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Cancer Immunology and Immunotherapy

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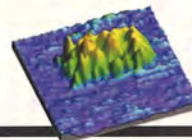
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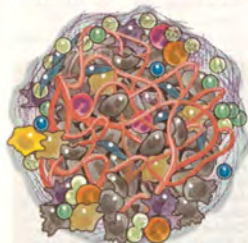
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Cancer immunotherapy harnesses the power of the immune system to kill tumors. These therapies aim to activate and expand T cells, such as those shown in blue, to specifically kill tumors (black). Current approaches

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REVIEWS

Neoantigens in cancer immunotherapy

Ton N. Schumacher^{1*} and Robert D. Schreiber^{2*}

The clinical relevance of T cells in the control of a diverse set of human cancers is now beyond doubt. However, the nature of the antigens that allow the immune system to distinguish cancer cells from noncancer cells has long remained obscure. Recent technological innovations have made it possible to dissect the immune response to patient-specific neoantigens that arise as a consequence of tumor-specific mutations, and emerging data suggest that recognition of such neoantigens is a major factor in the activity of clinical immunotherapies. These observations indicate that neoantigen load may form a biomarker in cancer immunotherapy and provide an incentive for the development of novel therapeutic approaches that selectively enhance T cell reactivity against this class of antigens.

Immunotherapies that boost the ability of endogenous T cells to destroy cancer cells have demonstrated therapeutic efficacy in a variety of human malignancies. Until recently, evidence that the endogenous T cell compartment could help control tumor growth was in large part restricted to preclinical mouse tumor models and to human melanoma. Specifically, mice lacking an intact immune system were shown to be more susceptible to carcinogen-induced and spontaneous cancers compared with their immunocompetent counterparts (1). With respect to human studies, the effects of the T cell cytokine interleukin-2 in a small subset of melanoma patients provided early clinical evidence of the potential of immunotherapy in this disease. In 2010, the field was revitalized by a landmark randomized clinical trial that demonstrated that treatment with ipilimumab, an antibody that targets the T cell checkpoint protein CTLA-4, improved overall survival of patients with metastatic melanoma (2). As a direct test of the tumoricidal potential of the endogenous T cell compartment, work by Rosenberg and colleagues demonstrated that infusion of autologous ex vivo expanded tumor-infiltrating lymphocytes can induce objective clinical responses in metastatic melanoma (3), and at least part of this clinical activity is due to cytotoxic T cells (4). Importantly, recent studies demonstrate that T cell-based immunotherapies are also effective in a range of other human malignancies. In particular, early-phase trials of antibodies that interfere with the T cell checkpoint molecule PD-1 have shown clinical activity in tumor types as diverse as melanoma, lung cancer, bladder cancer, stomach cancer, renal cell cancer, head and neck cancer, and Hodgkin's lymphoma (5). Based on the relationship between

pretherapy CD8+ T cell infiltrates and response to PD-1 blockade in melanoma, cytotoxic T cell activity also appears to play a central role in this form of cancer immunotherapy (6).

An implicit conclusion from these clinical data is that in a substantial fraction of patients, the endogenous T cell compartment is able to recognize peptide epitopes that are displayed on major histocompatibility complexes (MHCs) on the surface of the malignant cells. On theoretical grounds, such cancer rejection epitopes may be derived from two classes of antigens. A first class of potential cancer rejection antigens is formed by nonmutated proteins to which T cell tolerance is incomplete—for instance, because of their restricted tissue expression pattern. A second class of potential cancer rejection antigens is formed by peptides that are entirely absent from the normal human genome, so-called neoantigens. For the large group of human tumors without a viral etiology, such neo-epitopes are solely created by tumor-specific DNA alterations that result in the formation of novel protein sequences. For virus-associated tumors, such as cervical cancer and a subset of head and neck cancers, epitopes derived from viral open reading frames also contribute to the pool of neoantigens.

As compared with nonmutated self-antigens, neoantigens have been postulated to be of particular relevance to tumor control, as the quality of the T cell pool that is available for these antigens is not affected by central T cell tolerance (7). Although a number of heroic studies provided early evidence for the immunogenicity of mutation-derived neoantigens [reviewed in (8)], technology to systemically analyze T cell reactivity against these antigens only became available recently. Here, we review our emerging understanding of the role of patient-specific neoantigens in current cancer immunotherapies and the implications of these data for the development of next-generation immunotherapies.

