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Exploiting TCR Recognition of Shared Hotspot Oncogene-encoded Neoantigens

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SUMMARY

T-cell recognizable p53 hotspot mutations offer opportunities for immunotherapy and immune monitoring. Recognition of p53 mutations by peripheral blood CD8 and CD4 T lymphocytes has been revealed.

See related article by Malekzadeh et al., p. 1267

In this issue of *Clinical Cancer Research*, Malekzadeh and colleagues (1) show that CD8 and CD4 peripheral blood–specific T-cell clones for frequent mutations of TP53 can be enriched and their high-affinity T-cell receptors (TCR) cloned.

Neoantigens resulting from mutations are perceived as the most convenient tumor-rejection antigens because the central and peripheral tolerance mechanisms would not have acted to eliminate from the repertoire high-affinity TCRs recognizing them. Neoantigens can be encoded by genes unrelated to the malignant transformation (passenger mutations) or by proteins whose function is relevant for the malignant phenotype (driver mutations). Mutated oncogenic proteins are the preferred antigens in cancer immunotherapy, because antigen loss or silencing would damage the malignant phenotype of the cells.

Oncogenic mutations can be the result of loss of function or truncation of tumor suppressor genes or gain of function of oncogenes. If one were to be chosen the preferred antigen, it would be a gain-of-function oncogene mutation, due to the fact that loss of its dominant function cannot be endured by a cancer cell that needs to remain a cancer cell. The loss of function of tumor suppressor genes is less critically dependent on sequence but equally interesting and certainly to be preferred over passenger mutations.

P53 is the most commonly mutated antigenic protein across human malignancies and as a result of most of its described mutations it is frequently accumulated in the cytosol of cancer cells because of avoiding MMD2-targeting for proteosomal degradation. It is an absolute requirement for T-cell recognition of these mutations that the antigen attains correct access to the antigen-processing machinery and that at least one of its resulting digested peptide sequences would fit into the antigen-binding groove of an autologous class I or class II HLA antigen-presenting allelic product. A TCR in the repertoire interacting with the resulting HLA–peptide complex with sufficient avidity is necessary for a T-cell immune response to occur. Previous studies had found that tumor-infiltrating lymphocytes recognizing p53 mutations could be found reacting to their cognate antigen (2).

Malekzadeh and colleagues go on to retrieve p53 reactive T-cell populations from peripheral blood in patients with cancer, whose tumor expresses p53 mutations. Importantly, specific T cells discriminate the wild-type and the mutated sequence, and their reactivity to hotspot mutations that have previously been described to occur in many patients. Moreover, the HLA allele restriction for each case is ascertained. T-cell culture virtuosity permitted to raise sufficient quantities of p53-specific CD4 and CD8 T lymphocytes as to permit both cloning of their paired TCR α/β chains and functional assessments that are consistent with being categorized as middle to high affinity TCRs.

These findings mean outstandingly important consequences for immunotherapy cancer research (**Fig. 1**). These include the fact that oncogene-encoded neoantigens can be defined for adoptive T-cell therapy and vaccination. Furthermore, a collection of TCRs with specificities for frequent hotspot mutations and HLA restrictions can conceivably be built. Accordingly, autologous adoptive T-cell therapy based on retroviral TCR transfer becomes feasible, matching the mutation and the HLA antigen-presenting molecules of the patient with the intended TCR. In this regard, generating off-the-shelf collections of donor T cells transduced with relevant TCRs while gene-edited for elimination of endogenous TCRs and HLA alloantigens is an enticing possibility already feasible with the current progress of adoptive T-cell therapy and biotechnology (3). Notably the ability to perform these studies starting from peripheral blood samples may greatly simplify translation to the clinic (4).

A prominent clinical example of the potency of T-cell recognition of oncogene neoantigens was observed in a non–small cell lung cancer case treated with tumor-infiltrating lymphocyte cell cultures recognizing a K-RAS mutation who achieved an excellent clinical response with an immunoedited progressing lesion that actually had lost the HLA-C allele presenting the peptide derived from such K-RAS–driver mutation (5).

