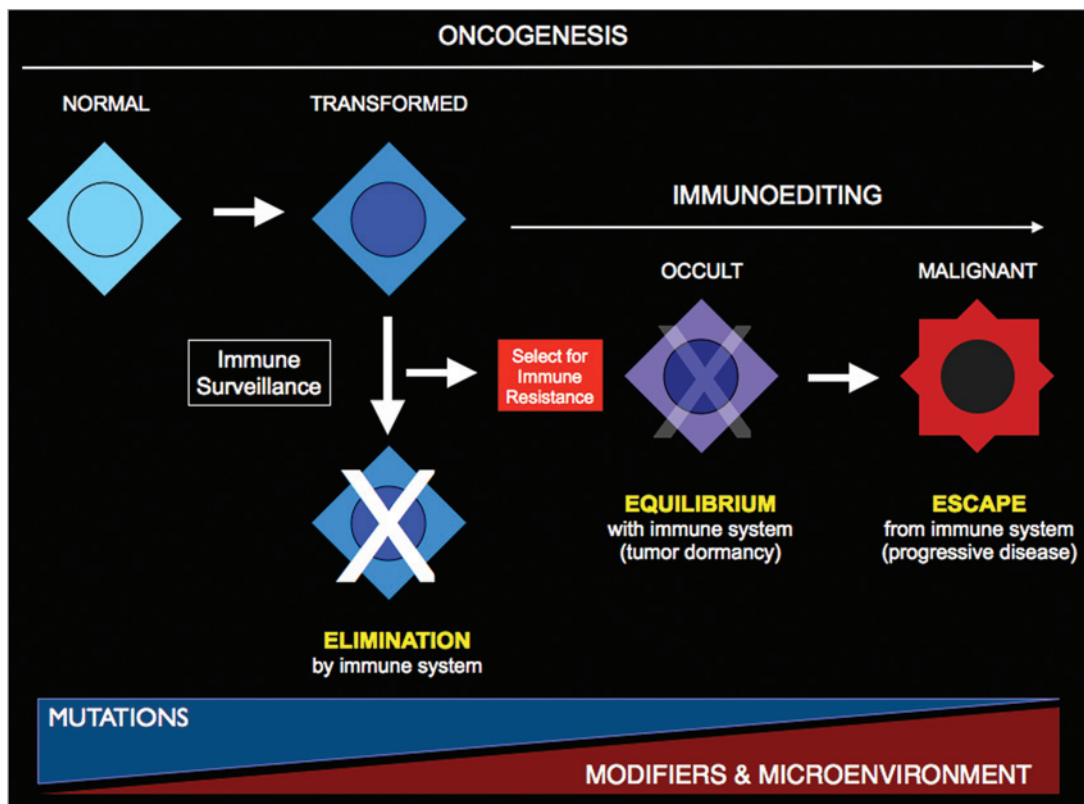


Figure 2. Synthetic model of immunoediting and oncogenesis. Oncogenesis creates neoantigens recognized by the immune system, but it also creates plasticity that drives a continuous battle between cancer cells and the immune system on the basis of evolving neoantigen recognition. Analogous to the manner in which bacteria can evolve resistance to antibiotics, but with the advantages of plasticity conferred by oncogenesis, cancer cells evolve tactics for immune resistance. The iteration of escape mechanisms evolved by cancer cells can lead to progressive states of equilibrium and escape, representing clinical dormancy or progressive disease, respectively. To the degree that arising cancer cell mutations may influence local immune modifiers and microenvironment which dominate tumor progression, they may remain forces in driving immune escape and thereby progression to clinical relevance. This model was presented previously in the context of IDO studies.¹³

support immunotherapy, as documented most extensively by Zitvogel and Kroemer and their colleagues.^{7,8} In terms of modern targeted cytotoxics, it is intriguing that the strongest examples such as Gleevec are effective because they not only kill cancer cells but also interfere with immune escape.⁹ It is also clear that modern and traditional cytotoxic approaches can benefit strongly from combination with agents that can reprogram inflammation and degrade tumor tolerance.^{10,11} In parallel, similar benefits may accrue from using these agents in the setting of radiotherapy and surgery, in the latter case to address preoperative inflammation that might be programmed to reduce metastatic risk. Looking forward, there seems to be huge promise in tripartite immunochemotherapy and related strategies in radiotherapy and surgery to improve cancer treatment, merging the best principles of what has been developed in diverse fields.

