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Assumptions of the tumor 'escape' hypothesis

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Abstract

The reasons why cancer cells are not destroyed by the immune system are likely to be similar, in most cases, to the reasons why normal cells are not destroyed by the immune system. Unfortunately for tumor immunologists, these reasons have not yet been fully elucidated. What is known, however, is that the lack of autoimmune destruction of normal tissue after immune activation is a finely regulated, highly orchestrated sequence of events. Viewed in this light, it is interesting to conceptualize the derangement of the tumor genome not merely as an engine that enables cancer cells to dodge immune recognition. The dysregulation characteristic of the transformed genome is also what makes tumor immunity, a specialized form of autoimmunity, possible.

Keywords

immunotherapy; tolerance; escape; CD8+ T cells; CD4+ T cells

Introduction

Every tumor that kills its host is a tumor that has not been eradicated by the immune system. It was hypothesized for years that spontaneous human tumors, failed express antigens recognizable by the immune system. It is now clear that tumor cells express an abundance of 'self' and 'foreign' (i.e. 'mutated-self') antigens. Despite the expression of these antigens, the immune system does not mount immune responses that consistently results in tumor rejection. The purpose of this review is not to summarize or catalogue all of the proposed mechanisms of tumor escape: that has been done more completely by others. [1–3] Instead, our goal here is to call into question assumptions underlying the tumor escape hypothesis and to critically evaluate the methods used to test the validity of proposed mechanisms. The fundamental immune response to both normal and transformed tissue may be characterized more by ignorance, tolerance and suppression than by evasion, escape and counterattack.

The current notion that tumor cells must 'escape' immune recognition is based largely on the idea that neoantigens expressed by tumor cells as a consequence of their genetic instability will be immunogenic. There is little doubt that the tumor contains a large number of mutations, but there is considerable doubt about what the immunological response to these potential immunogens will be. The 'self/non-self' theory of immune recognition teaches that new antigens produced by the tumor should lead to its immune rejection. One estimate puts the number of mutations in a tumor genome at >11 000 per cell. [4] There are two kinds of mutational events that can potentially generate new antigens recognizable by the immune system: point mutations that result in single base pair changes (and potentially single amino acid changes) and translocation events (which can produce long stretches of new protein). Both types of

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genetic changes have been documented to generate TA either as a direct result of the genetic change, or as a result of an aberrant antigen expression, processing or presentation. Base pair mutations have been shown to create new epitopes (e.g. see References 5,6). Chromosomal rearrangements, as evidenced on a gross level in a karyotype, are almost uniformly present early during tumor progression.[7] Chromosomal rearrangements can also result in the generation of new antigens potentially recognizable by the immune system (e.g. see Reference 8).

Mutational events in tumor cells are not the only time when new proteins can be encountered by the host. Organ transplantation can lead to vigorous rejection, but new work using living related donors has shown that organ transplantation can be radically improved. Five-year success rates in excess of 90% are observed in many centers, though patients must generally continue to take immunosuppressive drugs. Success rates for liver transplantation are also soaring. One wonders what the success rates would be if surgical trauma and organ ischemia could be reduced to zero.

Neoantigens also appear to be expressed by cells during events like puberty, pregnancy and senescence. An understanding of why these changes can occur without any apparent evidence of immune disturbance may shed light on our understanding of how tumors can express new antigens without engendering an immune response. The need for any form of tumor escape mechanism assumes that the ‘default’ in the relationship between the host immune system and a tumor is rejection, and that the tumor must escape this rejection. But this assumption may not be correct—the ‘default’ immune response to a tumor may be tolerance.

Can the tumor function immunologically as normal tissue?