Exome-guided neoantigen identification: Process considerations

A large fraction of the mutations in human tumors is not shared between patients at

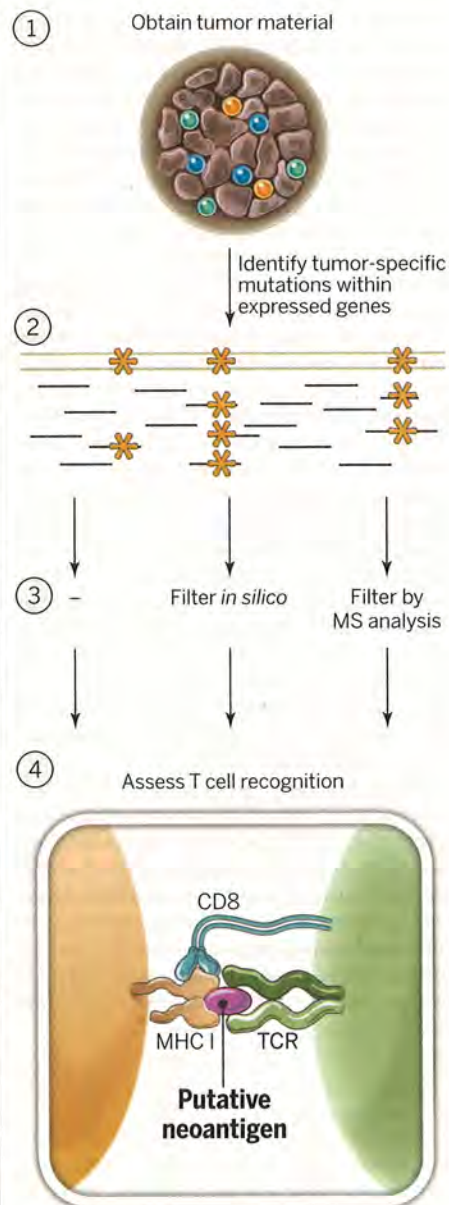


Fig. 1. Cancer exome-based identification of neoantigens. Tumor material is analyzed for nonsynonymous somatic mutations. When available, RNA sequencing data are used to focus on mutations in expressed genes. Peptide stretches containing any of the identified nonsynonymous mutations are generated in silico and are either left unfiltered (16, 17), filtered through the use of prediction algorithms [e.g., (10–13)], or used to identify MHC-associated neoantigens in mass spectrometry data (15, 20). Modeling of the effect of mutations on the resulting peptide-MHC complex may be used as an additional filter (20). Resulting epitope sets are used to identify physiologically occurring neoantigen-specific T cell responses by MHC multimer-based screens (13, 22) or functional assays [e.g., (11, 12)], within both CD8+ [e.g., (11–13, 19, 39)] and CD4+ (16, 18) T cell populations. Alternatively, T cell induction strategies are used to validate predicted neoantigens [e.g., (10, 20)].

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meaningful frequencies and may therefore be considered patient-specific. Because of this, technologies to interrogate T cell reactivity against putative mutation-derived neoantigens need to be based on the genome of an individual tumor. With the development of deep-sequencing technologies, it has become feasible to identify the mutations present within the protein-encoding part of the genome (the exome) of an individual tumor with relative ease and thereby predict potential neoantigens (9). Two studies in mouse models provided the first direct evidence that such a cancer exome-based approach can be used to identify neoantigens that can be recognized by T cells (10, 11). In brief, for all mutations that resulted in the formation of novel protein sequence, potential MHC binding peptides were predicted, and the resulting set of potential neoantigens was used to query T cell reactivity. Subsequent studies have demonstrated that cancer exome-based analyses can also be exploited in a clinical setting, to dissect T cell reactivity in patients who are treated by either tumor-infiltrating lymphocyte (TIL) cell therapy or checkpoint blockade (12, 13). Furthermore, following this early work, the identification of neoantigens on the basis of cancer exome data has been documented in a variety of experimental model systems and human malignancies (10–22).

The technological pipeline used to identify neoantigens in these different studies has varied substantially, and further optimization is likely possible (Fig. 1). Accepting the limitations of probing the mutational profile of a tumor in a single biopsy (23), the genetic analysis of the tumor itself can be considered a robust process. Specifically, based on the analysis of neoantigens previously identified by other means, the false-negative rate of cancer

exome sequencing is low—i.e., the vast majority of neoantigens occur within exonic sequence for which coverage is sufficient (24). At the same time, it is apparent from unbiased screening efforts—in which the entire collection of identified mutations was used to query T cell reactivity—that the vast majority of mutations within expressed genes do not lead to the formation of neoantigens that are recognized by autologous T cells (16, 17). Because of this, a robust pipeline that can be used for the filtering of cancer exome data is essential, in particular for tumors with high mutational loads.

