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Human cancer regression antigens

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Cytotoxic T-cells can recognize antigens that are presented on the surface of human tumor cells and thereby mediate cancer regression. Importantly, those immune interventions that have thus far proven most successful in the clinic — i.e. checkpoint blockade and tumor-infiltrating lymphocyte (TIL) therapy — enhance T-cell activity without a deliberate focus on specific antigens. Thus, one major question remains unsolved: what is the nature of the antigens that need to be recognized on human cancer to result in tumor control? Here we discuss the repertoire of human tumor antigens by three main parameters. Firstly, the extent to which these antigens are shared by larger patient groups; secondly, the degree of tumor-restrictive expression; and finally, the likelihood of antigen loss the moment selection pressure is applied. Using this framework, we describe those classes of antigens that can be considered preferable targets in both active and passive T-cell based cancer immunotherapy.

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General introduction

With the EMA and FDA registration of the anti-CTLA4 antibody Ipilimumab for the treatment of metastatic melanoma [1], and with the highly encouraging clinical data of anti-PD1 antibodies in a number of human malignancies [2•], cancer immunotherapy has reached mainstream oncology. Both anti-PD1 and anti-CTLA4 antibodies block inhibitory receptors on T lymphocytes and, based on data in mouse models, an involvement of the $CD8^+$ subset of cytotoxic T cells in their clinical activity is plausible. Direct evidence for the ability of cytotoxic T cells to mediate human cancer regression has been obtained in clinical trials of adoptive T-cell therapy. Specifically, recent trials with genetically engineered T cells rendered reactive towards human MHC class I restricted tumor antigens have shown clear antitumor effects, albeit sometimes accompanied by significant toxicity (see further below). Furthermore, infusion of CD8-enriched TIL has shown clinical activity in patients with metastatic melanoma [3].

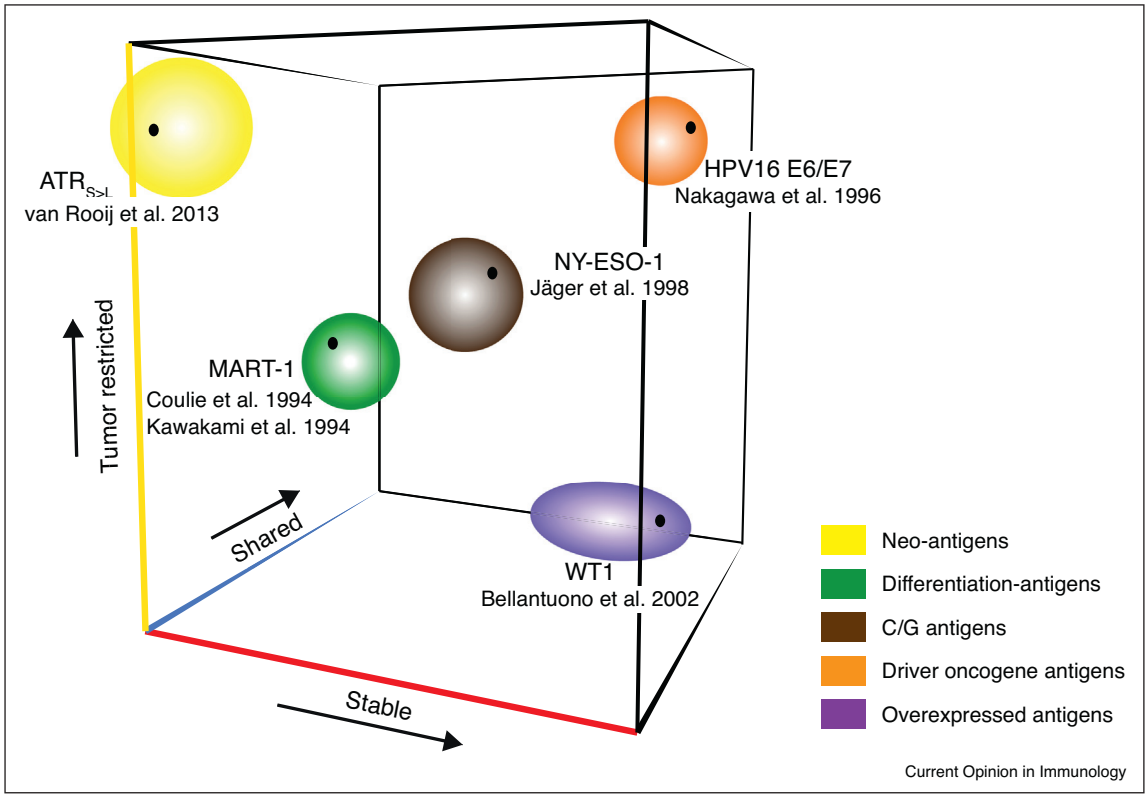
Collectively, these data indicate that at least part of the clinical activity of cancer immunotherapies is due to the recognition of MHC class I-restricted antigens that are expressed by human cancer cells. Interestingly though, the clinically most advanced form of immunotherapy, the blockade of T-cell checkpoint molecules, does not in any way aim to enhance T-cell reactivity towards specific tumor-associated antigens. Rather, T-cell checkpoint blockade 'merely' leads to an increase in the size and/or activity of the T-cell compartment towards a diverse pool of antigens. The observation that such antigen non-specific interventions can lead to cancer regression — and in the case of anti-PD1 with relatively little evidence for autoimmune toxicity — suggests that the T-cell compartment does have a baseline activity towards tumors that is up and above that towards healthy tissues. Nevertheless, should it become feasible to steer T-cell activity towards defined tumor-associated antigens, this would likely be of value.