The tumor microenvironment, like the microenvironment present in non-transformed tissue, may not favor the activation of immune cells. Thus, many or even most tumors may instead function immunologically as does normal tissue. The development of the still incipient field concerning the study of tumor escape mechanisms has paralleled the now established field of the study of how viruses escape immune recognition and destruction. The molecular mechanisms employed by viruses to evade immune recognition are many and varied. Viruses can interfere with seemingly all aspects of innate and adaptive host immune responses. Indeed, a great deal of immunology can be learned from viruses. [9]

If our understanding of the mechanisms used by tumors to escape immune recognition remains ill-defined by comparison, it is because the relationships between the tumor cells and the host immune system are so poorly understood. The impact of innate and adaptive immunity on viral challenge becomes immediately clear in a variety of genetic and acquired immunodeficiency syndromes. Immunodeficiency and immunosuppression have less of an immediate impact on the host’s susceptibility to tumor induction. In mice, there is evidence that interferon- mediated immunosurveillance exists.[10] In humans, an increased incidence of some kinds of malignancies is observed upon chronic immunosuppression, for example after organ transplantation or as a result of HIV infection. In many cases it is clear that these malignancies are secondary to infection with transforming viruses. The exercise of immunity to viruses is a daily occurrence, an absolute evolutionary necessity. But it remains unclear what role, if any, immunity to tumors has played during evolution or during the induction or growth of most human cancers.

If tumor can function immunologically as normal tissue, is an anti-tumor antigen (TA) immune response a form of autoimmunity? In the case of melanoma, where most progress has been made, the molecular targets of the anti-TA immune response include melanocyte tissue differentiation antigens such as gp100, MART-1/MelanA, tyrosinase and tyrosinase related proteins (TRP)—1/gp75[11] and TRP-2. These non-mutated antigens are involved in the

synthesis of melanin and give both melanocytes and deposits of melanoma tumor their dark pigment.

One consequence of the recognition of normal 'self' antigens may be vitiligo, the patchy and permanent loss of pigment from the skin and hair thought to result from the autoimmune destruction of pigment cells. Vitiligo has been correlated with objective shrinkage of deposits of metastatic melanoma in patients receiving high dose interleukin-2 (IL-2), a cytokine known to activate and expand T lymphocytes. It is not yet known whether targeting 'self' or 'foreign' antigens will be more successful in the immunotherapy of cancer. Some workers have asserted that mutated TA are superior targets for vaccine design because immune cells will not be tolerized to these antigens. However, recent work especially by Hy Levitsky's and Linda Sherman's groups, has shown that even the most immunogenic 'foreign' antigen, such as the hemagglutinin (HA) antigen from the Influenza A virus can be tolerizing when expressed peripherally (i.e. outside the thymus) either in normal cells or in tumor cells.[12–14] Thus, mutated or otherwise 'foreign' antigens may also induce peripheral tolerance when expressed by tumor cells.

Are there T cell precursors against tumor antigens?

The question of whether or not TA exist has been definitively answered and, given that many of these antigens have been identified by molecular cloning using T lymphocytes as probes, it is also clear that there are T cell precursors for these expressed antigens. The principle that T cells were critically important in the immune response was derived originally in mice with methylcholanthrene (MCA)-induced tumors. A large body of work in which T cell subsets were depleted either using antibodies or gene-knockout mice revealed that both CD8+ and CD4+ T cells could play a role in the anti-TA immune response.

Classical studies showed that mice immunized with irradiated MCA-induced sarcoma cells were fully protected against a subsequent challenge with that same tumor, but not with other tumors.[15] This protection was dependent on CD8+ T lymphocytes, whereas CD4+ T lymphocytes often played little if any role. Furthermore, adoptive transfer of pure populations of CD8+ T lymphocytes was shown to mediate tumor regression in mice.

Compared with the comprehensive studies using CD8+ T cells in tumor models, relatively little is known about how CD4+ T cells influence anti-TA immunity. Very early work demonstrated that disseminated murine leukemia could be eradicated by a combination of cyclophosphamide and adoptively transferred cells (now known as CD4+ T cells).[16,17] The most dramatic examples of the power of CD4+ T cells in the immune response to 'self' proteins can be found in murine models of autoimmune diseases such as experimental allergic encephalomyelitis (EAE), systemic lupus erythematosus (SLE) and diabetes. In these models disease can often be transferred to naive mice with purified, 'self' reactive CD4+ splenocytes or specific CD4+ T lymphocyte clones. Antigen-specific CD4+ T lymphocyte clones can also treat tumor through CD8+ T cells specific for the cognate antigen.[18] These studies and others suggest that the full activation of autoreactive CD4+ T cells may be an important immune component that is currently missing from many current clinical cancer vaccine trials.

