COMMENTARY

Harnessing shared antigens and T-cell receptors in cancer: Opportunities and challenges

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Blockade of inhibitory immune checkpoints (ICPs) has led to impressive clinical regressions in some patients with tumors like lung cancer or melanoma, which often carry a high mutational load (1). Somatic mutations expressed by tumor cells can provide a rich source of neoantigens, and it has been suggested that T cells against these antigens may be targets of ICP blockade (2, 3). Because the targets of somatic mutations typically differ in individual tumors, neoantigen-specific T cells exhibit little shared reactivity. However, mutational loads in human cancers vary greatly, and several solid tumors (e.g., hormone receptor-positive breast cancer, ovarian cancer, colon cancer), as well as hematological or pediatric tumors, often carry a much lower mutational burden (4). Interestingly, even in tumor types that typically do not express high mutational burden, the degree of T-cell infiltration predicts improved survival (5). There is an unmet need to understand and harness the properties of T cells infiltrating such tumors better. In PNAS, Munson et al. (6) identify several shared T-cell receptors in T cells infiltrating HLA $A2^+$ human breast cancers. These findings may set the stage for novel approaches to harness these T cells for therapy or prevention.

Most of the tumor-infiltrating T lymphocytes (TILs) express αβ T-cell receptor (TCR), with each TCR participating in the recognition of specific antigens. Recent advances in high-throughput sequencing are providing novel insights into TCR diversity and clonality of TILs (7). Most of the current studies are based on sequencing isolated single (e.g., TCR-β) chains, although single-cell or computational methods to analyze αβ pairs are emerging (7). Munson et al. (6) adapt an emulsion-based RT-PCR–based approach (8), wherein initial amplification of TCRs from limited numbers of TCRs within a lipid droplet allows identification of dominant TCR α/β partners. Analysis of TCRs from TILs or blood of patients with breast cancer revealed several shared TCR sequences with an enrichment of TCRs from the TRBV7 family. Most of the breast cancers analyzed in this study were hormone receptor-positive and Her2-negative, which typically carry a lower mutational load than triple-negative cancers (9). Because most patients in this study were HLA $A2^+$, the most immediate implication of shared TCR sequences is the possibility of shared antigenic targets recognized by these TCRs. Restricted TCR use is also a feature of emerging families of unconventional T cells that include autoreactive T cells and can recognize nonpeptide ligands (10). The findings of Munson et al. (6), although provocative, should be viewed as preliminary. In addition to the current limitation of small numbers of patients studied thus far, evaluation of TCRs from different regions of the same tumor, different lesions within the same patient, and lesions with different T-cell subsets will further refine the conclusions. Evaluation of functional properties of these T cells is also essential to understand their antitumor potential better.

Major families of shared tumor antigens may be classified based on whether they are restricted to a specific tissue or tumor type (versus multiple tumor types) and whether they represent tumor-associated self- versus altered self- or non–self-antigens (11) (Table 1). The best-studied examples of the former are melanocyte differentiation antigens (e.g., MelanA) studied in the context of melanoma. Increased levels of MelanA-specific T cells could be detected in tumor draining lymph nodes in melanoma (12), similar to the findings described by Munson et al. (6). Epitopes derived from viral oncoproteins in virus-induced malignancies or recurrent oncogenic mutations could, in principle, also be shared across several patients and provide an attractive target for immunotherapy. Tumor-associated alterations in self-proteins/oncogenic drivers (e.g., HER2 in breast cancer, SOX2 in lung cancer) (13, 14) or peptides resulting from tumor-associated alterations in signaling networks (e.g., phosphopeptides) may also serve as antigenic targets shared across several patients (15). A major class of potentially shared antigens is cancer/germ-line (C/G) genes, which are aberrantly expressed on a subset of diverse types of cancer cells (16). Several members of this family have been extensively studied and shown to be immunogenic. C/G antigens, such as MAGE and NY-ESO-1, have been explored both as targets for vaccines and adoptive cellular therapies (17, 18). One potential limitation of

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See companion article on page 8272.

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Table 1. Broad classes of shared antigens in cancer

Type	Example(s)	Ref.
Differentiation antigens	MelanA, gp110, tyrosinase	(12)
Aberrantly expressed tumor-associated antigens	Her2, Muc-1	(13)
C/G antigens	MAGE family, NY-ESO-1	(16)
Stemness antigens	SOX2, OCT4	(19)
Viral oncoproteins	HPV E6	(11)
Recurrent somatic mutations	B-Raf V600E (melanoma)	(11)

targeting C/G antigens is that they are often expressed by only a subset of tumor cells and their functional significance for most cancers is not known. Another distinct and growing class of shared antigens relates to genes implicated in regulating stemness, an essential functional property of cancer (19). For example, T cells against SOX2, an embryonal stem cell gene were recently correlated with reduced risk of progression to myeloma in a prospective trial (20). It is unlikely that the shared TCRs identified by Munson et al. (6) target viral antigens or oncogenic mutations. Identifying the nature of antigens recognized by these TCRs may provide a novel approach for immunotherapy, if these TCRs are found to mediate antitumor effects.

Although most of the current efforts in cancer immunotherapy are directed toward targeting tumor-associated neoantigens (3), discovery of shared TCRs and/or antigens is particularly relevant for tumor types with lower mutational burden. Targeting shared antigens is also logistically simpler, particularly in the setting of cancer prevention. Shared TCRs may, in principle, also be exploited for adoptive cellular therapies (21). Adoptive transfer of TILs isolated from tumor tissue has yielded promising results in human melanoma. However, the ability to expand adequate TILs can be limited based on availability of tumor tissue. The finding by Munson et al. (6) that the tumor-bearing draining lymph nodes are further enriched for tumor-associated shared TCRs suggests the possibility that, in addition to tumors, tumor-draining lymph nodes may serve as a useful source for these TCRs. Because many of the shared antigens represent self-proteins, one of the potential limitations of TCRs against these antigens is the low affinity of these TCRs, which may then translate to reduced antitumor potential (22). In some instances, potent TCRs against these antigens may cross react with antigens expressed on normal tissues, leading to toxicity (23). Nonetheless, targeting shared TCRs or antigens may emerge as an important strategy for immunoprevention, as well as therapy of human cancers, particularly the subset with low mutational burden.

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