Understanding CAR Organization and Immune Pathway Modulation

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CARs (chimeric antigen receptors) are bioengineered synthetic receptors that consist of 4 domains namely, an extracellular target antigen-binding domain, a hinge region, a transmembrane domain, and one or multiple intracellular signaling domains (Figure 1). Introducing these modular receptors in immune cells such as T-cells, helps them to better recognize and eliminate cancer cells expressing the specific target antigen. Although treatment with CAR-T cells has produced remarkable and durable clinical results (1), many challenges limit their therapeutic efficacy (2). Lack of knowledge in understanding the membrane organization and downstream signaling of CARs in order to activate T-cells and the resulting modulation of immune response pathways by modifying CAR design (Figure 2), such as altering signaling domains, contributes to the stalled advancement of the treatment (3).

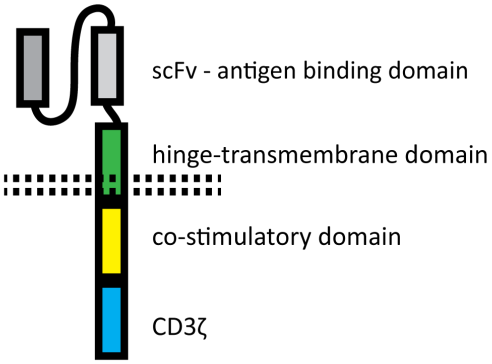

Fig 1: Schematic representation of CAR structure

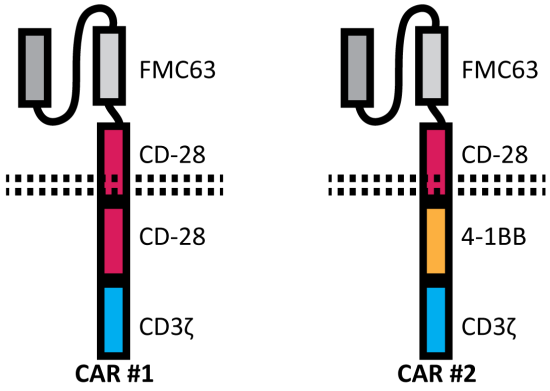

Fig 2: Schematic representation of CARs used in study

To gain mechanistic insights into CAR organization and their downstream adaptors, we utilize confocal and single molecule resolution total internal reflection fluorescence (TIRF) microscopy to capture the spatiotemporal organization of both receptors and adaptors, directly in live immune cells. We aim to compare different CARs with varying signaling domains (Figure 2): a detailed biophysical characterisation of CAR signalling will help us to obtain a quantitative understanding of (a) how CARs re-wire T-cell signalling cascades and (b) to which extent signalling patterns are general or specific to different CAR designs. Ultimately, we hope our results will provide vital information to optimize the design of more sophisticated and efficient CARs.

References

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