We now understand in part how CD4+ T lymphocytes help initiate and maintain the anti-TA immune response.[19–21] CD4+ T cells regulate antigen-specific immune responses by regulating the functions of other components of the immune system, including B lymphocytes and CD8+ T lymphocytes. Conversely, under some conditions, CD4+ T cells can be preferentially activated by B cells. In the experimental B16 tumor system, B lymphocytes, under the control of CD4+ T cells, play an important role in inducing both autoimmunity and anti-TA immunity. CD4+ T lymphocytes also appear to attract and activate other non-antigen-specific components of the immune system including eosinophils, macrophages, dendritic cells

and other antigen presenting cells (APC). Nevertheless, tumor cells can grow in the presence of CD4+ T cell precursors specific for antigens expressed by tumor cells.[13] Hence, there is a need to understand more fully the reasons for this lack of tumor recognition.

Suggested guidelines for evaluating evidence for theories of tumor escape

Many theories of immune escape are described that are intuitively appealing, or that have some correlative data in the mouse or human, but for which there is no direct experimental evidence. How does one go about evaluating the actual evidence for each of these theories of immune escape? What kind of data would be particularly convincing?

One example of a convincing hypothetical experiment might be the following: The growth rate or lethality of a tumor is increased when the tumor escape mechanism is conferred upon the tumor. In its most pure form, the wild-type of the tumor used in this experiment is rejected in immunocompetent animals, but can now grow rapidly and lethally in normal animals after acquiring the given escape mechanism. Conversely, the following scenario could be played out for a given tumor escape mechanism that starts with a wild-type tumor that grows rapidly and lethally in an immunocompetent animal. Blocking the 'escape' mechanism should lead to the reduced growth rate, treatment or rejection of that tumor. Note that this later scenario is one that would most commonly be encountered, and also is the scenario that has the greatest therapeutic implication. As for correlative studies in humans, it is difficult or impossible to derive any clear mechanistic understanding unless one has supporting data in animal models.

The molecular bases for proposed tumor escape mechanisms can be separated conceptually into a number of groupings including those mechanisms having to do specifically with the mutability of cancer cells and those shared by many normal cells in the body. The first group includes mechanisms related to the inherent genetic instability of tumor cells (e.g. see, References 22–26) while examples of the second group include the lack of expression of costimulatory molecules (B7-1/CD80, B7-2/CD86 and CD40L), the induction of suppressor cell activity, and the production of immunoinhibitory substances (TGF-_ and IL-10) and other immunoregulatory strategies employed by the host.

It is likely that the development of highly successful immunotherapies will result in the outgrowth of tumors that are not susceptible to the therapeutic intervention. For example, effective antigen specific vaccines may lead to antigen loss variants. However, the current evidence in animal models is sometimes non-existent, often incomplete, and rarely, compelling. There is clearly no consensus concerning the molecular mechanisms used by tumors to 'escape' immune recognition. A few examples:

1. FasL has been proposed as a mediator of the tumor 'counterattack'. We have elucidated the theoretical and technical problems with these experiments elsewhere.[27–30] To summarize, however, all controlled experiments in which FasL is expressed in animal tumor models does not result in escape, but instead results in more rapid rejection (see Reference 29).
2. We and others have proposed the loss of $_2$-microglobulin ($_2$-μ) as a mechanism of immune escape. However, the work by Karre, *et al.* in animal models demonstrated that the loss of $_2$m resulted in exquisite sensitivity to NK cells and tumor elimination, not escape and MHC class I molecules inhibit NK cell killing.[31] Although some human melanoma cells have also been shown to loose $_2$-μ with clinical progression, human $_2$m deficient cells are also susceptible to NK cell-mediated killing.[23,32] Does this evidence point clearly to $_2$m loss as a mechanism of immune escape? The alternative explanation is that $_2$m is lost because of increasing derangement in the transformed genome and a mutation 'hotspot' at the $_2$m locus.[33] Indeed, the

mutability of the _2m locus may have unexplored protective functions. [Note: The same argument can be made about other mechanisms that decrease or eliminate MHC class I expression on the surface such as loss of MHC class I heavy chain and loss, mutation or downregulation of TAP or LMP components].