Yet even while painting a rosy picture of the future, it is clear that great challenges will remain. The ever growing complexity and cost of personalized care models makes them arguably weak for future application, given the acute pressures on physicians, health care providers and payers to address the aging, debt-ridden societies of the developed world. Trends in oncology are clearly toward data-heavy decision making processes and personalized care, but while there are compelling reasons for these trends cost challenges may make them impossible to achieve or sustain. Must every cancer be treated as a personalized disease? Since the immune system naturally deals with complexity, it may still be possible to achieve what molecular biology long promised, and then reneged upon, which is a small set of generalized approaches to treat any cancer. If immunochemotherapy principles can be developed to achieve this,

will it be possible to do so cheaply? From a practical standpoint, there should be increasing attention devoted to off-the-shelf vaccines, generic small molecules, and off-patent chemotherapeutics that might generate low cost solutions. While this may not be the near future, it must be the more distant future, with younger scientists thinking of invention as much as discovery as the field enters what at the opening of the 21st century may finally be the end of the beginning in the goal of eradicating cancer.¹²

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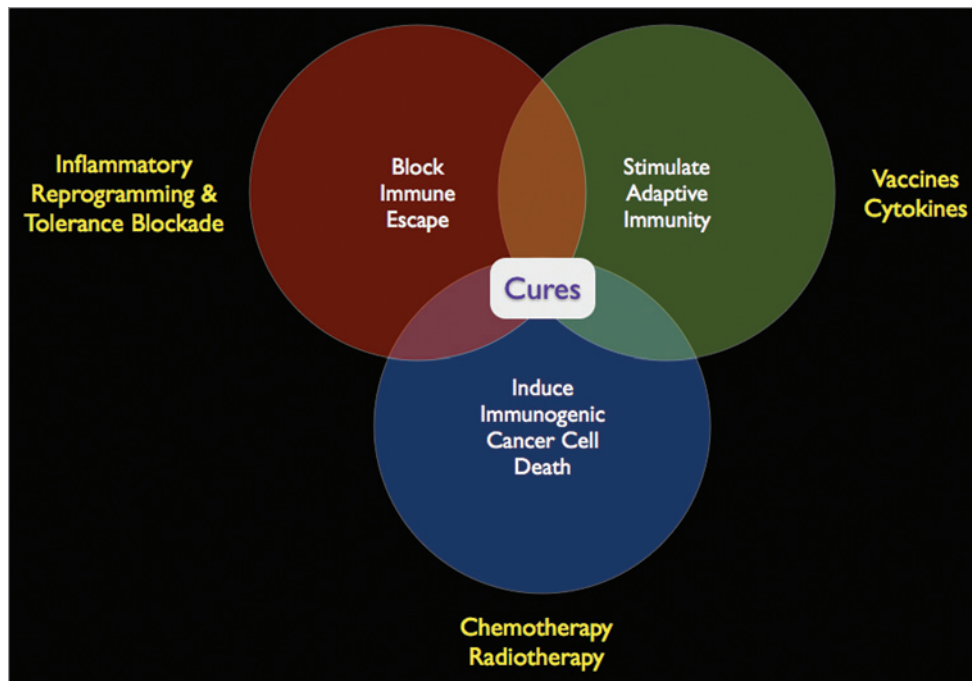


Figure 3. Immunotherapy of the future. The new synthesis of immunological thought with the mainstream of cancer research is stimulating the creation and evaluation of new combinations of therapies that can stimulate the immune system, relieve the immune blockades erected by tumor cells (which have historically hampered immunotherapy), and trigger pro-immunogenic tumor cell deaths. Immune blockades erected by tumors are associated with an altered inflammatory “flavor” of their microenvironment, switching its character from antagonistic to supportive for tumor outgrowth. Conceptually, therapeutics that reprogram the inflammatory “flavor” or block tolerance may prove to be genetically overlapping in action, as suggested by studies of IDO pathway inhibitors.⁵

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