Published in final edited form as:

J Immunother. 2001 ; 24(3): 193–194.

Hierarchy, Tolerance, and Dominance in the Antitumor T-Cell Response

Nicholas P. Restifo

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, U.S.A

T-cell responses to any given epitope can be inhibited or “dominated” by simultaneous exposure to antigens on the same or different molecules (1,2), but the molecular events underlying the phenomenon of immunodominance are poorly understood. The reasons why one epitope is immunodominant are complex, but one quality that immunodominant epitopes from viruses share is that they tend to be among the peptide fragments that are best able to form high-affinity, stable complexes with restricting major histocompatibility class (MHC) molecules. A report in this issue addresses the question of why the best-binding, most immunodominant epitopes of the type generally discovered by virologists may not be the ones found by tumor immunologists (3).

With the identification of tumor-associated antigens recognized by T cells in the early 1990s, there were vigorous debates about whether the epitopes that had been identified were indeed correct. In the case of melanoma, the affinities of the epitopes from melanocyte differentiation antigens seemed to be significantly lower than expected. In some cases, such as what appears to be the immunodominant epitope from human MART-1 restricted by HLA-A*0201 (4), the affinity of the peptide epitope was logs lower than the affinities measured for viral epitopes with the same restriction element. First viewed by some as an aberration, it now appears that the antigenic epitopes recognized by tumor-reactive T cells can often bind with relatively poor avidity to their restricting MHC molecules.

Predicting immunodominant peptides that can be targets for recognition by T cells, also known as allele-specific epitope forecasting, can be done in a variety of ways, but one of the best predictors is the use of computer programs that predict the ability of peptides to form stable complexes with T cells. One of these computer programs is designed for a wide variety of MHC alleles and is available on a public website at http://bimas.cit.nih.gov/molbio/hla_bind/

Viewed from the world of viral immunology, the ability of some tumor-derived peptides to form stable complexes with their restricting HLA molecules is poor. For example, an epitope derived from melanoma antigen recognized by T-cell 1 (MART-1) starting at position 27 and having the amino acid sequence AAGIGILTV is ranked ninth of all possible nonamers from this relatively small protein. Perhaps more striking, its predicted half-time of disassociation from HLA-A*0201 is 580-fold lower than the best possible nonamer binder from MART-1. In another example, gp100, a particularly useful peptide with a starting position of 209 (5), is ranked 46th of all possible nonamers and has a predicted half-time of disassociation that is approximately 390-fold lower than the best binder in the molecule. A similarly poor binder for self-gp100 was found in the mouse (6).

One key difference between many tumor antigens and those from the world of virology is that these antigens are present on normal “self” tissues and thus may be capable of tolerizing immune responses to them. Indeed, self-tolerance has been observed in mouse models of immune reactivity to melanocyte differentiation antigens (7,8). How do the mechanisms of self-tolerance affect immune responses to the hierarchy of immune responses to epitopes derived from tumor-associated antigens?

Celis et al (3) have analyzed this question in a mouse model in which the SV40 large T antigen is specifically expressed in the prostate glands of male C57BL/6 mice, referred to as the TRAMP model (transgenic adenocarcinoma of the mouse prostate) (9). The model used by Celis is based in part on the analyses by Satvir Tevethia et al, who found that immune responses to the SV40 large T antigen could be classified in a hierarchical system (10). When Celis immunized TRAMP mice with an epitope described by Tevethia as immunodominant (designated IV), no immune responses were observed, although immune responses to a control antigen, ovalbumin, were normal. However, immune responses to a sub-dominant epitope (called V) from SV40 large T antigen were preserved in TRAMP mice (3).

Immune responses to SV40 large T epitopes have been previously studied in a different but related transgenic mouse model called 501 (11). Whereas expression of the SV40 large T antigen is driven by the rat probasin promoter in TRAMP mice, the 501 model instead uses an α -amylase promoter: TRAMP mice develop prostate tumors, 501 mice develop osteosarcomas. Tevethia found that CD8⁺ T cells specific for epitope IV were detected in transgenic mice but were progressively deleted in mice that had developed osteosarcomas, as evidenced by staining with H2-Kb/epitope IV tetramers. In contrast to Celis, Tevethia also found the development of complete tolerance to the immunorecessive epitope V in transgenic mice, but only at 12 months, a ripe old age for a mouse.

Although partial protection using an immunorecessive epitope from SV40 large T antigen in a BALB/c-based model has been described (12), to the best of our knowledge neither group has yet reported the results of experiments addressing the impact of subdominant epitope-specific immune responses on the therapy of either one of these tumor models. The findings in these models teach us what may be important lessons about the relationship of immune tolerance and immunodominance in the self-antigen setting.