3. To take another example, like most normal cells in the body, tumor cells generally do not express costimulatory molecules, such as B7-1 (CD80) and B7-2 (CD86). In the absence of costimulation, T cells tend to become anergic. In the non-tumor bearing setting, the lack of B7 molecule expression on normal cells has been hypothesized to protect against autoreactivity. B7-1 and B7-2 are expressed on professional APC and on a variety of other tissues after exposure to inflammatory cytokines.[34] But is this the reason that tumor cells escape immune recognition?

Transfection of tumor cells with both isoforms has been used successfully to trigger their immunemediated rejection of experimental mouse tumors, which have some inherent immunogenicity. [35] Rejection is not observed when B7 molecules are inserted into less immunogenic tumors.[36] Nonimmunogenicity is a category into which most, if not all, human tumors would fall, thus a lack of expression of the CD80 and CD86 costimulatory molecules is unlikely to be a global explanation for immune escape. However, a greater understanding of the interactions of costimulatory molecules with negative regulatory molecules, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) may enable more directed interventions.[37]

Understanding the poor immunogenicity of tumors: Bench to bedside and back again

Despite cancer cells' expression of clearly immunogenic molecules, the host does not always mount an effective immune response to these antigens. A number of groups have conducted experiments in which highly immunogenic foreign antigens, such as the hemagglutinin protein from influenza,[13] the _-galactosidase (_-gal) enzyme from *E. coli*, [38] and the ovalbumin (OVA) protein from the chicken are expressed in tumor cells. [39] The results are fairly uniform: tumors tend to grow progressively, retaining their lethality despite the expression of a foreign and highly immunogenic protein by the tumor cell. The same can be said for self-antigen models. For example, B16 is a spontaneous mouse melanoma model that is lethally transplantable to syngeneic C57BL/6n mice and expresses the mouse homologs of major tissue differentiation antigens such as gp100, MART-1, TRP-1 and TRP-2.[40–42]

In the mouse models cited above, many of the proposed causes for tumor escape can be ruled out by a combination of *in vivo* and *in vitro* testing. For example, experimental tumors can be verified to express _2m, the relevant MHC restriction element and intact antigen processing machinery by simply showing that specific recognition by T cells.

Other factors, such as the production of known immunoinhibitory factors can also be evaluated. Precursor frequency of T cells specific for particular TA can be evaluated using tetramers. Alternatively, T cell precursor frequency can be tightly controlled using T cell receptor transgenic mice.

Mouse experiments in our laboratory and others clearly show that target antigen expressing tumors that have intact antigen processing machinery and that exist in an environment where T cell precursors clearly exist (such as a TCR transgenic mouse) can still grow lethally. Alternative immune mechanisms designated *tolerance* and *ignorance* have been used to explain why the immune system fails to recognize such tumors. Tolerance generally refers to the lack of a destructive immune reaction to a given antigen and is often defined as an acquired unresponsiveness to antigen. In the tumor context, we might distinguish an active state of

tolerance, in which the immune system undergoes a functional and phenotypic change after encounter with antigen, from ignorance, a passive process where immune cells do not have any contact with the antigen that alters their phenotype or function. Although there is undoubtedly some degree of ignorance to TA, there is clear evidence that host T cells can be sensitized to TA (43 and NP Restifo, unpublished results).

In conclusion, it remains unclear what mechanisms are employed by tumor cells to 'escape' immune destruction. Ultimately, the reasons why cancer cells are not destroyed by the immune system may be the same reasons why normal cells are not destroyed by the immune system. Unfortunately, the mechanisms of tolerance have not yet been fully elucidated.

Intriguing explanations for why tumors (and normal tissues) are not destroyed involves suppressor antigen presenting cells expressing markers that include CD11b, Gr-1 and CD31 and suppressor T cells that are CD4+CD25+.[44–47] These cells have clear importance in tumor models as well as in autoimmunity in experimental animals. Our ability to develop new immunotherapies in patients with cancer will depend on our understanding of the fundamental biology underlying the apparently tolerant relationship between immune and transformed cells.

