Human Tumor Immunology at the Molecular Divide

Olivera J. Finn

*J Immunol* 2007; 178:2615-2616; doi: 10.4049/jimmunol.178.5.2615

http://www.jimmunol.org/content/178/5/2615

---

**References**

This article cites 16 articles, 5 of which you can access for free at: 
http://www.jimmunol.org/content/178/5/2615.full#ref-list-1

**Subscription**

Information about subscribing to *The Journal of Immunology* is online at: 
http://jimmunol.org/subscription

**Permissions**

Submit copyright permission requests at: 
http://www.aai.org/About/Publications/JI/copyright.html

**Email Alerts**

Receive free email-alerts when new articles cite this article. Sign up at: 
http://jimmunol.org/alerts

---

*The Journal of Immunology* is published twice each month by The American Association of Immunologists, Inc., 1451 Rockville Pike, Suite 650, Rockville, MD 20852

Copyright © 2007 by The American Association of Immunologists. All rights reserved.

Print ISSN: 0022-1767 Online ISSN: 1550-6606.
Human Tumor Immunology at the Molecular Divide

Olivera J. Finn

In the mid-1980s, as a young investigator at Duke University running a human immunology laboratory with interest in T cell allograft rejection, I was becoming very confident in my ability to grow human alloreactive T cell lines from small biopsies of kidney allografts and use them to define their Ag specificity. Overly confident, as befitted my inexperience, I decided to use the same successful in vitro T cell culture system to isolate and characterize human tumor-specific T cells. I was very lucky, and the efforts of my students and colleagues over the next 4 years resulted in a paper reporting a discovery of an Ag on human adenocarcinomas that is recognized by human T cells (1). I was proud of this result but also aware that the cellular assays we used had limitations, and even though we believed that our conclusions were correct, we could not completely exclude other much less important alternative explanations. What gave credence to our work and to similar work performed in the two decades preceding us was the publication in 1991 of this month’s Pillars of Immunology article (2). In it, the authors reported successful cloning of a gene that encoded a human melanoma Ag recognized by CTLs. I consider this article to be the molecular divide between the “old” human tumor immunology that postulated but could not prove the existence of tumor Ags and the “new” tumor immunology that uses these Ags and genes that encode them to understand tumor immunity and design effective immunotherapy.

