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Sadia Ilyas and James C. Yang

Cancer immunotherapy is a rapidly evolving field that exploits T cell responses to tumor-associated Ags to induce tumor rejection. Molecular identification of tumor rejection Ags has helped define several classes of Ags, including tissue differentiation and tumor germline Ags. The ability to genetically engineer Ag-specific receptors into T cells provides an opportunity to translate these findings into therapies. New immunotherapy agents, notably checkpoint inhibitors, have demonstrated unprecedented efficacy in certain cancers. However, the nature of the Ags driving those beneficial immune responses remains unclear. New evidence suggests that tumors express immunogenic, tumor-specific epitopes generated from the same mutations that drive cancer development. Correlations between cancer types responding to immunotherapies and the frequency of somatic mutations may clarify what drives natural anti-tumor immune responses. This fusion of tumor immunology and genetics is leading to new ways to target this class of ideal tumor-specific Ags and could allow the application of immunotherapy to many cancers. The Journal of Immunology, 2015, 195: 5117–5122.

Adoptive T cell transfer can mediate in vivo tumor regression as demonstrated by murine tumor models and clinical responses in trials using autologous tumor-infiltrating lymphocytes (TILs) derived from human melanomas (1). Further work has shown that the native T cell response in TILs can recognize a variety of tumor-associated Ags (TAAAs) expressed in the context of MHC. However, difficulties in finding reactive T cell populations for transfer for most other cancer types prompted studies to understand the molecular nature of the Ags recognized by clinically effective TILs. In parallel with these studies, highly efficient methods for genetically modifying human T cells have been developed that have allowed the transduction of tumor-reactive TCRs into lymphocytes for use in clinical trials. This review will also summarize the development of methods for identifying TAAs in the context of T cell immunotherapy and present the prominent findings that have shaped our understanding of T cell–based immunological tumor rejection and pointed the way to new treatment approaches in cellular immunotherapy.

The molecular identification of human TAAs began with the demonstration of tumor-reactive T cells in cancer patients. These could be acquired either from PBLs (stimulated in vitro) (2) or from culturing TILs resident in many melanomas (3). The major factors that determine whether an Ag is a good target are 1) tumor specificity, 2) immunogenicity (ability to generate a T cell response, often measured by tumor recognition, cytokine release, and/or cytolysis), and 3) prevalence and level of expression on tumor cells. There are several strategies that can be employed to identify the Ags mediating T cell recognition of tumor, and selecting one approach versus another can lead to finding very different types of Ags.

Background

The earliest efforts to molecularly define the precise Ags on tumors responsible for T cell recognition were based on the seminal work by Boon and colleagues (4). First working with murine tumors and then with human melanoma, they showed that genes encoding Ags could be identified by screening tumor DNA libraries by transfecting them into cell lines that expressed the proper MHC allele for presentation, but were not recognized. Then by adding the tumor-reactive T cell clone from peripheral blood, the gene conferring recognition could be identified when it triggered TNF release from the T cells. Although very labor intensive, this method was the initial way that a large number of such Ags were discovered by multiple investigators. It required starting with a tumor-reactive T cell, so most such Ags were associated with human melanoma. The observation that TILs from melanoma, when expanded in vitro with IL-2, frequently displayed autologous tumor recognition made TIL a ready source of T cells to be used in Ag cloning. Additionally, that human melanomas could frequently be established as stable tumor lines in vitro (unlike other common human epithelial cancers) facilitated the demonstration that T cells could indeed be tumor reactive. Van der Bruggen et al. (5) were the first to identify MAGE-1, a cancer germline Ag, as a melanoma-associated Ag recognized by T cells. Tumor germline Ags are characterized by their expression in the testis and on tumors. Epitopes from these Ags are not recognized in the testis, as those cells do not express class I MHC, thereby making them attractive targets for T cell immunotherapy (Table I). This was then followed with the discoveries that a series of proteins associated with pigment production in melanomas and melanocytes were...
frequently targets for T cells. This latter class of Ags, often referred to as tissue differentiation Ags (normal proteins expressed as a consequence of a specific function of the target tissue), constituted most TAAs initially discovered. This was because in melanomas and melanocytes, they were very highly expressed and therefore were overrepresented in cDNA libraries from these tissues. Additionally, to avoid the burdensome task of making many cDNA libraries, when a tumor was cross-recognized by other allogeneic T cells (via a common MHC allele), its cDNA library was often screened rather than make a new cDNA library from each patient’s tumor. Kawakami et al. (6) have shown that Ags can be found by screening cDNA libraries from allogeneic tumors. With the development of techniques for genetically engineering new T cell specificities into PBLs to target the tissue differentiation Ags, it was quickly realized that even tiny amounts of these Ags expressed by important normal tissues could cause unacceptable toxicities (Table I) (7). The melanoma/melanocyte family of Ags mediated severe skin rash and depigmentation as well as eye and ear inflammation (due to normal melanocytes at these locations), whereas carcioembryonic Ag targeting led to life-threatening colitis (7, 8). Thus, even though antitumor activity was achieved, it was at a prohibitive cost. Subsequently, targeting this family of ubiquitous Ags has lost much of its initial appeal.