Successful tumor immunotherapies may represent the induction of autoimmunity and the breakdown of the myriad and redundant mechanisms of immune tolerance at the target cell level due in large part to mutations and translocations in the transformed genome. Once tolerance is dysregulated, tumor immunity, a form of autoimmunity, becomes possible. While autoimmune disease is generally a disorder of the immune system, 'autoimmune' destruction of the tumor may be the ultimate result of dysregulation in the tumor cell.

References

1. Ferrone S, Finerty JF, Jaffee EM, Nabel GJ. How much longer will tumor cells fool the immune system? Immunol Today 2000;21:70–72. [PubMed: 10712001]
2. Marincola FM, Jaffee EM, Hicklin DJ, Ferrone S. Escape of human solid tumors from T-cell recognition: molecular mechanisms and functional significance. Adv Immunol 2000;74:181–273. [PubMed: 10605607]
3. Pawelec G, Heinzel S, Kiessling R, Muller L, Ouyang Q, Zeuthen J. Escape mechanisms in tumor immunity: a year 2000 update. Crit Rev Oncog 2000;11:97–133. [PubMed: 11005508]
4. Stoler DL, Chen N, Basik M, Kahlenberg MS, Rodriguez-Bigas MA, Petrelli NJ, Anderson GR. The onset and extent of genomic instability in sporadic colorectal tumor progression. Proc Natl Acad Sci USA 1999;96:15121–15126. [PubMed: 10611348]
5. Dubey P, Hendrickson RC, Meredith SC, Siegel CT, Shabanowitz J, Skipper JC, Engelhard VH, Hunt DF, Schreiber H. The immunodominant antigen of an ultraviolet-induced regressor tumor is generated by a somatic point mutation in the DEAD box helicase p68. J Exp Med 1997;185:695–705. [PubMed: 9034148]
6. Baurain JF, Colau D, van Baren N, Landry C, Martelange V, Vikkula M, Boon T, Coulie PG. High frequency of autologous anti-melanoma CTL directed against an antigen generated by a point mutation in a new helicase gene. J Immunol 2000;164:6057–6066. [PubMed: 10820291]
7. Shih IM, Zhou W, Goodman SN, Lengauer C, Kinzler KW, Vogelstein B. Evidence that genetic instability occurs at an early stage of colorectal tumorigenesis. Cancer Res 2001;61:818–822. [PubMed: 11221861]
8. Wang RF, Wang X, Rosenberg SA. Identification of a novel major histocompatibility complex class II- restricted tumor antigen resulting from a chromosomal rearrangement recognized by CD4(+) T cells. J Exp Med 1999;189:1659–1668. [PubMed: 10330445]
9. Zinkernagel RM. Immunology taught by viruses. Science 1996;271:173–178. [PubMed: 8539616]
10. Kaplan DH, Shankaran V, Dighe AS, Stockert E, Aguet M, Old LJ, Schreiber RD. Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. Proc Natl Acad Sci USA 1998;95:7556–7561. [PubMed: 9636188]

