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This information is current as of May 27, 2022.

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J Immunol 2018; 201:825-826; ;
doi: 10.4049/jimmunol.1800827
<http://www.jimmunol.org/content/201/3/825>

Supplementary Material <http://www.jimmunol.org/content/suppl/2018/07/23/201.3.825.DC1>

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The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852
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Print ISSN: 0022-1767 Online ISSN: 1550-6606.



From Cancer Immune Surveillance to Cancer Immunoediting: Birth of Modern Immuno-Oncology

Wolf H. Fridman

We were at the dawn of the millennium. Cancer science was dominated by genomic studies that established that the disease results from modifications of genes in somatic cells by mutations, amplifications, or deletions, allowing limitless replication of the transformed cells. Identification of mutations in driver oncogenes or tumor-suppressor genes, and of the signaling pathways they dominate, had strongly impacted cancer management as they guided the development of targeted chemotherapies aimed to selectively interfere with cancer cell-specific biology. The role of tumor-induced angiogenesis was beginning to unravel, but the impact of patients' immunity in controlling cancer growth and spread was largely ignored. Indeed, in a classical review published in 2000, D. Hanahan and R.A. Weinberg (1) highlighted six hallmarks of cancer but did not mention interactions of tumor cells with the host immune system.

At that time, cancer immunology was not seriously considered, and when it was, it had a rather bad reputation. However, cancer immunologists had provided insights all along the 20th century both through clinical observations and experimental data. On clinical grounds, W.B. Coley (2) had observed, as early as in 1891, that a patient with sarcoma presenting a strong post-surgery erysipelas infection due to *Streptococcus pyogenes* experienced a complete regression of his cancer. Coley hypothesized that the antitumor effect was due to the patient's immune reaction and started to treat patients with live, and then killed, bacteria. It was quite toxic, but bacillus Calmette–Guérin vaccine is still being used as an adjuvant therapy for superficial bladder cancer. Moreover, the higher incidence of cancers in immunodepressed individuals could have been considered as evidence for immune control of cancers. However, because the malignancies were virally induced in the vast majority of cases, it was considered as proving, as was already known, that the immune system recognizes infectious pathogens and not tumor cells. The therapeutic successes of allogeneic bone marrow transplantation in the treatment of hematological malignancies did not support that patients were able to recognize their own tumors because cells from a healthy individual, and not from the patient, were injected. That there was a possible immune reaction of patients against their malignant cells was, however, supported by

reports, for example, in leukemia (3), or by the identification of melanoma-associated Ag, recognized by a patient's T lymphocytes (4). Numerous mouse models have also shown that tumors could be specifically rejected and that they induced a memory immune response, but most models that used transplanted tumors and rejection were attributed to transplantation immunity rather than to tumor immunity. Nevertheless, a theory known as "cancer immune surveillance" was independently elaborated in the 1950s by M.F. Burnet (5) and L. Thomas (6). It proposed that the immune system could eliminate nascent tumor cells because the latter possess new Ags and provoke an immune reaction with regression of the tumor and no clinical hint of its existence. Again, opponents to the immune surveillance theory underlined the fact that it would be impossible to demonstrate that something that does not exist could have existed.

In a seminal study, the R.D. Schreiber's group (7) succeeded in 2001 in establishing the foundations of modern immuno-oncology. First, they showed that chemically induced sarcoma grew better, and more rapidly, in immunoincompetent mice than in wild type animals because the former either lack lymphocytes, owing to the loss of the RAG gene or their inability to respond to IFN- γ because of the loss of the IFN- γ receptor gene, or STAT-1. Second, they demonstrated immune surveillance by showing that all mice with a RAG2 or double RAG2^{-/-} STAT1^{-/-} knockout spontaneously developed tumors. These tumors were not induced by viruses but resemble some of the major malignancies of humans, such as breast, lung, or colon. The authors then introduced a new concept of cancer immunoediting by the host immune system. They showed that 40% of chemically induced tumors from immunoincompetent mice were rejected when transplanted into immunocompetent hosts, whereas no rejection occurred when transplants were performed with tumors coming from syngeneic immunocompetent mice. This experiment clearly demonstrated that immunoediting had occurred in immunocompetent animals, even if they had been incapable of rejecting their own tumor, allowing their escape from immune control. Finally, the authors showed that tumor rejection was due to T cell-mediated immune responses, which were dependent on both CD4 and CD8 T cells. Tumor rejection was followed by immunological memory, and rejection of IFN- γ -insensitive tumors could be restored by transfection of MHC class I and TAP 1 genes.

This rather short manuscript thus contains all the demonstrations that establish immuno-oncology as a major partner

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of cancer biology and cancer therapy. It led to the elaboration by R.D. Schreiber and colleagues (8) of a novel theory for tumor immunity known as the “three E’s theory.” The theory proposed three steps: 1) elimination of tumors at an early stage (previously known as the immune surveillance hypothesis), 2) equilibrium when the immune system controls the tumor, and 3) escape when tumor cells are fully immunoevaded and grow without immune control. The three E’s is still the theory accepted worldwide as the template to understand interactions of cancer cells with the host immune system. The theory also prompted clinical teams to demonstrate the generally favorable impact of intratumoral T cells on patient outcomes (9), providing strong prognostic markers and paving the way for the exploding field of immunotherapies (10). This groundbreaking work contributed to our understanding that mutations in cancer genomes impact immune responses (11), further linking genetics to immunity. It is therefore not exaggerated to state that the paper by Schreiber and colleagues (7) is the founding work of modern immuno-oncology, inspiring a whole generation of scientists and clinicians to conduct the therapeutic revolution (12) that we are witnessing in the field of cancer.

Disclosures

The author has no financial conflicts of interest.

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