The results of these studies confirm and apply to the tumor setting principles first elucidated by Sercarz, Kourilsky, and colleagues, who found a reversal of hierarchy when the antigen being assessed was also expressed in normal tissue (13,14). In the Celis model appearing in this issue, immune responses to the subdominant epitope may not have been tolerized, but they nevertheless remained relatively weak. Thus, these data suggest that immune responses to self-tumor antigens in humans are directed against subdominant epitopes that have relatively low affinities to their restricting MHC molecules, and against which T-cell immune responses are poor in comparison with viral or nontolerized immunodominant epitopes. The challenge that immunotherapists face is to enhance the immunogenicity of these weak antigens and to keep self-reactive T cells activated at the tumor site (15,16).

References

1. Chen W, Anton LC, Bennink JR, et al. Dissecting the multifactorial causes of immunodominance in class I-restricted T cell responses to viruses. *Immunity* 2000;1212:83–93. 83–93. [PubMed: 10661408]
2. Kiedl RM, Rees WA, Hildeman DA, et al. T cells compete for access to antigen-bearing antigen-presenting cells. *J Exp Med* 2000;192:1105–13. [PubMed: 11034600]
3. Grossmann ME, Davila E, Celis E. Avoiding tolerance against prostatic antigens with subdominant peptide epitopes. *J Immunother* 2001;24:237–241.

4. Kawakami Y, Eliyahu S, Delgado CH, et al. Cloning of the gene coding for a shared human melanoma antigen recognized by autologous T cells infiltrating into tumor. *Proc Natl Acad Sci USA* 1994;91:3515–9. [PubMed: 8170938]
5. Rosenberg SA, Yang JC, Schwartzentruber DJ, et al. Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastatic melanoma. *Nat Med* 1998;4:321–7. [PubMed: 9500606]
6. Overwijk WW, Tsung A, Irvine KR, et al. gp100/pmel 17 is a murine tumor rejection antigen: induction of self-reactive, tumoricidal T cells using high-affinity, altered peptide ligand. *J Exp Med* 1998;188:277–86. [PubMed: 9670040]
7. Colella TA, Bullock TN, Russell LB, et al. Self-tolerance to the murine homologue of a tyrosinase-derived melanoma antigen: implications for tumor immunotherapy. *J Exp Med* 2000;191:1221–32. [PubMed: 10748239]
8. Overwijk WW, Lee DS, Surman DR, et al. Vaccination with a recombinant vaccinia virus encoding a “self” antigen induces autoimmune vitiligo and tumor cell destruction in mice: requirement for CD4 (+) T lymphocytes. *Proc Natl Acad Sci USA* 1999;96:2982–7. [PubMed: 10077623]
9. Greenberg NM, DeMayo F, Finegold MJ, et al. Prostate cancer in a transgenic mouse. *Proc Natl Acad Sci USA* 1995;92:3439–43. [PubMed: 7724580]
10. Mylin LM, Bonneau RH, Lippolis JD, et al. Hierarchy among multiple H-2b-restricted cytotoxic T-lymphocyte epitopes within simian virus 40 T antigen. *J Virol* 1995;69:6665–77. [PubMed: 7474076]
11. Schell TD, Knowles BB, Tevethia SS. Sequential loss of cytotoxic T lymphocyte responses to simian virus 40 large T antigen epitopes in T antigen transgenic mice developing osteosarcomas. *Cancer Res* 2000;60:3002–12. [PubMed: 10850449]
12. Newmaster RS, Mylin LM, Fu TM, et al. Role of a subdominant H-2Kd-restricted SV40 tumor antigen cytotoxic T lymphocyte epitope in tumor rejection. *Virology* 1998;244:427–41. [PubMed: 9601511]
13. Cibotti R, Kanellopoulos JM, Cabaniols JP, et al. Tolerance to a self-protein involves its immunodominant but does not involve its subdominant determinants. *Proc Natl Acad Sci USA* 1992;89:416–20. [PubMed: 1370355]
14. Benichou G, Fedoseyeva E, Olson CA, et al. Disruption of the determinant hierarchy on a self-MHC peptide: concomitant tolerance induction to the dominant determinant and priming to the cryptic self-determinant. *Int Immunol* 1994;6:131–8. [PubMed: 7511927]
15. Restifo NP. Building better vaccines: how apoptotic cell death can induce inflammation and activate innate and adaptive immunity. *Curr Opin Immunol* 2000;12:597–603. [PubMed: 11007365]
16. Restifo NP, Rosenberg SA. Developing recombinant and synthetic vaccines for the treatment of melanoma. *Curr Opin Oncol* 1999;11:50–7. [PubMed: 9914879]