How can such filtering be performed? With the set of mutations within expressed genes as a starting point, two additional requirements can be formulated. First, a mutated protein needs to be processed and then presented as a mutant peptide by MHC molecules. Second, T cells need to be present that can recognize this peptide-MHC complex. In two recent preclinical studies, presentation of a handful of predicted neoantigens by MHC molecules was experimentally demonstrated by mass spectrometry (15, 20), and this approach may form a valuable strategy to further optimize MHC presentation algorithms. At the same time, the sensitivity of mass spectrometry is presently still limited, thereby likely resulting in a substantial fraction of false negatives. For this reason, but also because of logistical issues, implementation of this approach in a clinical setting is unlikely to happen soon. Lacking direct evidence for MHC presentation, as can be provided by mass spectrometry, presentation of neoantigens by MHC class I molecules may be predicted using previously established algorithms that analyze aspects such as the likelihood of proteasomal processing, transport into the endoplasmic reticulum, and affinity for the relevant MHC class I alleles. In addition,

gene expression levels (or perhaps preferably protein translation levels) may potentially also be used to help predict epitope abundance (25).

Although most neoantigen identification studies have successfully used criteria for epitope prediction that are similar to those previously established for the identification of pathogen-derived epitopes [e.g., (12, 13)], Srivastava and colleagues have argued that neoantigens in a transplantable mouse tumor model display very different properties from viral antigens and generally have a very low affinity for MHC class I (14). Although lacking a satisfactory explanation to reconcile these findings, we do note that the vast majority of human neoantigens that have been identified in unbiased screens do display a high predicted MHC binding affinity (24, 26). Likewise, minor histocompatibility antigens, an antigen class that is conceptually similar to neoantigens, are correctly identified by classical MHC binding algorithms (27). Moreover, the mutations that were identified in a recent preclinical study as forming tumor-specific mutant antigens that could induce therapeutic tumor rejection when used in tumor vaccines (15) were not predicted to be significant using the Srivastava approach. Another potential filter step that has been suggested examines whether the mutation is expected to improve MHC binding, rather than solely alter the T cell receptor (TCR)-exposed surface of the mutant peptide. However, with examples of both categories in both mouse models and human data, the added value of such a filter may be relatively modest (11, 15, 20, 26). For MHC class I restricted neoantigens, conceivably the biggest gain in prediction algorithms can be made with respect to identification of the subset of MHC binding peptides that can successfully be recognized

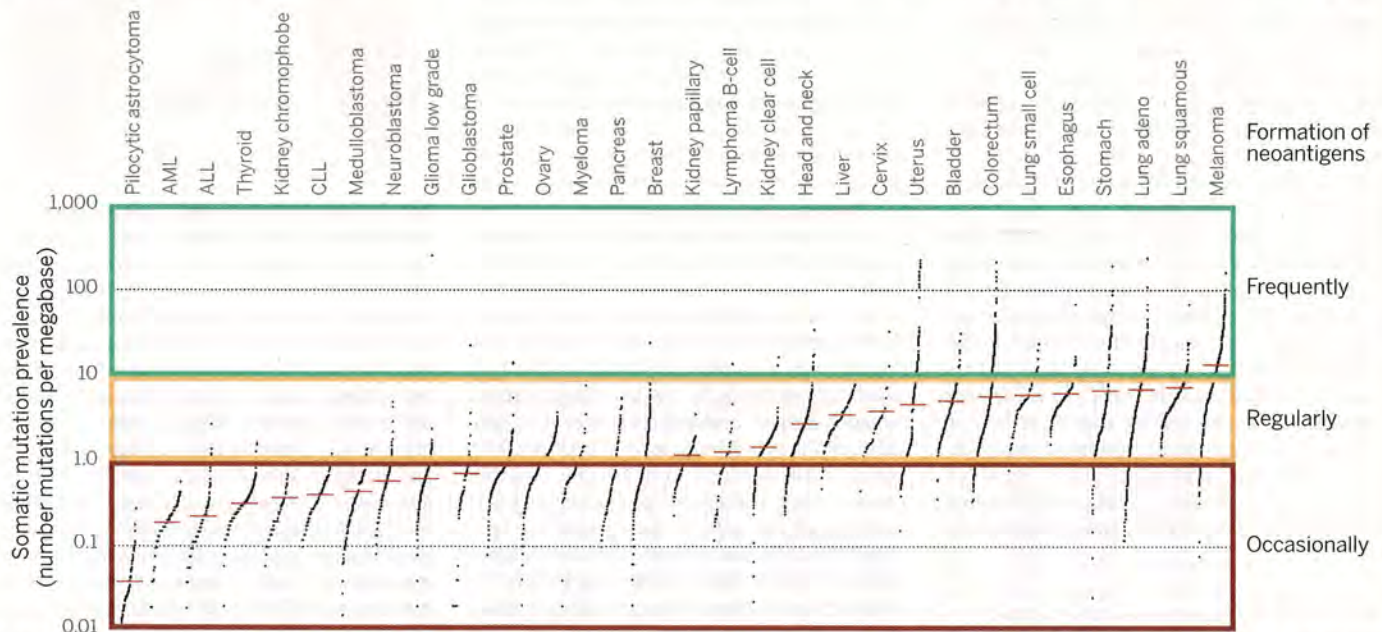


Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (50). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

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