The first human tumor antigen recognized by autologous T cells, MAGE-A1, was identified by van der Bruggen and coworkers some 20 years ago [4], and in the subsequent decades, literally hundreds of tumor-associated T-cell epitopes have been described [5,6•]. However, as already pointed out in a landmark review by Gilboa in 1999 (well worth re-reading) [7], not all tumor-associated antigens will be equally attractive targets, both with respect to potential to induce cancer regression, with regard to safety, and with regard to the hurdles faced in clinical implementation.

A cube with tumor-associated antigens

The repertoire of human tumor-associated antigens can be evaluated with respect to three main characteristics: firstly, the extent to which antigens are shared between tumors of different patients; secondly, the degree to which antigens are selectively expressed by tumor cells, and finally, the ease with which tumor cells will lose expression of these antigens when immune pressure is applied. In this conceptual framework, each tumor antigen is a 'dot' in a three dimensional space, depending on how it scores with respect to these three characteristics. The 'sweet spot' in this cube is easy to define, antigens that are fully tumor restricted, that are shared between patients and that remain expressed even when T cell pressure is exerted. Alas, the sweet spot is relatively empty and we expect that further antigen discovery

Figure 1



A cube with tumor antigens: 3-D representation of human tumor-associated antigens: Axes represent the likelihood of antigen retention upon T-cell pressure (X), degree of tumor restricted expression (Y), and degree of sharing between patients (Z). Each colored sphere shows a simplified representation of a group of antigens, defined within the text. Within each sphere a representative example is given. Yellow: neo-antigens (ATR$_{S>L}$ [44••]), green: differentiation antigens (MART-1 [9,10]), brown: C/G antigens (NY-ESO-1 [46]), orange: driver oncogene antigens (HPV16 E6 and E7 [47]), purple: overexpressed antigens (WT1 [48]).

efforts will not change this. As such, it is essential to determine which characteristics we consider more or less important when aiming to enhance T-cell reactivity towards defined tumor antigens (Figure 1).

Axis I: From shared antigens to patient-specific antigens

Historically, many research groups have focused on the identification of antigens that are expressed by tumors of large groups of patients, for the simple reason that it offered the promise of off-the-shelf therapeutic vaccines that could be used broadly. Because of this preference and because of experimental bias ('who wants to work on T cells that only recognize one tumor'), a large majority of the epitopes that we currently know are derived from such shared antigens.

Shared antigens may either be restricted to a specific tumor type, or may be expressed by many different tumor types. An example of the latter class is formed by the cancer/germline (C/G) antigens, with the added note that expression is generally only seen in a rather small fraction of tumors of a given type (see for instance [8]). A second group of shared antigens is formed by proteins that display a cell lineage-specific expression pattern, such as the melanocyte differentiation antigens that are expressed in the majority of melanomas (for instance [9,10]). Likewise, antigens derived from viruses that are associated with cellular transformation, such as the HPV antigens in for instance cervical cancer and head and neck cancer, can also be considered 'shared'. Finally, a series of epitopes has been described that is derived from proteins that are overexpressed within tumor cells, such as the WT1 antigen in leukemia [11].

While the shared antigens thus form a relatively heterogeneous group, at the other end of this axis we find only one specific group of antigens, those antigens that arise as a consequence of somatic mutations. Most neo-antigens are due to random mutations that are unrelated to cellular transformation and these antigens can therefore be considered highly patient-specific [12]. It should be noted though that a subgroup of the mutated neo-antigens is to some extent shared between patients. Specifically, those neo-antigens that are formed as a consequence of