Mass spectrometry is another tool that several groups have used to successfully identify epitopes of tumor Ags that may be recognized by CTLs. Slingluff and colleagues (9) demonstrated that tandem mass spectrometry with chromatography separation could be used to identify and sequence an MHC-bound peptide on a tumor line (YLEPGPVTA, gp100280–288) that was recognized by several CTL lines. Utilizing this approach, they also identified several predominant epitopes from MART-1 and gp100 (10). Krüger et al. (11) reported that they were able to identify many novel tumor Ags associated with renal cell carcinoma using peptide elution coupled with mass spectrometry.

In parallel with the use of expression cloning to identify tumor Ags that triggered T cell responses, there was an effort to find TAAs recognized by B cells (12). NY-ESO-1, a tumor germline Ag, was identified using this approach (13). Total RNA was extracted from cell lines and benign and malignant tissues. A cDNA library was constructed from the tumor of a patient with esophageal squamous cell carcinoma. This library was expressed in *Escherichia coli* lysate and then screened for Ig binding from the patient’s autologous serum. The reactive clones were then found to be from eight different genes, designated NY-ESO-1–8. Of these, NY-ESO-1 appeared to only be expressed in the testis and the tumor mRNA, and not on normal tissue, by RT-PCR. NY-ESO-1 has been reported to be expressed by ∼80% of synovial cell sarcomas as well as 10–50% of metastatic melanomas and breast, ovarian, and lung cancers (14–16). The presence of a high-affinity IgG serum response implies that there are at least CD4+ T cell responses in these patients, and both MHC class I and class II responses were subsequently delineated and cloned. A clinical trial was conducted using cultured autologous T lymphocytes transduced with a retrovirus to express a high-affinity anti–NY-ESO-1 TCR in patients with tumors expressing NY-ESO-1 (17). Eleven of 18 treated patients with synovial cell sarcoma achieved objective responses with one sustained complete response. Eleven of 20 patients with melanoma had objective clinical responses; three were complete responses ongoing at ∼40 mo.

Other tumor germline Ags have also been identified and targeted in a similar fashion. After Boon and colleagues (5) identified the MAGE-A1 gene in 1991, >25 members have been identified in the MAGE family. MAGE-A is a multigene family that has 12 homologous genes (18). MAGE-A3 is one of the more frequently expressed TAAs in a variety of tumors, including melanoma (19). A high-avidity HLA-A*0201–restricted TCR against MAGE-A3 was generated by immunizing HLA-A2 transgenic mice with the MAGE-A3 peptide, aa 112–120 (KVAELVHFL). This murine TCR, which readily

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**Table I. Targeting of TAAs in T cell immunotherapy**

<table>
<thead>
<tr>
<th>Class</th>
<th>Advantages</th>
<th>Concerns</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue differentiation Ags</td>
<td>Shared Ags</td>
<td>Expression on normal tissues Potential for on-target, off-tumor toxicity</td>
<td>MART-1 gp100 CEA CD19</td>
</tr>
<tr>
<td>Tumor germline (“tumor/testis”) Ags</td>
<td>Off-the-shelf treatments can be developed</td>
<td>Potential for on-target, off-tumor toxicity</td>
<td>NY-ESO-1 MAGE-A3</td>
</tr>
<tr>
<td>Normal proteins overexpressed by cancer cells</td>
<td>Off-the-shelf treatments can be developed</td>
<td>On-target, off-tumor toxicity</td>
<td>hTERT EGFR Mesothelin</td>
</tr>
<tr>
<td>Viral proteins a</td>
<td>Off-the-shelf treatments can be developed</td>
<td>Low frequency of virus-associated cancers</td>
<td>HPV EBV MCC</td>
</tr>
<tr>
<td>Tumor-specific mutated Ags</td>
<td>Tumor specific, thus minimal risk of on-target, off-tumor toxicity</td>
<td>Currently requires surgical resection for next-generation sequencing</td>
<td>Mum-1 β-Catenin CDK4 ERBB2IP</td>
</tr>
<tr>
<td></td>
<td>Shared driver/hot-spot mutations can potentially be targeted</td>
<td>Most immunogenic mutations identified so far are patient specific</td>
<td></td>
</tr>
</tbody>
</table>