In the era of modern immunotherapy, such hotspot mutations have also implications to study and follow relevant antitumor immune responses either pretreatment and/or on-treatment with checkpoint inhibitors or other immunotherapy strategies. The fact that TCRseq or HLA-multimers could identify such TCRs among the peripheral repertoire has the potential for the development of most interesting biomarkers. Recognition of p53 mutations by peripheral CD8 and CD4 T lymphocytes has been revealed. The role of CD4 in cancer immunology is doubtlessly very important, although it remains understudied in humans.

In summary, T-cell recognizable p53 hotspot mutations offer opportunities for immunotherapy and immune monitoring. A future in which immunotherapies based on collections of TCRs specific for

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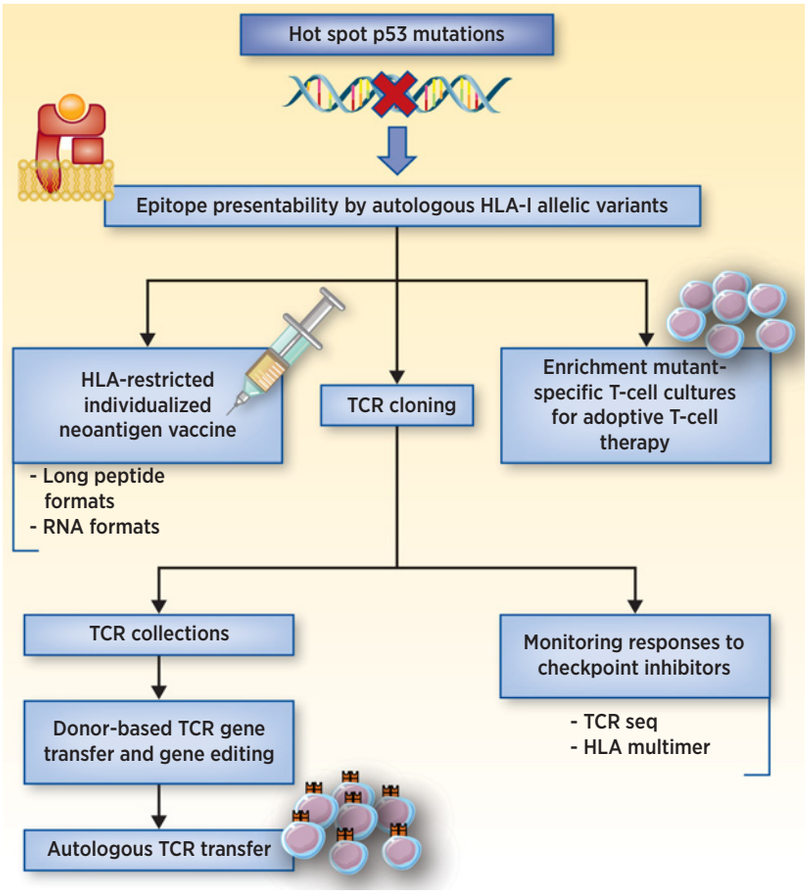

Figure 1.
Diagram of the therapeutic approaches and consequences derived from the fact that hotspot frequent mutations in the tumor suppressor gene *TP53* give rise to HLA-presented epitopes recognizable expressed by CD8 or CD4 TCRs. Importantly these studies can be extended by using peripheral blood T lymphocytes from patients with cancer.

hotspot oncogene mutations restricted by HLA alleles is envisioned. Our progress in this regard will owe much to the pioneers studying its existence and defining their functional properties.

Disclosure of Potential Conflicts of Interest

I. Melero is a paid consultant for Bristol-Myers Squibb, Roche, AstraZeneca, Pharmamar, Alligator, Numab, F-star, Servier, and MSD, and reports receiving commercial research grants from Alligator, Bristol-Myers Squibb, Roche, and Pharmamar. No potential conflicts of interest were disclosed by the other authors.

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