Commentary

Cancer Antigens: Immune Recognition of Self and Altered Self

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A tacit assumption of cancer immunology has been that tumors express non-self or "foreign" antigens. The recent identification of a handful of potentially immunogenic cancer antigens shows that they are not truly foreign. Although the boundary between self and non-self is not well-defined, this first look at cancer antigens fits more with a self/altered self paradigm than with the non-self paradigm for antigens recognized in infectious diseases.

Tumor-specific Antigens in Animal Models

The experimental foundation for cancer immunology comes largely from studies of immune rejection of chemically- and UV radiation–induced tumors in syngeneic mice. The antigens defined in these mouse systems are potent, tumor-specific determinants, recognized by CTLs that are expressed by tumor cells but not by normal cells or even by independently derived tumors (1, 2). Studies by Boon and co-workers have provided a model for the origin of tumor-specific antigens, using the mouse P815 mastocytoma tumor (3–6). Treatment of P815 cancer cells in vitro with a mutagen was used to generate variant cancer cells, called tum^-, that failed to produce tumors because of stimulation of strong CTL responses. The mutagen generated single nucleotide mutations in coding regions, altering solitary amino acids and creating new antigens for a CTL response to altered self. These single amino acid mutations provided either a new epitope for TCR recognition or a new agretope for binding to MHC molecules (3, 4). In either case, epitope or agretope, the antigen was tumor specific because it was presented through MHC only by the mutagenized malignant clone. The determinants were unique to the tumor, even though the original, nonmutated gene could be ubiquitously expressed, providing a structural basis for tumor-specific recognition (3).

A striking finding was that immunization with mutagenized tum^- cells could induce protection against the parental tumor cells, even if the original tumor was a poorly immunogenic, spontaneous tumor (5, 6). These experiments provide a strong indication that even apparently weakly immunogenic cancers can be rejected by an immune response after effective immunization. Thus, all tumors may have antigens that can be recognized by the immune system, but the immunogenicity of these antigens can vary from potent antigens in chemically induced tumors to low inherent immunogenicity in spontaneous tumors.

Recognition of point mutation is not the only model for tumor rejection in the P815 model. Two CTL clones against P815 variants reacted with the product of a gene, called P1A, that was completely identical to the gene present in normal tissues of the mouse (7). The antigen encoded by P1A was expressed not only by P815, but also by an unrelated mast cell line derived from the syngeneic mouse strain. This finding raised the prospect that shared, nonmutated antigens can be recognized by T cells on tumors of the same histologic type.

Recognition of Differentiation Antigens on Human Cancers

A body of data over the past two decades has determined that the immune repertoire of persons with cancer contains B and T cells that recognize antigens expressed by autologous cancer cells. Thus, tolerance to human cancer, if it exists, does not delete the immune repertoire against the cancer cell. The known universe of immunogenic antigens (i.e., defined by structure or sequence) on human cancers is small, but is expanding rapidly (Table 1). In contrast to the classical mouse studies, the human immune system appears to recognize antigens expressed by normal tissues. The immune repertoire to melanoma is the most extensively characterized of any cancer in humans. The serological analysis of human melanoma has shown that antigens expressed on cancer cells reflect the differentiation state of the normal cell counterpart (melanocyte) at the same stage of differentiation (8). Immune recognition of melanocyte differentiation antigens has been demonstrated for high affinity IgG autoantibodies against melanoma (9). This paradigm of differentiation antigens is now being revisited based on recent knowledge of T cell recognition of human melanoma. This is exemplified by a report in this issue by Coulie et al. (10) and two reports by Kawakami et al. (11, 12) describing an antigen, called Melan-A or melanoma antigen recognized by T cells 1 (MART-1), expressed by melanoma, melanocytes, and pigmented retinal cells but not other normal tissues. This melanocyte differentiation antigen was presented to CTL of at least 11 different persons through class I MHC HLA-A2.1 molecules expressed by mela-

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Table 1. *Antigens on Autologous Human Cancers Recognized by Antibody or T Cell Responses*

	Antigen	Tumor type	Normal tissue expression	Comments	Rf
Antibody	gp75/*brown*	Melanoma	Melanocytes	Melanosomal protein	13
	Gangliosides (GM2, GD2)	Melanoma	Neuroectoderm-derived tissues	Carbohydrate antigens	20
	Melanotransferrin	Melanoma	Melanocytes, other tissues	Potential unique determinant	21
	HER2/neu	Breast	Epithelium	Overexpressed on a proportion of cancers	22
	p53, nonmutant	Breast	Most cells	No recognition of mutant p53	23
	T,Tn,sialylTn	Breast	Epithelium	Carbohydrate antigens	20
T cell	MAGE-1,3	Melanoma, lung, and other cancers	Testes	Not expressed by melanocytes	17 18
	Tyrosinase/*albino*	Melanoma	Melanocytes	Melanosomal protein	12
	MUC1	Pancreas, breast	Epithelium	Non-MHC restricted	24 9
	Melan-A/MART-1	Melanoma	Melanocytes	Melanocytes and retina	10 11 14
	pMel17/*silver*?	Melanoma	Melanocytes	Melanosomal protein	15

Antigens with known structures that are recognized on autologous tumor cells.
Rf, reference number.

noma (10–12). This defines a true shared tumor antigen, expressed by tumors in different hosts and recognized by more than one patient.