*Not included in this review.

CEA, carcinoembryonic Ag; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; hTERT, human telomerase reverse transcriptase; MCC, Merkel cell carcinoma.
triggers human T cell activation through association with human CD3, was then used in a clinical trial to treat HLA-A*0201 patients with metastatic cancer that expressed MAGE-A3 (7). Nine patients were treated with a preparative chemotherapy regimen, infusion of anti–MAGE-A3 TCR-modified PBLs, followed by high-dose IL-2. Of these nine patients, five had objective clinical regression of their cancer. However, three patients experienced severe neurologic toxicities. Further investigation showed that the anti–MAGE-A3 TCR cross-recognized the homologous epitope on MAGE-A12, also presented by HLA-A2. Further study showed that although MAGE-A3 could not be found in the human brain, MAGE-A12 is expressed by a subset of neurons in the human brain. In summary, although the germline tumor family of Ags remains one class of TAAs to target with genetically engineered T cells, their range of expression on normal tissues must be assessed for each candidate Ag and, as with all normal-sequence self-proteins, there is the potential for significant toxicities.

**Targeting normal proteins overexpressed by cancers.** A third class of normal self-proteins that have been targeted by T cell therapies are proteins that are minimally expressed by healthy, normal tissues, but are constitutively over expressed by tumors as part of their malignant phenotype (Table I). These include epidermal growth factor receptor, human telomerase reverse transcriptase, p53, carbonic anhydrase IX, and similar proteins. Because they are major contributors to the malignant phenotype, tumors cannot simply downregulate them and escape immune recognition, and this makes them attractive targets. However, they have normal functions in some tissues either at low levels or under selected conditions. The successful targeting of this class of TAAs relies on the concept of a “window” between tumor and normal tissue expression that might allow a safe and effective immune attack on cancers. Yet it is difficult to measure expression of any protein by every normal tissue under every physiological condition, and protocols targeting these molecules have demonstrated the potential hazards. This class of Ags has largely been targeted using novel chimeric receptors. Chimeric Ag receptors (CARs) are fusion proteins that incorporate Ab-derived Ag-binding regions and intracellular T cell activation domains. Because CARs recognize intact cell-surface proteins, CARs are not HLA restricted and can be used to treat patients without regard to HLA haplotypes. CARs have shown good clinical activity when used to target CD19, a target that is only expressed on normal and malignant B cells. Treatment with a variety of anti–CD19 CARs has shown a high rate of tumor regression, including complete regressions in chemorefractory patients with B cell lymphomas and leukemias (20–22). In this case, the normal tissue expressing the Ag (i.e., the B cell) is not essential to survival, as patients can receive Ig and can be treated for infections.

This CAR approach was also used to target carbonic anhydrase IX, which is frequently overexpressed on clear cell renal cell carcinoma. A single-chain chimeric Ag receptor was constructed and then transduced into PBLs using a retroviral vector (23). Three patients were initially treated with sequential dosing of this cell therapy. All three patients developed hepatic toxicity evidenced by transaminisits and hyperbilirubinemia after four to five infusions, which resulted in cessation of the treatment. To further understand the liver toxicity associated with these cells, a liver biopsy from the first patient showed cholangitis with T cell infiltration around the bile ducts. Carbonic anhydrase IX was found to be expressed on bile duct epithelial cells (24). This represents another example of limiting “on-target, off-tumor” toxicity from targeting Ags that are minimally expressed in normal tissues. In another tragic example, a CAR targeting ERBB2 (HER-2/neu, derived from trastuzumab) caused fatal lung injury, thought to be triggered by low HER-2/neu expression in the lungs (25).

