CD137 as a biomarker for tumor-reactive T cells: finding gold in the desert

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Running title: CD137 as a selection marker for tumor-reactive T cells

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Abstract

Although human cancer is often surrounded by immune cells, only a small number is tumor-reactive T cells which recognize tumor antigens and are able to eliminate cancer cells. Ye and colleagues now found that many of these tumor-reactive T cells are marked by expressing CD137, a T cell costimulatory receptor.

In this issue of Clinical Cancer Research, Ye and colleagues utilize CD137 as a marker to successfully enrich and expand tumor-specific T cells from cancer tissues for adaptive immunotherapy (1). Adoptive cell therapy (ACT) has been very effective in clinical treatment of advanced melanoma. It involves isolation, \textit{ex vivo} activation and expansion of autologous cancer-specific T cells from cancer patients to large numbers, which will eventually be transferred back to patients to combat cancer. Approaches to ACT using autologous cells genetically engineered to express antitumor T-cell receptor is under vigorous development (2). The immunogenicity of melanomas makes them feasible for adoptive cell therapy. Tumor-reactive T cells can be derived from the blood or the surgically resected tumors of melanoma patients, though the latter is more enriched in tumor-reactive T cells. The first clinical trial of adoptive T cell transfer using TILs demonstrated a significant objective response among metastatic melanoma patients (3). Later on, lymphodepleting regimen was given to patients prior to cell transfer to improve the persistence of the transferred cells. In addition, efforts have been made to shorten the culture period \textit{in vitro}, which is believed to improve the quality of T cells for transfer. A recent clinical trial from the NCI indicates that transfer of short-term cultured TILs together with lymphodepleting chemotherapy can trigger tumor regression in up to 50% of metastatic melanoma with manageable toxicity (4).

A prerequisite to ACT is the isolation of sufficient number of tumor-specific T cells from the patient. TILs are a mixture of different T cell subsets. TILs are composed of T cells with effector memory phenotype, and many of them are anergy or exhibit exhausted phenotype originally described in chronic viral infection. Significant numbers of immunosuppressive cells, including both Foxp3+ and Foxp3- regulatory cells, are also observed in TILs from most types of cancer. Thus, the rationale of ACT is to identify the
ideal T cell subtype to maximize the anti-tumor immune response while eliminating suppressor T cells from TILs. The identification of cancer-associated antigens has spurred interest in the derivation and transfer of CD8+ T cell clones for cancer therapy in late 1990s. However, cases of cancer recurrence caused by antigen loss have been documented, arguing against the using of T cell clones with limited epitope recognition. In addition, tumor antigens for many cancers other than melanoma are still not well characterized. Therefore it is valuable to look for alternative biomarker for tumor-reactive T cells, without the identity of tumor antigens.

CD137, also called 4-1BB, is a member of TNF receptor superfamily with T cell costimulatory functions (5). Signaling through CD137 by its natural ligand CD137L, or agonistic antibody, promotes T cell expansion, sustains their survival and enhances their cytolytic effector functions. Naïve T cell does not express CD137; upon stimulation, activated T cells transiently express high level of CD137, which disappears rapidly. Memory T cells respond to CD137 signal directly to expand. However, they express minimal level of surface CD137, and local signals in the bone marrow and liver contribute to CD137 upregulation on memory T cells (6). Interestingly, CD137 was seen to be selectively upregulated upon alloantigen stimulation, and CD137 depletion was able to remove allo-reactive T cells during hematopoietic transplantation (7). Similarly, CD137 expression could be used to isolate the full repertoire of CD8+ T cells in response to antigen without the knowledge of epitope specificities (8). Thus, the expression of CD137 on T cells is tightly regulated, and is extremely sensitive in response to antigen stimulation.

In this study, Ye et al made effort to see whether CD137 could be used as a marker to selectively isolate tumor-specific T cells from TILs (Figure 1). They found that CD137 is preferentially expressed on T cells directly isolated from tumor or ascites of human ovarian cancer. Overnight incubation with autologous tumor cells significantly increased the frequency of CD137+ T cells in TILs, which seems to be antigen-specific. The antigen-dependent CD137 upregulation was further confirmed when the author used T cell lines with known antigen specificity. When T cells were isolated and separated from
tumors based on CD137 expression, the CD137+, but not the CD137-negative T cells, were able to respond to autologous tumor cell stimulation. More importantly, when tumor cells and human T cells are co-transferred into immunodeficient mice, only CD137+ T cells could inhibit tumor cell growth \textit{in vivo}.

Many T cell co-receptors associated with T cell exhaustion are expressed on TILs, including PD-1, TIM-3, and LAG3 (9). Recently PD-1 has been reported to be used as a biomarker to isolate tumor-reactive T cells (10). However, the quality of those T cells has not been fully investigated. In this study, Yu and colleagues sorted out different T cell subsets from TILs based on the expression of CD137 and PD-1, and compared their response to tumor antigen stimulation. CD137+ TILs produced significantly more IFN-\(\gamma\) than PD-1+ cells upon tumor stimulation. As CD137 expression on T cell is transient in response to stimulus, CD137+ TILs represents a group of newly recruited T cells. On the contrary, PD-1+ T cells are exhausted resident TILs, which constantly expose to tumor antigen. In all, CD137 represents a superior biomarker for tumor-reactive T cells with good quality.

Overall the study by Ye and colleagues described a new way of isolating human TILs effectively for ACT. With this approach, the broad diversity of antigen receptors (TCRs) of TILs is preserved, which should help to prevent cancer cells with mutated antigen from escaping. In addition, this method is applicable to both melanoma and ovarian cancer without known antigen specificity. As each round of stimulation drives the cells further toward terminal differentiation or exhaustion, this method could enrich enough reactive cells after fewer divisions, which could have a direct impact on the quality of selected cells. Finally, the selective upregulation of CD137 receptor on tumor-reactive T cells in human cancer by Ye also validates CD137 monoclonal antibody (mAb)–targeting cancer immunotherapy. Consistently, the anti-tumor effect of CD137 agonist mAb has been seen in various types of mouse tumor models (11). Early trial of CD137 mAb in cancer showed very promising clinical results, whereas severe hepatitis was seen in patients (12). Therefore, it will be interesting to see whether agonist CD137 mAb could also enhance TIL functions during \textit{in vitro} selection process so we can double the benefit.
Reference


Figure legend

Figure 1. Isolating CD137+ T cells from cancer tissues for ACT. CD137 is selectively expressed on tumor-reactive T cells in TILs. After the enrichment of these CD137+ cells from single cell suspension of cancer tissues, these cells undergo rapid expansion process to generate enough T cells to be infused back into the same patient.
Figure 1:

- Homogenization and separation
- CD137 selection
- Expansion
- Surgery
- Re-infusion

Legend:
- Cancer cell
- CD137 + T cell
- PD-1 + T cell
- Regulatory T cell
- Other T cells
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