ADVANCES IN NATURAL KILLER CELL THERAPIES

Harnessing the immune system has become the cornerstone of the development of new oncology therapies. Initially the primary focus was on activating the adaptive immune system, which includes T- and B-cells that have a wide range of receptors to identify and attack different antigens[1]. Lifting the immune-checkpoint blockage via the inhibition of receptors and ligands like PD-1, PD-L1, CTLA-4 and LAG-3 with monoclonal antibodies have been shown to be successful and indeed, pembrolizumab (Keytruda®) is a blockbuster drug with about $17 billion in sales in 2021[2]. However, there are challenges with activating T-cells including exhaustion where prolonged exposure to cancer antigens in an immunosuppressive environment reduces the effector function of T-cells. Additionally, "cold" tumors that do not secrete antigens at a sufficient level to mount an immune response are difficult to treat with immune therapies. Similarly, tumors that do not have T-cells in the vicinity and are considered to be "immune deserts" would not show a meaningful response to checkpoint inhibitors. Overcoming these challenges has become a major area of focus for the next-gen immune therapies.

One area of interest that has gained a lot of interest is activating the innate immunity especially NK or natural killer cells. NK cells have been shown to have a cytotoxic effect and also secrete cytokines and chemokines including TNF-alpha that induces an inflammatory response and IFN-gamma that activates several immune cell types including NK cells[3]. NK cells mount the first response to an antigen challenge and are able to directly lyse tumor cells without the need for antigen presentation[3]. They also perform surveillance to differentiate tumor and normal cells based on changes in expression of cell surface receptors[3]. One of the more desirable characteristics of NK cells is the ability to kill cells that are adjacent to the targeted tumor cell expressing the appropriate surface activating receptor, which is optimal when targeting highly heterogeneous tumors. Additionally, NK cell-based therapies have been shown to have a favorable safety profile in human clinical trials[4], which has given the field confidence to move forward with drug development.

An exciting development in cancer cell therapies is the development of CAR-NK cells[4]. CAR-T cells have been clinically successful and 6 CAR-T therapies have been approved by the FDA[5] for hematological cancers including multiple myeloma and acute lymphoblastic leukemia (ALL). However, all approved CAR-T therapies are autologous and are difficult to scale as they are dependent on harvesting sufficient T-cells from cancer patients that have to be rapidly expanded and engineered to be infused back into the patient. CAR-NK cells are being evaluated as a viable alternative for CAR-T cells as allogeneic CAR-NK cells have been shown to be effective in preclinical studies[4]. This could pave the way for off the shelf CAR-NK cell therapies that would be scalable and accessible to many patients in a short period of time.

NK cells express various activation and inhibition signals on the cell surface and the cell killing activity is typically induced when the activation signals are greater than the inhibition signal. One activation receptor is CD16 that has been shown to recognize antibodies targeting specific tumor antigens to trigger ADCC or antibody-dependent cell-mediated cytotoxicity[3]. Recently, a presentation at the AACR 2022 meeting showed data that advanced NK cell activation via the use of a bispecific antibody that targeted CD16A (CD16 isoform) and CD30 that is expressed on specific lymphoma cells[6]. Patients treated with NK cells that were activated by the bispecific antibody showed an astounding 89% overall response rate for relapsed/refractory lymphomas. While there are treatment options for relapsed lymphomas including an effective antibody-drug conjugate (brentuximab vedotin), in some cases, the tumors become resistant to all therapies leaving patients with minimal therapeutic options. Since the bispecific antibody can bind both NK cells and lymphoma cells, it serves as a bridge to bring the 2 cell types proximally, allowing the NK cell to directly kill tumor cells[6].

Positive patient results in relapsed or treatment refractory cancers suggests that NK cells have potential to be approved for early and late lines of treatments, so that patients who have almost no other therapeutic options have a chance.

References:

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