**Identifying and targeting tumor-specific mutated proteins.** A fourth class of TAAs that can induce an immune response are mutated proteins encoded by genes specifically mutated in tumors (Table I). These can be so-called “driver” mutations driving the malignant process or “bystander” mutations arising at random from either carcinogenic exposure or tumor genetic instability. Although driver mutations are much more attractive as targets, tumor cells can be effectively killed by targeting any mutation, regardless of its oncologic significance. The first such naturally occurring T cell responses to tumor-associated mutated epitopes were described 20 y ago.

Coulie et al. (26) first described in 1985 a tumor-specific mutation in MUM-1 that was recognized by CTLs generated by a mixed autologous lymphocyte/melanoma culture. The mutation, which substituted isoleucine for the native serine residue at a TCR-contact residue in the epitope, actually occurred just beyond the end of exon 2 in an intronic region, with the Ag being translated from an incompletely spliced RNA message. Other mutated gene products provoking T cell responses have been identified, including a CDK4 gene in a melanoma that resulted in a change from an arginine to a cysteine at amino acid 24 (27). This mutation created an epitope with an HLA-A2.1 binding motif not present in the native protein and allowed recognition by autologous CTLs. Robbins et al. (28) found a mutated β-catenin gene that encoded for a melanoma tumor-specific Ag. Screening the autologous tumor cDNA library identified a cDNA clone encoding β-catenin, with a single point mutation changing a serine to a phenylalanine at a TCR contact residue within an HLA-A2.1-binding 9-mer peptide. The patient’s normal tissue did not express this Ag, and the T cell did not recognize wild-type β-catenin. Twelve allogeneic melanoma samples were also tested and this mutation was not identified, suggesting that this immunogenic mutation was both patient- and tumor-specific. The difficulties in identifying such patient-specific reagents and translating them into therapy for each patient were daunting at the time, and attention turned to shared, nonmutated tumor target Ags as described above. However, as presciently noted by Coulie et al. (26) in their 1985 paper, “antigens resulting from point mutations ought to be absolutely specific for the tumor, and technical progress may make the identification of such antigens so easy that treatment of patients bearing tumors with such individually specific tumor antigens will become feasible.”

Tumor-specific mutated proteins represent the ideal Ags for cellular immunotherapy because they are not only highly tumor specific but could be very immunogenic because they are seen as “foreign” (i.e., not subjected to negative thymic selection, such as normal self-epitopes). Advances in next-generation DNA sequencing have accelerated studies on the immune response to this class of TAAs (29). Recently, melanoma TILs that recognized their autologous tumor with a known HLA restriction were examined for the prevalence of
T cell reactivity to mutated epitopes. Whole exomic sequencing of tumor and normal DNA was used to identify nonsynonymous tumor-specific mutations. Then, for every mutated protein, every possible 9 or 10 amino acid epitopes that could contain the variant amino acid (19 candidate epitopes for each point mutation) were vetted for potential binding to the presenting HLA allele using binding prediction algorithms. All potential epitopes were then ranked in order of predicted HLA affinity and only the top 25–40 were synthesized. T cell recognition was assessed against these top binders by pulsing them onto HLA-appropriate APCs and adding the tumor-reactive TILs. In all three of the melanoma TILs initially examined, anti–mutation reactivity was found against this highly selected set of candidate-mutated epitopes (31). This provided a possible explanation for why successful melanoma TIL therapy did not induce any apparent autoimmunity and could work in some patients, despite not finding reactivity against the usual array of self-antigens. In total, seven mutated epitopes in three patients were shown to be T cell targets for three TIL infusion products. Melanoma proved to be the most highly mutated human cancer type, presumably due to UV mutagenesis (32).

A parallel discovery of T cells recognizing a mutated melanoma Ag in a patient with tumor regression in response to CTLA4 blockade has also been reported (33). Using whole exomic sequencing and HLA-binding algorithms, T cell responses against two patient-specific mutant epitopes were found in this patient. Tetramer analysis of peripheral blood samples from pretreatment and during treatment showed that after 5 wk of ipilimumab, the dominant T cell response against an epitope encoded by mutated ATR (with a change that after 5 wk of ipilimumab, the dominant T cell response against this highly selected set of candidate-mutated epitopes was still detectable (31). This provided a possible explanation for why successful melanoma TIL therapy did not induce any apparent autoimmunity and could work in some patients, despite not finding reactivity against the usual array of self-antigens. In total, seven mutated epitopes in three patients were shown to be T cell targets for three TIL infusion products. Melanoma proved to be the most highly mutated human cancer type, presumably due to UV mutagenesis (32).

