CAR-T Review

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Abstract

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Introduction

CAR-T History

Features of CARs that improved over autologus cell therapy 1. MHC-unrestricted 2. Don't have to resect tumors to harvest T-cells 3. Known antigens 4. Avoids the difficulties (sort of) of ex-vivo expansion of TILs 5. Risk of anergy or cell death in the infused product 6. Tumors are able to escape TCR therapy by downregulating HLA or modifying their processing of antigen. 7. TCR activity would be limited to either HLA class I epitopes (CD8+ CTLs) or HLA class II (CD4+). To get both activity, would need multiple genes 8. Limited to peptide antigens, can't get at carbohydrate or glycolipid antigens (or least only rarely) 9. Difficult to find CTL epitopes that are active – "widely presented TAAs are predominantly produced by endogenous processing of intracellular self-proteins." Thymic presentation of these TAAs results in T-cell repertoire that is devoid of high-avidity TAA-specific CTLs, due to self-tolerance" [1]

- 1986: First transfer of a specific TCR to a lymphocyte (in a mouse)[2]
- 1999: First transfer of a specific TCR into lymphocytes to target a human tumor antigen, MART-1 (melanoma)[3]. They were clones from an HLA-A2+ patient-derived T-cell clone.
- 1999: First use of first-generation CAR-T in lymphocytes from humans[4]. scFv-based zeta-chain fusion receptor termed Pz-1 that is specific for prostate-specific membrane antigen (PSMA)
- 2001: First identification of in vivo activity of a TCR-transduced T cell. Target was influenza
 nucleoprotein (NP) peptide. The mice were injected with EL4 thymoma tumor cells that express NP,
 and efficacy and homing of the transduced T-cells was identified. There was complete tumor
 eradication.

• By 2003, a review listed 23 different tumor antigens that have been targeted by genetically modified T cells. Of tehse, some were

CAR-T Biology

Challenges in solid tumor

Trafficking

Tumor microenvironment

Target selection

- The most prevalent cancer-specific mutations are not presented on common HLA alleles. This may in part be due to early immune-based negative selective pressure that allows only those driver alterations that are not immunogenic to be presented [5]. For instance, an attempt to find neo-antigens that bind to known driver mutations yieled a frequency of < 3% for any given HLA type[6].
- HLA alleles are highly polymorphic across the 3 HLA Class I alleles (A, B, C) there are over 13,000 alleles [7].

- Note that CD19, which is the most targeted and first approved target, is widely expressed on all B-cells. The toxicity is predicatable: B-cell aplasia, which can be tolerated with IVIG etc.
- The target should be stable, and this become more difficult with more unstable genomes that can escape by losing expression of the target. For instace, the most common escape for CD19-directed thearpy is trunacting mutations and copy-number changes leading to LOH[8].

Therapeutic strategies

Expanding targets

PC CAR-T

Modifying the TME

ARMORED CARS

Different effector cells

NK therapy

Production

Leukophoresis and enrichment

Transfection

 Retroviral vectors are commonly used, but others systems include adenoviral and non-viral systems #### Allogeneic CAR-T

Current efforts by tumor

Practical management

Toxicity

• (Distinguish between on- and off-target)

Future directions and conclusion

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