The Melan-A antigen is now the fourth autoantigen on human melanoma that is specifically expressed by normal melanocytes. CTL clones of one of the patients who responded to Melan-A also recognized another normal melanocyte constituent, tyrosinase, presented by HLA-A2.1 (10, 13). This patient did not have overt signs of autoimmunity (e.g., depigmentation) and yet had an extraordinarily good clinical course after multiple resections of metastatic melanoma. Although one cannot generalize too much from a single patient, clues often arise from these case studies. In this case, the clue is that immune responses to restricted melanocyte differentiation antigens might prevent progression of the cancer.

The identity and cellular localization of Melan-A remains unknown. However, three other autoantigens on melanoma are transmembrane glycoproteins expressed within melanosomes, the melanocyte-specific organelle that is the site of melanin synthesis. These are tyrosinase (the product of the *c* or *albino* locus), gp75 (the product of the *brown* locus), and gp100 (mapping near or within the *silver* locus) (9, 13–15). A peptide within gp100 defines another shared epitope, recognized by CTL from nine melanoma patients (14–16). It is worth pointing out that each of these products is the human homologue of a gene or genetic region that determines coat color in the mouse. Why melanosomal glycoproteins are so readily recognized by the immune system remains a mystery.

Another model for recognition of self molecules is exemplified by the MAGE-1 and MAGE-3 antigens systems (17, 18). MAGE-1 and -3 are expressed on melanoma (and other tumor types), but not on normal melanocytes or most other normal tissues. In normal tissues, MAGE-1 and -3 appear to be restricted to the testes (17, 18). Although the exact cell type in the testes is not yet identified, the MAGE genes could be regulated during spermatogenesis or early development and then remain silent (except after malignant transformation). Discovering the functions of these genes will provide further insights.

There are several points to make about this universe of human cancer antigens (Table 1). First, these studies are at an early stage, and the majority of work in human cancer to date has been done in melanoma. It would be premature to generalize to all cancers at this point. Second, the majority of antigens recognized by the immune system is expressed both by the malignant cell and normal cell counterpart (e.g., melanoma and melanocyte), and therefore represents an apparent autoimmune recognition. Third, the evidence to date reflects immune repertoire, i.e., it is not yet possible to know whether T cell or antibody responses truly represent immune

rejection of cancer. Distinguishing immune repertoire from a protective immune response in vivo and in situ will be critical. Evidence for high titer, high affinity IgG antibody responses or high precursor frequencies of T cells is consistent with a specific immune response to the tumor in vivo, but it is possible that these responses are not to the tumor but to tissue injury or some other event in the host.

If self proteins of human cancer can be recognized by CTLs, can T cells recognize mutations, for instance *ras*, *p53*, or other altered alleles? Mutations in *ras* and *p53* are not common in human melanoma, and it is too early to know the frequency of immune recognition of these mutations in other cancers. These are certainly attractive targets. However, whether these are realistic epitopes for the immune response is uncertain. Evidence points to the likelihood that there are T cells in the immune repertoire that can recognize mutant *ras* peptides (19). Yet it is possible that many mutations are not presented to the immune system on MHC molecules of human cancer cells. Presentation would require appropriate processing and trimming of peptides, transport to the correct compartment for MHC binding, and expression of an appropriate MHC allele that could accept the peptide. If strongly immunogenic mutations were presented by the tumor, clones could be destroyed by an immune response, but surviving tumor clones could avoid the response by mutation or down-regulation of the gene encoding the peptide, or by down-regulation of MHC, peptide transporter, or other escape routes. In particular, if the mutation is not crucial to maintaining the malignant or metastatic phenotype, then subclones not expressing the mutant peptide might readily survive.

Mutations appear to accumulate progressively in human cancers, particularly during later stages of tumor progression. In contrast, chemically induced tumors acquire a large number of mutations simultaneously at an early stage of tumor development. The expression of potent unique tumor rejection antigens in chemically induced tumors may reflect the acquisition of a large number of mutations early in tumor progression, allowing less chance for selection by the immune system, and providing a stochastic model for recognition of these unique antigens.

Final Comments

Human studies of immune responses to cancer have shown that normal differentiation antigens are recognized by the host. In this respect, tumor immunology shares common features with the study of autoimmune disease. Both fields are concerned with the immune response to cellular antigens and the role of this response in the pathogenesis of disease. However, the therapeutic goals of tumor immunology—to induce or augment the immune response against transformed cells—are the opposite of those for autoimmune diseases. Exploration of the immune repertoire against human cancer points to restricted differentiation antigens as a starting point for understanding the antigens recognized on cancer cells.

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