11. Wang RF, Parkhurst MR, Kawakami Y, Robbins PF, Rosenberg SA. Utilization of an alternative open reading frame of a normal gene in generating a novel human cancer antigen. J Exp Med 1996;183:1131–1140. [PubMed: 8642255]
12. Morgan DJ, Kreuwel HT, Fleck S, Levitsky HI, Pardoll DM, Sherman LA. Activation of low avidity CTL specific for a self epitope results in tumor rejection but not autoimmunity. J Immunol 1998;160:643–651. [PubMed: 9551898]
13. Staveley-O'Carroll K, Sotomayor E, Montgomery J, Borrello I, Hwang L, Fein S, Pardoll D, Levitsky H. Induction of antigen-specific T cell anergy: An early event in the course of tumor progression. Proc Natl Acad Sci USA 1998;95:1178–1183. [PubMed: 9448305]
14. Morgan DJ, Kurts C, Kreuwel HT, Holst KL, Heath WR, Sherman LA. Ontogeny of T cell tolerance to 85 *N. P. Restifo et al*. peripherally expressed antigens. Proc Natl Acad Sci USA 1999;96:3854–3858. [PubMed: 10097127]
15. Prehn RT, Main JM. Immunity to methylcholanthreneinduced sarcomas. J Natl Cancer Inst 1957;18:769–774. [PubMed: 13502695]
16. Greenberg PD, Cheever MA, Fefer A. Eradication of disseminated murine leukemia by chemoimmunotherapy with cyclophosphamide and adoptively transferred immune syngeneic Lyt-1 +2- lymphocytes. J Exp Med 1981;154:952–963. [PubMed: 6974221]
17. Greenberg PD, Kern DE, Cheever MA. Therapy of disseminated murine leukemia with cyclophosphamide and immune Lyt-1+,2- T cells. Tumor eradication does not require participation of cytotoxic T cells. J Exp Med 1985;161:1122–1134. [PubMed: 3921652]
18. Surman DR, Dudley ME, Dudley WW, Restifo NP. Cutting edge: CD4+ T cell control of CD8+ T cell reactivity to a model tumor antigen. J Immunol 2000;164:562–565. [PubMed: 10623795]
19. Ossendorp F, Mengede E, Camps M, Filius R, Melief CJ. Specific T helper cell requirement for optimal induction of cytotoxic T lymphocytes against major histocompatibility complex class II negative tumors. J Exp Med 1998;187:693–702. [PubMed: 9480979]
20. Toes RE, Schoenberger SP, van der Voort EI, Offringa R, Melief CJ. CD40-CD40Ligand interactions and their role in cytotoxic T lymphocyte priming and anti-tumor immunity. Semin Immunol 1998;10:443–448. [PubMed: 9826577]
21. Toes RE, Ossendorp F, Offringa R, Melief CJ. CD4 T Cells and their role in antitumor immune responses. J Exp Med 1999;189:753–756. [PubMed: 10049938]
22. D'Urso CM, Wang ZG, Cao Y, Tatake R, Zeff RA, Ferrone S. Lack of HLA class I antigen expression by cultured melanoma cells FO-1 due to a defect in B2m gene expression. J Clin Invest 1991;87:284–292. [PubMed: 1898655]
23. Maio M, Altomonte M, Tatake R, Zeff RA, Ferrone S. Reduction in susceptibility to natural killer cell-mediated lysis of human FO-1 melanoma cells after induction of HLA class I antigen expression by transfection with B2m gene. J Clin Invest 1991;88:282–289. [PubMed: 1905328]
24. Restifo NP, Esquivel F, Kawakami Y, Yewdell JW, Mule JJ, Rosenberg SA, Bennink JR. Identification of human cancers deficient in antigen processing. J Exp Med 1993;177:265–272. [PubMed: 8426105]
25. Restifo NP, Kawakami Y, Marincola F, Shamamian P, Taggarse A, Esquivel F, Rosenberg SA. Molecular mechanisms used by tumors to escape immune recognition: immunogenetherapy and the cell biology of major histocompatibility complex class I. J Immunother 1993;14:182–190.
26. Restifo NP, Marincola FM, Kawakami Y, Taubenberger J, Yannelli JR, Rosenberg SA. Loss of functional beta 2-microglobulin in metastatic melanomas from five patients receiving immunotherapy. J Natl Cancer Inst 1996;88:100–108. [PubMed: 8537970]
27. Chappell DB, Zaks TZ, Rosenberg SA, Restifo NP. Human melanoma cells do not express Fas (Apo-1/CD95) ligand. Cancer Res 1999;59:59–62. [PubMed: 9892185]
28. 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]
29. Restifo NP. Not so Fas: Re-evaluating the mechanisms of immune privilege and tumor escape. Nat Med 2000;6:493–495. [PubMed: 10802692]
30. Restifo NP. Countering the 'counterattack' hypothesis. Nat Med 2001;7:259. [PubMed: 11231598]

