Neoantigen: A Long March toward Cancer Immunotherapy

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Running title: Neoantigen for Adoptive T-cell Therapy
Summary

Somatic mutations in cancer give rise to neoantigens. Technology revolutions in cancer genomics and immunology have made it possible to rapidly identify neoantigens for cancer vaccines. Leisegang and colleagues report that it is practical to rapidly identify neoantigens for adoptive T cell therapy in a mouse tumor model.
In this issue of *Clinical Cancer Research*, a new development in adoptive T cell therapy experimental mouse tumor model is reported by Leisegang et al. (1).

In retrospect, the 1990s were considered a golden period for tumor immunology when many tumor antigens recognized by T cells were identified. The antigens reported by Boon and colleagues in both murine and human cancers (2, 3) were derived from genes that are over-expressed in cancer and fetal tissues (4). The second class of unmutated antigens recognized by tumor-reactive T cells is tissue-specific antigens that are also found in tumor cells (5). These unmutated tumor antigens were favored for cancer vaccines and cancer therapy because they are present in a high proportion of human cancers. However, the classical study by Prehn and Main (6) has cast a long shadow on the utility of the shared tumor antigen as their in vivo analysis showed that tumor rejection antigens are by and large individually specific. In supporting this notion, Ramarathinam et al. reported that, although multiple lineages of murine tumor cells P1A, the first unmutated tumor antigens to be identified, were not cross-protective (7). While cancer patients have a high frequency of T cells specific for unmutated antigens, these T cells were unable to control cancer growth (8). Consistent with this notion, the first transgenic mice that expressed unmutated tumor antigen-specific TCR on all T cells were not able to reject tumors that express the antigen, P1A (9). The poor therapeutic effect of these T cells may have been predicated because the host must have developed mechanisms to either eradicate or functionally restrain the T cells that can potentially target self-tissues.

The concept that cancer cells must express neoantigen can be traced back more than 60 years when Prehn and Main demonstrated that tumor antigens are individually
specific (6). Its validation must wait for more than 40 years, when Schreiber and colleagues reported the first identification of tumor antigen that are derived from mutations (10). While the drawbacks of targeting unmutated tumor antigens have raised the potential significance of targeting neoantigens, the challenge of identifying and targeting individually specific neoantigens must wait for both technology revolution and wider acceptance of their significance in cancer immunotherapy. In this issue, in mouse tumor induced by ultraviolet irradiation, Schreiber and colleagues provided the first and unequivocal evidence that neoantigens can be targeted for cancer immunotherapy.

Cancer genomics have revealed a large number of mutations in clinical cancer samples. The technical advances in rapid identifications for personalized cancer treatment have intrigued immunologists into targeting these mutations for cancer immune therapy. Meanwhile, advances in targeting CTLA-4 and PD-1 pathways allowed one to identify high mutation burden as biomarkers for therapeutic responses. Further, recent attempts to mind the mutations in cancer suggest an abundance of neoantigens for immune targeting. One such attempt was reported by the Srivastava’s laboratory several years ago with successful attempts to identify mutations in cancer cell lines that can be used as potential therapeutic vaccines (11).

De novo identified neoantigens which have been explored for cancer vaccines but rarely for adoptive T cell therapy. Since a therapeutic vaccine has never been as successful as a preventive vaccine even in cases of viral infection, the impact of neoantigen-based vaccination is considerably less than that of immunotherapy using T cells that recognize the neoantigens. Obviously, more is needed to develop adoptive T cell therapy from
mutations identified by genomics. The work reported by Leisegang et al. (1) marked a major advance toward neoantigen-based immunotherapy.

Leisegang et al. (1) used an UV-induced carcinoma to test the notion of immunotherapy (Figure 1). The authors divided the cancer into 20 fragments in order to identify antigens that were shared among different fragments. Taken a page from evolution biologists, Leisegang et al identified trunk antigens that were shared among all fragments. As expected, a high number of trunk antigens existed in a given tumor, which suggested a rich source of neoantigens. Using a publically accessible computation program, the authors sought for mutations that can yield high affinity epitope in the mouse MHC class I and choose one with the highest prevalence for production of antigen-specific T cells. Surprisingly, the antigen chosen by the unbiased approach turned out to be the same as neoantigen identified nearly 20 years ago (12). The historical coincidence speaks volumes for the significance of this antigen in cancer biology and suggests that while neoantigen is cancer-specific, it does not have to be individually specific for each cancer. As such, a personalized T-cell therapy may not have to be as personal as one might have predicted from the classical studies of Prehn and Main (6).

Leisegang et al. (1) then identified TCR for antigen-specific T cell line and transduced the TCR into polyclonal T cells. The transduced T cells were found highly efficient in lysing tumor cells expressing the antigen and induced a significant therapeutic response in mice bearing large tumors from which the neoantigen was identified in the first place. The therapeutic response is much improved if the antigen is over-expressed or if the adoptive therapy was combined with irradiation, where complete rejection without recurrence was observed in a high proportion of mice with large tumor burden.
The extent of antigen loss in tumor cells are comparable between this study and earlier studies using transgenic T cells specific for unmutated tumor antigen P1A (13). The similarity suggests that immune evasion is an obstacle not only for therapy based on unmutated tumor antigens but also for neoantigens. How might such a barrier be overcome?

Leisegang et al. (1) have demonstrated that such evasion can be avoided to a large extent by combination with irradiation therapy. Irradiation has been shown to enhance immune response through induction of type I interferon. By reducing tumor burden, irradiation may reduce the number of tumor cells with pre-existing clones with either deletion or loss of expression of the tumor antigen. Consistent with this notion, Leisegang et al. showed that the recurrent tumors consists of those with deletion and those without deletion but lack gene expression.

Development of a therapy-resistance clone is nothing new in cancer and infectious diseases. Traditionally, such mutations are best dealt with through the use of drug cocktails. Fortunately, given the large number of neoantigenic epitope identified, immunologists are richly endowed with targets for combination therapy. Since approaches for all antigens are substantially the same, combination therapy with multiple TCRs are clearly feasible.

The most important aspect of the current study is that with some minor modification based on existing technology, the concept can be translated into clinical trials targeting neoantigens in human cancer. Such modification may include identification of TCR from tumor-infiltrating cells rather than from T cells generated from peptide immunization.
(Figure 1). Since identification of TCR from tumor-infiltrating cells has been successful, it is anticipated that one would be able to identify the missing link between these T cells and their antigens and use the TCR for adoptive cancer therapy.

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References


Figure legend

Figure 1. **Neoantigen-specific adoptive T cell therapy.** The top of the figure depicts the approach used by Leisegang et al. (1), while the bottom illustrates possible modifications for a practical adaptation for clinical translation. NGS, next-generation sequencing; TIL, tumor-infiltrating lymphocytes.
Figure 1:

In silico analysis for high-affinity MHC ligands as neoantigen candidates.

High-depth NGS for abundant mutations.

Piece-by-piece NGS for "trunk" mutations.

Generation of neoantigen-specific T cells for TCR identification.

Single-cell analysis of TIL for TCR identification.

Lentivirus TCR

Adaptive therapy

TIL

IL2, etc.

TCR

Research.
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