Even though it took some time, it was ultimately possible to design appropriate mouse experiments that conclusively showed that tumors can be recognized by the immune system and that immune responses are tumor specific and protective (3, 4). Without knowing the specific targets on the tumors, it was still possible to explore the relative importance of various immune effector mechanisms as they became better defined, all in secure knowledge that they were indeed relevant to tumor immunity because tumors either went away, if these mechanisms functioned properly, or killed the animal if they did not. The two decades that followed the first successful mouse experiments saw an explosion of studies of tumor immunity in animal models. Spontaneous tumors, UV-induced tumors, and virally induced tumors all were shown to be under the surveillance of the immune system by tumor-specific Abs and T cells. The main motivation for all of these studies was to understand human tumor immunity better; however, evidence that human tumors are also under Ag-specific immune surveillance was difficult to obtain. Since the ultimate proof, tumor rejection, so easily obtained in animal models, was not a possibility when studying human immunity, other forms of hard evidence were sought. This is where the specificity of immune recognition played an especially important role. At a minimum, it was possible to show that either Abs or lymphocytes derived from cancer patients preferentially recognized tumor cells vs normal cells. It is astounding to read papers published on this topic in the 1970s (5–8) and to realize that all of the experiments were performed without the benefit of the detailed knowledge we have now of the nature of Ag presentation and Ag recognition, especially in regard to cellular immunity. In parallel to showing specific recognition of tumor cells, it was important to provide an independent, corroborative proof that there are in fact differences between normal cells and tumor cells that the immune system would be expected to see. That effort was very much helped by the advent of hybridoma technology (9). Every tumor immunologist could immunize a mouse with a human tumor of his or her choice, generate mAbs, and look for those that react with tumor cells and not normal cells. The decade that followed witnessed great excitement as mAbs were used to purify human tumor Ags that then could be characterized biochemically and thus become real entities to be further interrogated for their antigenicity to the human immune system (10, 11). However, this was still the era before the discovery of the TCR for Ag, and while MHC restriction was an accepted phenomenon, there was no knowledge yet of T cell recognition of Ags as small peptides bound to MHC molecules. One major discovery at that time that put T cell tumor immunity research on a more sure footing was that of IL-2, a T cell growth factor that allowed long-term cultures of tumor-specific T cell lines as well as T cell clones (12, 13). Being able to grow from cancer patients T cell clones whose tumor specificity could be tested repeatedly and rigorously provided considerable confidence that theobserved reactivity was real. Furthermore, because of their exquisite specificity, T cells, like mAbs, could be used to define the Ags that they recognized. In the several years that preceded the publication of the 1991 paper (2), there was intense focus on establishing tumor-specific T cell lines and clones for various tumor types. Most of the work was done in melanoma primarily due to a higher degree of success in establishing melanoma cell lines that could then be used to provide antigenic stimulus to autologous T cells in vitro. Collectively, this work showed that tumor-specific T cells were the standard TCR αβ T cells that in the case of CTLs were HLA class I restricted. The exact Ags or epitopes recognized by these cells remained elusive. The breakthrough that came with the 1991 paper was foreshadowed by the work of the same group in a mouse...
tumor model published several months earlier (14). In that paper, the authors used a cosmid library made from a mouse mastocytoma P815 to transfect target cells and tumor-specific CTL clones to select transfectants that become CTL targets. From these transfectants, a gene was retrieved, which was found to be identical in sequence between tumor and normal tissues. Its expression, however, was limited to tumor cells only, explaining the tumor specificity of the CTL. This same methodology was then used in an attempt to clone a gene that might encode a human tumor Ag. A panel of CTL clones was derived from a melanoma patient that could kill the melanoma cell line established from the same patient. Extensive analysis of the function of these CTL clones showed that they had distinct specificities such that melanoma cells resistant to lysis by some clones were susceptible to lysis by other clones. A correct assumption was made that tumor cells resistant to lysis had lost the CTL target Ag. A cosmid library was prepared with DNA from tumor cells that were susceptible to CTL lysis and thus presumably expressed the Ag. Resistant tumor cells were transfected with these cosmids, cloned, and tested for reacquired susceptibility to CTL lysis. By repeating transfection experiments with smaller pools of cosmids, a transfectant was finally isolated that carried a cosmid with a 12-kb DNA fragment that could transfer the expression of the Ag. The number of cosmids clones screened and transfections performed is mind-boggling, but at the end of this tour-de-force project, the author had the first human tumor Ag, "MAGE" (melanoma Ag). Even with this one cloned gene, and already in this first paper, the authors were able to make important new observations relevant to the nature of human tumor Ags. They found out, for example, that this Ag was a normal, nonmutated gene that is activated in many melanomas and in some other cancers but silent in normal tissues. They also discovered that small fragments of the gene could transfer expression of the Ag, suggesting that they encoded antigenic peptides sufficient for CTL recognition. Finally, by being able to transfer Ag expression into many different cells, they concluded that the major presenting molecule of the antigenic peptide was HLA-A1.

Once this paper was published, the new molecular era of human tumor immunology began with the all-out effort in tumor Ag discovery. The various methods that combined genetic and biochemical approaches with immunological assays have all been highly labor intensive and have required tremendous commitment of investigators’ time and resources. However, having melanoma Ag MAGE1 as proof that tumor Ags do exist justified all the future efforts in search of these molecules. The result has been a long list of well-defined tumor Ags, many of which are being tested as targets for immunotherapy (15, 16).

References