31. Kambayashi T, Michaelsson J, Fahlen L, Chambers BJ, Sentman CL, Karre K, Ljunggren HG. Purified MHC class I molecules inhibit activated NK cells in a cell-free system in vitro. Eur J Immunol 2001;31:869–875. [PubMed: 11241292]
32. Porgador A, Mandelboim O, Restifo NP, Strominger JL. Natural killer cell lines kill autologous beta2-microglobulin-deficient melanoma cells: implications for cancer immunotherapy. Proc Natl Acad Sci USA 1997;94:13140–13145. [PubMed: 9371813]
33. Parnes JR, Sizer KC, Seidman JG, Stallings V, Hyman R. A mutational hot-spot within an intron of the mouse beta 2-microglobulin gene. EMBO J 1986;5:103–111. [PubMed: 3514206]
34. Liebowitz DN, Lee KP, June CH. Costimulatory approaches to adoptive immunotherapy. Curr Opin Oncol 1998;10:533–541. [PubMed: 9818232]
35. La Motte RN, Sharpe AH, Bluestone JA, Mokyr MB. Importance of B7-1-expressing host antigen-presenting cells for the eradication of B7-2 transfected P815 tumor cells. J Immunol 1998;161:6552–6558. [PubMed: 9862681]
36. Chen L, McGowan P, Ashe S, Johnston J, Li Y, Hellstrom I, Hellstrom KE. Tumor immunogenicity determines the effect of B7 costimulation on T cell-mediated tumor immunity. J Exp Med 1994;179:523–532. [PubMed: 7507508]
37. Chambers CA, Kuhns MS, Egen JG, Allison JP. Ctla-4-mediated inhibition in regulation of T cell responses: mechanisms and manipulation in tumor immunotherapy. Annu Rev Immunol 2001;19:565–594. [PubMed: 11244047]
38. Wang M, Bronte V, Chen PW, Gritz L, Panicali D, Rosenberg SA, Restifo NP. Active immunotherapy of cancer with a nonreplicating recombinant fowlpox virus encoding a model tumor-associated antigen. J Immunol 1995;154:4685–4692. [PubMed: 7722321]
39. McCabe BJ, Irvine KR, Nishimura MI, Yang JC, Spiess PJ, Shulman EP, Rosenberg SA, Restifo NP. Minimal determinant expressed by a recombinant vaccinia virus elicits therapeutic antitumor cytolytic T lymphocyte responses. Cancer Res 1995;55:1741–1747. [PubMed: 7536130]
40. Zhai Y, Yang JC, Spiess P, Nishimura MI, Overwijk WW, Roberts B, Restifo NP, Rosenberg SA. Cloning and characterization of the genes encoding the murine homologues of the human melanoma antigens MART1 and gp100. J Immunother 1997;20:15–25. [PubMed: 9101410]
41. Overwijk WW, Tsung A, Irvine KR, Parkhurst MR, Goletz TJ, Tsung K, Carroll MW, Liu C, Moss B, Rosenberg SA, Restifo NP. 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;188:277–286. [PubMed: 9670040]
42. Overwijk WW, Lee DS, Surman DR, Irvine KR, Touloukian CE, Chan CC, Carroll MW, Moss B, Rosenberg SA, Restifo NP. 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;96:2982–2987. [PubMed: 10077623]
43. Marincola FM, Rivoltini L, Salgaller ML, Player M, Rosenberg SA. Differential anti-MART-1/MelanA CTL activity in peripheral blood of HLA- A2 melanoma patients in comparison to healthy donors: evidence of in vivo priming by tumor cells. J Immunother 1996;19:265–277.
44. Bronte V, Wang M, Overwijk WW, Surman DR, Pericle F, Rosenberg SA, Restifo NP. Apoptotic death of CD8+ T lymphocytes after immunization: induction of a suppressive population of Mac-1 +/Gr-1+ cells. J Immunol 1998;161:5313–5320. [PubMed: 9820504]
45. Bronte V, Chappell DB, Apolloni E, Cabrelle A, Wang M, Hwu P, Restifo NP. Unopposed production of granulocyte-macrophage colony-stimulating factor by tumors inhibits CD8+ T cell responses by dysregulating antigenpresenting cell maturation. J Immunol 1999;162:5728–5737. [PubMed: 10229805]
46. Shevach EM. Regulatory T cells in autoimmmunity. Annu Rev Immunol 2000;18:423–449. [PubMed: 10837065]
47. Bronte V, Apolloni E, Cabrelle A, Ronca R, Serafini P, Zamboni P, Restifo NP, Zanovello P. Identification of a CD11b(+)/Gr-1(+)/CD31(+) myeloid progenitor capable of activating or suppressing CD8(+) T cells. Blood 2000;96:3838–3846. [PubMed: 11090068]