

Cancer immunotherapies: where we stand? where we will go?

Editorial

By accumulating milestone discoveries in the field linking cancer and immunology, immunotherapy of cancer have now been transitioning from a promising possibility to many successful realities. In 2013, cancer immunotherapies have been deemed as the top “breakthrough of the year” in *Science*, the America’s leading journal, beating out all other contenders. The approval by FDA of two immunotherapeutic drugs, Ipilimumab (melanoma) and Provenge (prostate cancer), has generated more renewed interest for immunotherapy of cancer. Several recent clinical trials are increasingly encouraging and demonstrating the power of immunotherapeutic approaches to treat cancer, especially for very advanced and metastatic cancer. Although, a complete response remains infrequent (10-20%),^{1,2} cancer immunotherapy represents the last chance to treat those patients with metastatic diseases that are resistant to conventional therapies, and the developments of safe and more powerful immunotherapeutic weapons carry many hopes to save life of the patients.

The majority of cancer immunotherapies take advantage of activating tumor-specific Cytotoxic T lymphocytes (CTLs), which specifically target and lyse of tumor cells. Tumors can develop multiple immunosuppressive mechanisms to evade the effector arms of the immune system, turning down most of the immunotherapeutic strategies. One of the most significant advances to date has been the identification and targeting of the immune checkpoints that inhibit effector T-cell function, such as Cytotoxic T lymphocyte-associated protein 4 (CTLA4), Programmed cell death-1 (PD-1).³ Clinical blockage of these checkpoints removes the T cell impediment, resulting in the reactivating of tumor-killing CTLs with durable object responses lasting for many years.^{1,4} More recently, pre-clinical data also demonstrate that a triple therapy in combination of anti-CTLA4, anti-PD-1 and therapeutic vaccination, provides a more profound rejection of experimental tumors.⁵

The immune checkpoints may actually be setup by the immune system itself to prevent the hyper-activating of T cells, while tumor cells utilize this mechanism to escape from the immune attack. Nevertheless, tumor cells are efficient in creating the immunosuppressive networks, turning their immune foes to their supporters. One of the major evidences is that dendritic cells (DCs), which are professional antigen-presenting cells to induce tumor-specific T cell responses, may associate with acquisition of tolerogenic/immunosuppressive activities in cancer settings.⁶ The cancer immunosuppressive milieu can render DCs to acquire regulatory instead of stimulatory capacities, by inducing molecular pathways activation in DCs. Removal the cells involved in immunosuppressive networks, such as regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSCs); neutralization of the immunosuppressive factors, such as IL-10, TGF- β , IL-6, VEGF, M-CSF and PGE2; or turning off the signaling pathways in DCs, such as MAP kinases (MAPKs), JAK/STAT3 and PI3K/Akt, will provide novel approaches that synergize to augment antitumor immunity.

Volume 1 Issue 1 - 2014

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Received: April 26, 2014 | **Published:** April 29, 2014

Another promising cancer immunotherapy field is adoptive cell therapy (ACT). ACT in clinical trials using type I cytotoxic CD8+T (Tc1) cells combined with lymph-depletion, active immunization and high doses IL-2 have resulted in objective responses in large portion of patients with advanced melanoma.^{2,7} However, durable complete responses observed in only 5-15% of treated patients, largely due to these Tc1 cells display end-effector and exhausted features and have a short lifespan after ACT.⁸ Immunologists are now working on identification and generation of novel T cells subsets,⁹⁻¹² which possess enhanced persistence, appropriate homing, and acquisition of cytolytic effector function *in vivo*. We also believe that better understanding of the mechanisms of T helper cell-provided help to CD8+ T cell will substantially contribute to the optimal antitumor effect of ACT.¹³⁻¹⁵

One last issue for cancer immunotherapy is to ameliorate the current cancer vaccine protocols. Cancer vaccines have shown objective response in most clinical trials, but a question remains for why these increased numbers of circulating tumor-specific T cells in patients do not cause tumor shrinkage.¹⁶ One group looked insight into this problem recently and found that vaccination with gp100 peptide emulsified in IFA (commonly used in clinical trials) primed gp100-specific CTLs, which were accumulated not in tumors but rather at the persisting, antigen-rich vaccination site.¹⁷ They subsequently proposed a short-lived formulation to overcome these limitations of IFA-based vaccine. We also constructed a unique and universal adjuvant system to hyperactive antitumor immunity, which is a DNA-based vaccine containing six copies of target epitope in a linear alignment as an immunogen that flanked with optimized immunoadjuvants.¹⁸⁻²⁰ This construct is able to provoke superior immune response even much stronger than the DNA vaccine-priming and protein-boosting method.²¹ Therefore, innovative vaccination strategies will facilitate the improvement of current cancer immunotherapeutics.

Overall, we should appreciate the great efforts that have been made by our predecessors to develop more and more efficient cancer immunotherapies, which have finally turned into approved

immunotherapeutic drugs for clinical usage. Standing on their shoulders, we have the chances to working for the new generation immunotherapeutic approaches and bringing more fruitful results within reach, which will be real and near-term benefits to patients fighting against cancer.

Acknowledgements

None.

Conflicts of interest

Author declares there are no conflicts of interest.

Funding

None.

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