In summary, new evidence has suggested that cancers responsive to checkpoint therapy (41). However, one exception seems to be the high rates of response of clear cell renal carcinoma to IL-2 (42), anti-CTLA4 (43), or anti–PD-1 (44) despite a low frequency of tumor-specific mutations. Overall, these findings have reinvigorated cancer vaccine efforts by incorporating tumor DNA sequencing into the selection of target epitopes (45).

Recently, a new method has been developed to identify immunogenic tumor-associated mutations uses minigenes to display mutated epitopes to T cells. In this approach, whole exomic sequencing of the tumor and normal cell DNA is completed to identify nonsynonymous mutations. The mutated amino acid residues and flanking 12 amino acids on both sides are encoded by a “minigene” of 75 nucleotides. Eight to 15 different minigenes are then concatenated into longer tandem minigene (TMG) constructs. These TMGs are cloned into an expression vector, transcribed as RNA, and electroported into the patient’s own dendritic cells to display the 8–15 candidate epitopes in the context of all of the patient’s MHC loci. T cells (typically TILs) are then added and reactivity is screened for. Using this technique Lu et al. (46) have been able to rediscover T cells in melanoma TILs known to recognize tumor-specific neoantigens as well as discover new mutated Ags not identified by standard expression cloning.

Significantly, this technique can be extended to tumors that were previously thought to be less immunogenic, such as gastrointestinal cancers. In a recent demonstration of the potential of this technology, mutation-specific CD4+ T cells were identified, isolated, and administered to a patient with metastatic cholangiocarcinoma (47). A metastatic lung lesion was excised from this patient and used to generate TILs. Whole exomic sequencing was completed on the tumor as well as PBLs, which identified 26 nonsynonymous tumor-associated mutations. Minigenes encoding all 26 variant amino acids and the 12 flanking amino acids from the normal protein sequence on each side were created for each mutation and assembled into three TMGs. Reactivity of the TILs against these mutations was detected by coculturing the TILs with TMG-transfected autologous APCs and measuring IFN-γ release. Reactivity was identified against one of the tandem minigenes, and further evaluation showed that the TILs recognized a mutated epitope in Erb-B2–interacting protein (ERBB2IP) presented by MHC class II. Prior to these discoveries, the patient had been treated with bulk-expanded TILs without selection. In retrospect, ~25% of this TIL infusion of 40 billion cells was CD4+ T cells reactive with mutant ERBB2IP. The patient had a minor response lasting 7 mo before developing progressive disease. Three lung biopsies confirmed that the ERBB2IP mutation was still present in her relapsing lesions. Subsequently, a TIL product containing 120 billion T cells with 95% of these being the same CD4+ T cell population reactive with mutant ERBB2IP was prepared and transferred. The patient had a much more dramatic partial response by Response Evaluation Criteria in Solid Tumors criteria and 20 mo afterward is showing continued regression following this second treatment.

Conclusions
In summary, new evidence has suggested that cancers responsive to checkpoint inhibitors may be those with an abundance of
potential tumor-specific target Ags generated by a high frequency of mutations. However, most cancers do not seem to respond to these agents, perhaps due to an inadequate repertoire of tumor-reactive T cells. The administration of autologous T cells derived from melanomas has shown that adoptive T cell transfer can be a potent therapeutic modality capable of inducing complete and durable regressions of metastatic disease. Some nonmutated tumor-associated self-antigens have been effectively targeted with autologous lymphocytes gene engineered with TCRs or CARs, but there is a paucity of safe targets for those off-the-shelf reagents. The advent of methods to rapidly identify T cells reactive with tumor-specific mutations may allow selection or selective expansion of native T cells for administration to change the repertoire of available tumor-reactive T cells. This latter possibility could open the door to safe and effective cellular-based immunotherapies for most human tumors. Adoptive therapy protocols are now under way to test this possibility by identifying and administering mutation-reactive T cells to a wide variety of patients with advanced cancer. Lastly, it is likely that the addition of reagents targeting the immunosuppressive tumor microenvironment could greatly augment outcomes from adoptive T cell therapy, and these combination regimens will be actively investigated in the near future.

Disclosures

The authors have no financial conflicts of interest.

References

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