MODULATION OF ENGINEERED IMMUNE CELL RECEPTOR TRANSLATION USING NONCODING SEQUENCE ELEMENTS

Tech ID: 31681 / UC Case 2020-053-0

PATENT STATUS

Patent Pending

BRIEF DESCRIPTION

It would be beneficial to control the expression of engineered immune cell receptors for use in cell-based cancer immunotherapy, known as adoptive cell therapy (ACT), or in other cell-based therapies using engineered regulatory T cells (engineered Tregs) to treat immune dysfunction such as autoimmunity or organ transplant rejection. In these therapies, immune cells such as T cells or natural killer (NK) cells are genetically modified to express an engineered cell surface receptor that directs these immune cells to tumor cells or specific tissues expressing a target ligand recognized by the receptor, thereby leading to tumor cell destruction (ACT) or moderated immune reaction (engineered Tregs). However, it has been found that ACT can suffer from severe toxic side effects due to overactivation of engineered immune cells used in ACT such as CAR T-cells, due to signaling by the engineered cell surface receptor. Conversely, overactive immune cells can become exhausted and lose efficacy over time. Present attempts to regulate CAR expression do not account for control exerted at the level of protein synthesis. It would therefore be useful to be able to tune the activity of immune cells engineered for ACT or for treatment of immune dysfunction, by either increasing or decreasing the protein synthesis of the engineered immune cell surface receptor, i.e. the engineered TCR or CAR. This research describes compositions and methods for selectively increasing or decreasing the protein synthesis of engineered immune cell surface receptors using noncoding sequences in the 3'-untranslated region (3'-UTR) of messenger RNAs (mRNAs) encoding the engineered TCRs or CARs. These 3'-UTR sequences are sensitive to regulation by translation initiation factor eIF3 and can be used to modulate the strength and time duration of TCR or CAR protein synthesis.

SUGGESTED USES

The use of engineered TCRs or CARs involves genetically modifying T cells or NK cells with a DNA sequence encoding the engineered TCR or CAR. The noncoding elements disclosed herein can be stably introduced into primary T cells, NK cells and induced pluripotent stem cells (iPSCs) that are subsequently differentiated into T cells or NK cells. These modified cells can then be expanded and used for ACT, organ transplantation, or treatment of autoimmune diseases.

ADVANTAGES

- higher crosslinking efficiency compared to 254 nm CLIP
- diagnostic T-to-C transitions in the sequence at positions where the RBP crosslinks to the RNA

RELATED MATERIALS

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

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OTHER INFORMATION

KEYWORDS

engineered, NK cell, transplant, autoimmune, cancer, T cell, T-cell, TCR, CAR, immune cell receptor, adoptive cell therapy, ACT

CATEGORIZED AS

- **Biotechnology**
- Genomics
- Health

RELATED CASES

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