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Editorial

Advancements in immunotherapy: A paradigm shift in cancer treatment

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Emergence of immunotherapeutic strategies of cancer treatment has opened a new direction towards targeted therapy with minimal side-effects. Immunotherapy harnesses patients own immune system to eradicate cancer cells further to reduce toxic effects of classical chemo and radiotherapy. Since last decade various types of immunotherapeutic strategies such as use of monoclonal antibodies, which block cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed cell death-1 (PD-1), dendritic cell vaccines and chimeric antigen receptor (CAR) T cells have shown a tremendous success in clinical trials for several types of cancers.

Amongst these strategies, engineered T cell therapies have demonstrated great promise for the treatment of different types of cancers. The initial study by Sharma and Allison[1] showed that blocking of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) is capable of enhancing tumor cell killing ability of T cells. This particular observation enlightened a path towards more comprehensive studies to identify immune checkpoints which could be blocked to trigger robust anti-cancer immune responses. Since then blockade of immune checkpoints have changed the treatment strategies for cancers. More specifically, inhibitors of PD-1, PD-L1 and CTLA-4 have been found to effect the immunological responses in cancer cells which may trigger adverse immune reactions and are usually well tolerated than chemotherapy drugs. Understanding PD-1/PD-1 ligand (PD-L1) which is highly expressed on tumor cells and causes exhaustion and dysfunctionality in T cells that avoid immune response has led to the development of PD-L1 inhibitory drugs such as Atezolizumab and Avelumab. These drugs have shown significantly increased survival of patients with minimal side effects in solid tissue tumors. However, further to improve benefits from immune checkpoint blockades, combinatorial strategies are under investigation.

Another approach of using dendritic cell (DC) vaccines has emerged as a potent cancer vaccine in last decade. DCs are professional antigen-presenting cells (APCs) which act as a bridge between innate and adaptive immune system. Two of the most important limitations of DC vaccines are limited source of specimen and complicated procedure to generate these vaccines. Hence, the current era of immunotherapy has led to the evolvement of adoptive cell transfer (ACT) technology which includes collecting and using patients' own immune cells to treat individual cancer. Several types of ACT such as TILs, TCRs, and CARs have been introduced till date; however, one that has advanced the furthest in clinical development is called CAR T-cell therapy.

In 2017, two CAR T-cell therapies were approved by the Food and Drug Administration (FDA), USA for treating acute lymphoblastic leukemia (ALL) in children and advanced lymphomas in adults. Nevertheless, researchers caution that, in several aspects CAR T cells and other forms of ACT are in their early days of development. Therefore different forms of ACTs are still being developed. A recent study by Montel-Hagen et al[2] published in Cell Stem Cell reported organoid-induced differentiation of conventional T cells from human pluripotent stem cells. This method of differentiation permits generation of naive, antigen-specific T cells having antitumor activity from T cell receptors engineered

pluripotent stem cells (PSCs). As a platform for therapeutic T cell generation, PSCs-artificial thymic organoid (ATO) system present the opportunity to combine various other technologies to gene-modify, screen and expand self-renewing PSC clones for the unlimited production of non-alloreactive and optimized T cells, which could serve as the basis for the development of universal, ‘‘off-the-shelf’’ T cell therapies.

In just the last few years, developments in CAR T cells and other ACT approaches have greatly accelerated with better understanding of identifying how these therapies work in patients. In the next few years these strategies may push immunotherapy in reality for treating advanced cancers.

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