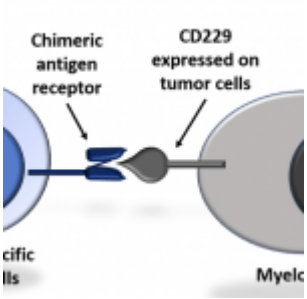
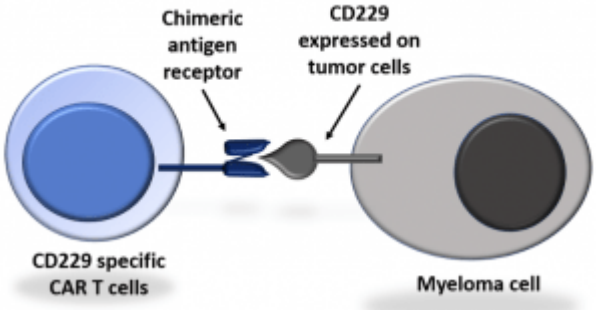
CD229 CAR: New therapy for multiple myeloma





Multiple myeloma (MM) is a clonal plasma cell malignancy which causes an incurable disease. MM develops in bone marrow and causes bone lesions with fractures, kidney failure, bone marrow failure, and immunoparesis with fatal infections. It usually occurs around the age of 60 and is more common in men than women. With the current available treatment cure is not achieved, however, treatment is associated with a five-year survival of about 49%.

Chimeric antigen receptor (CAR) T cells are genetically engineered T cells expressing extracellular single chain variable fragment (ScFv) adopted from antibody and intracellular signalling domain adopted from T cells. CART cells upon adoptive transfer recognize the target tumor cells through ScFv and exert cytotoxic effector functions to kill them. Earlier studies with adoptive transfer of CAR T cells targeting B cell maturation antigen (BCMA) has resulted in high overall response rates in MM patients [1]. However, loss of antigen and low progression free survival (>1 year) are issues with the therapy. In addition, on target off tumor effect also observed, where BCMA specific CAR T cells target normal T and B cells in the patients.

Radhakrishnan *et al* from university of Utah have developed CAR T cells targeting SLAM receptor CD229/LY9. LY9 (CD229) is expressed on hematopoietic cells including B and T cells , functions as a homophilic adhesion receptor and acts as a unique inhibitory cell-surface receptor regulating the size of the thymic innate $CD8^+$ T-cell pool and the development of *invariant* Natural Killer T (*i*NKT) cells [3]. The authors have shown that CD229, but not BCMA expressed on transitional and memory B cells, highlighting the rationale of CD229 CAR over BCMA CAR T cells that CD229 CAR T cells killed memory B cells, a potential reservoir for clonotypic MM cells. The authors also showed that CD229 cells do not show fratricide i.e they do not kill the other T cells specifically activated T cells as they lower the CD229 expression after activation. However, CD229 CART cells targets naïve healthy $CD229^{high}$ T cells. In vitro studies showed that CD229 CAR T cells efficiently killed CD229 expressing MM cell lines. Moreover, the adoptively transferred CD229 CAR T cells also killed MM cell lines in xenograft mouse models.

Overall the work by Radhakrishnan et al highlights another target for CAR T cells for the treatment of MM patients. Although the results are promising in preclinical study, a favourable response by the MM patients in the clinical trial will be truly encouraging.

Journal Article: Radhakrishnan *et al.*, 2020. CD229 CAR T cells eliminate multiple myeloma and tumor propagating cells without fratricid. Nature Communications

Summary by Rushikesh Patil

References

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Characterization of mouse CD229 (Ly9), a leukocyte cell surface molecule of the CD150 (SLAM) family. *Tissue Antigens*(2007) **70**:355–62. d

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