Review of: "Emerging Strategies in TCR-Engineered T Cells"

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Cancer is a leading cause of death worldwide, and the number of cases globally continues to increase. Traditional cancer treatments, including surgery, chemotherapy, radiation therapy and targeted therapy, have demonstrated very limited efficacy for cancer patients with late-stage disease. Cancer immunotherapy, particularly adoptive cell transfer (ACT), has shown great promise in the treatment of cancer patients, including those who are refractory to standard therapies. Remarkable clinical responses have been obtained from ACT of patient-derived tumor infiltrating lymphocytes TILs , chimeric antigen receptor (CAR)-modified T cells (CAR-T) and T cell receptor (TCR)-engineered T cells (TCR-T). Although TIL-based ACT is effective against melanoma, it is not working well in treating the other solid cancers, even though TILs can be also isolated from other solid tumors including colorectal cancer, breast cancer, lung cancer and ovarian cancer. This may be due to that it is very difficult to isolate tumor-specific TILs, which are not present in all patients or contain very few tumor-specific T cells for therapeutic efficacy. Despite the great success to date with CAR -T cells in the treatment of patients with B cell malignancies, clinical trials using CAR-T cells targeting solid cancers have achieved limited efficacy and observed ‘on-target, off-tumor responses’ with serious consequences due to the lack of ideal cancer antigens on cancer cell surface. However, TCR-T cells can recognize epitopes derived from both cell-surface and intracellular targets and have achieved encouraging clinical responses in treating cancer patients with refractory *melanoma*, synovial *sarcoma and multiple myeloma.* Therefore, TCR-T cells may hold great promise for the treatment of solid cancers.

In this review paper entitled “Emerging Strategies in TCR-Engineered T Cells”, Wei et al have summarized basic, translational, and clinical insights into the challenges and opportunities of ACT, and pointed out that TCR-T cell-based ACT has potential to become a powerful tool for fighting cancers, especially solid tumors where other approaches have been less effective. The authors highlighted the importance of targeting tumor-specific antigens, especially neoantigens (neoAgs) and outlined a strategy of combining neoAg vaccines, checkpoint blockade therapy, and adoptive transfer of neoAg-specific TCR-T cells to produce a truly tumor-specific therapy. Indeed, the success of cancer immunotherapy relies largely on the identification of suitable cancer antigens for the generation of effective cancer vaccines and antigen-specific T cells.

Currently there are very few ideal tumor-specific antigens for the development of ACT for solid cancer treatment. In addition to cancer-testis antigens (such as NY-ESO-1) and tumor-causing oncogenic viral proteins, which are recognized as good targets for TCR-T cells, neoAgs are ideal tumor-specific antigens, and every cancer patient may have his/her own potential neoAgs as immunological targets for cancer immunotherapy. Therefore, it would be great if the authors have provided more detailed information on how to effectively identify useful neoAgs in a fast manner, which could be used to produce a truly tumor-specific therapy for each individual cancer patients in the future.

To sum up, Wei et al have given an excellent review on the field of ACT, and TCR-T cell-based ACT holds great promise for the treatment of solid cancers. Future directions of cancer immunotherapy may include: (1) Identification of ideal cancer antigens; (2) Enhancing in vivo *trafficking* , persistency and survival of adoptively transferred T cells; 3 Identification of cancer biomarkers for ACT-based therapy; and 4 Combinational immunotherapy to improve efficacy. We have enjoyed reading this review paper very much and believe that the other readers will also love it.