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Preview

CAR NK Cell Therapy for T Follicular Helper Cells

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T follicular helper (T_{FH}) cells are associated with the development of both autoimmune disease and T cell malignancies. In this issue, Reighard et al.,[1] describe the design of PD-L1 chimeric antigen receptor (CAR) NK cells that effectively target and eliminate T_{FH} cells.

The first CAR T cells were designed and tested in the late 1980s.[2] The basic premise for the generation of CAR T cells was to use a patient's own T cells, genetically modify them to better recognize and kill cancer cells by expressing a chimeric receptor specific for a particular cancer-associated antigen, and then reinfuse the modified T cells back into the patient. Subsequent studies improved the efficacy of CAR T cell therapy by adding costimulatory signals and cytokine secretion capacity to the cells. These modifications led to CAR-T cell therapy showing some remarkable results in patients.[3,4]

Despite the success of CAR T cells, they do have significant adverse effects that include cytokine release syndrome (CRS) and neurotoxicity. Consequently, research focus increased to genetically modify NK cells with CARs to enhance their known tumor-killing capacity. CAR NK cells have an improved toxicity profile relative to CAR T cells and may make the treatment more accessible to patients. T cells must be genetically matched to individuals to avoid graft versus host disease (GVHD). When the patient's own T cells cannot be used, a complex gene-editing process is required to produce allogeneic CAR T cells. By contrast, there is no such requirement for allogeneic CAR NK cells. CAR NK cells are now actively pursued in a clinical setting. These include the treatment of hematologic malignancies and solid tumors.[5,6]

T follicular helper (T_{FH}) cells interact with B cells to induce the differentiation of B cells that can produce high-affinity antibodies which provide long-term immunity following infection and vaccination.[7,8] However, dysregulated T_{FH} cells are associated with the development and severity of several autoimmune diseases and T cell malignancies, where the frequency of T_{FH} cells in peripheral blood provides a marker for disease progression. Indeed, the central role of T_{FH} cells in many diseases has made them a major target for therapeutic modulation. The study by Reighard et al.[1] provides evidence supporting the use of CAR NK cells to reduce the load of PD-1-expressing T_{FH} cells in human disease. The approach described effectively reduced or eliminated T_{FH} cells in peripheral blood, providing exciting proof-of-principle evidence for the use of CAR NK cells in T_{FH}-driven diseases.

PD-L1 expressing CAR NK-92 cells were designed, and generated, and observed to degranulate in response to ligand and Raji human B cell lymphoma cells that have been engineered to express high levels of human PD-1, but not in the absence of PD-1 expression on target cells. Co-culture of CAR NK-92 cells with human tonsillar $CD4^+$ cells resulted in a 7-fold reduction in $CXCR5^+$ $PD\text{-}1^+$ T_{FH} cells. By contrast, co-culture of control NK-92 cells and tonsillar $CD4^+$ T cells had no such effect on T_{FH} cells. Since T follicular regulatory (T_{FR}) cells express very high amounts of cell-surface PD-1, it was curious to observe that CAR-NK cells had less effect on T_{FR} cells than T_{FH} cells. Nevertheless, the addition of CAR-NK cells, but not NK cells, to 3 day SEB-stimulated tonsillar $CD4^+$ $CXCR5^+$ T and $CD27^+$ B cell co-cultures reduced both B cell proliferation and antibody production, indicating that T_{FH} cell elimination had the dominant effect on B cell function in this setting.

To test the effect of CAR NK-92 cells *in vivo*, a humanized mouse model of lupus-like disease was generated by reconstitution with cord blood leukocytes prior to pristane injection. The resulting mice exhibit elevated antibody production, $PD\text{-}1^+$ $CD4^+$ T cells, and splenomegaly. Treatment of these mice with CAR NK-92 cells reduced both the splenomegaly and the numbers of $CD4^+$ T cells, with a proportionally greater loss of $CD4^+$ T cells expressing high amounts of PD-1. Following infusion, CAR-NK-92 cells were found in the spleen and liver of recipient humanized mice. However, for T_{FH} cell depletion to therapeutically modify autoimmune disease, CAR NK cells may have to gain access to follicular tissues, germinal centers, and ectopic GCs. Future studies for clinical application will need to test this promising strategy on primary human cells and to validate the migration of CAR-NK cells into these important target sites, which may require further modifications.

REFERENCES

1. Reighard, S.D., Cranert, S.A., Rangel, K.M., Ali, A., Gyurova, I.E., de la Cruz-Lynch, A.T., Tuazon, J.A., Khodoun, M.V., Kottyan, L.C., Smith, D.F., et al. (2020). Therapeutic Targeting of Follicular T Cells with Chimeric Antigen Receptor-Expressing Natural Killer Cells. Cell Rep. Med. *1*, this issue, 100003-1–100003-10.
2. Gross, G., Waks, T., and Eshhar, Z. (1989). Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc. Natl. Acad. Sci. USA *86*, 10024–10028.
3. van der Stegen, S.J., Hamieh, M., and Sadelain, M. (2015). The pharmacology of second-generation chimeric antigen receptors. Nat. Rev. Drug Discov. *14*, 499–509.

4. Tokarew, N., Ogonek, J., Endres, S., von Bergwelt-Baildon, M., and Kobold, S. (2019). Teaching an old dog new tricks: next-generation CAR T cells. Br. J. Cancer *120*, 26–37.

5. Chiossone, L., Dumas, P.Y., Vienne, M., and Vivier, E. (2018). Natural killer cells and other innate lymphoid cells in cancer. Nat. Rev. Immunol. *18*, 671–688.

6. Miller, J.S., and Lanier, L.L. (2019). Natural Killer Cells in Cancer Immunotherapy. Annu. Rev. Cancer Biol. *3*, 77–103.

7. King, C., Tangye, S.G., and Mackay, C.R. (2008). T follicular helper (TFH) cells in normal and dysregulated immune responses. Annu. Rev. Immunol. *26*, 741–766.

8. Vinuesa, C.G., Linterman, M.A., Yu, D., and MacLennan, I.C. (2016). Follicular Helper T Cells. Annu. Rev. Immunol. *34*, 335–368.