METHODS AND COMPOSITIONS COMPRISING MHC CLASS I PEPTIDES

BACKGROUND OF THE INVENTION

[0001] This application claims priority of U.S. Provisional Patent Application No. 63/176,477, filed April 19, 2021, which is hereby incorporated by reference in its entirety.

I. Field of the Invention

[0002] This invention relates to the field of treatment of cancer.

II. Background

[0003] Adoptive T cell therapy (ACT; also referred to as an "adoptive cell transfer") has shown significant promise as a method for treating melanoma; unfortunately, this approach has also been hindered by limitations including toxicity towards non-cancerous tissues. ACT generally involves which involves infusing a large number of autologous activated tumor-specific T cells into a patient, e.g., to treat a cancer. ACT has resulted in therapeutic clinical responses in melanoma patients (Yee 2002; Dudley 2002; Yee 2014; Chapuis 2016). Generally, to develop effective anti-tumor T cell responses, the following three steps are normally required: priming and activating antigen-specific T cells, migrating activated T cells to tumor site, and recognizing and killing tumor by antigen-specific T cells. The choice of target antigen is important for induction of effective antigen-specific T cells.

[0004] While several tumor-associated antigens have been identified for melanoma and a handful of other solid tumor malignancies, there are few immunogenic targets for pancreatic, ovarian, gastric, lung, cervical, breast, and head and neck cancer. Identification and validation of novel epitopes and target antigens for these common and difficult to treat malignancies is warranted.

SUMMARY OF THE INVENTION

[0004a] In one aspect, provided herein is an engineered T-cell Receptor (TCR) comprising a TCR-a region and a TCR-b region, wherein the TCR-a region comprises a CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:21, 22, and 23, respectively and the TCR-b region comprises a CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:28, 29, and 30, respectively.

[0004b] In another aspect, provided herein is a polypeptide comprising the TCR of as described herein, wherein the polypeptide is bi-specific.

[0004c] In another aspect, provided herein is a fusion protein comprising the TCR or polypeptide as described herein and a CD3 binding region and wherein the CD3 binding region comprises a CD3-specific fragment antigen binding (Fab), single chain variable fragment (scFv), single domain antibody, or single chain antibody.

[0004d] In another aspect, provided herein is one or more nucleic acid(s) encoding for the TCR, fusion protein, or polypeptide as described herein.

[0004e] In another aspect, provided herein is a cell comprising the TCR, fusion protein, or polypeptide as described herein or the nucleic acid as described herein.

[0004f] In another aspect, provided herein is a composition comprising the polypeptide, fusion protein, or TCR as described herein, the nucleic acid(s) as described herein, or the cell as described herein.

[0004g] In another aspect, provided herein is a method of making an engineered cell comprising transferring the nucleic acid as described herein into a cell.

[0004h] In another aspect, provided herein is use of the composition as described herein in the manufacture of a medicament for treating or preventing cancer in a subject or for stimulating an immune response in a subject, wherein the cancer is a Hormad1-expressing cancer.

[0004i] In another aspect, provided herein is the composition as described herein for use in therapy.

[0005] The current disclosure fulfills a need in the art by providing methods and compositions for treating and vaccinating individuals against cancer. Accordingly, aspects of the disclosure relate to an isolated peptide comprising at least 70% sequence identity to a peptide of IYNGKLFDL (SEQ ID NO:1) or SSSQESVPK (SEQ ID NO:2). Also disclosed is a molecular complex comprising a peptide of the disclosure and a MHC polypeptide. Further aspects relate to pharmaceutical compositions comprising the isolated peptide, molecular complexes, nucleic acids encoding the peptide, expression vectors, and host cells comprising the nucleic acids and peptides of the disclosure. Also provided is an *in vitro* isolated dendritic

WHAT IS CLAIMED IS:

1. An engineered T-cell Receptor (TCR) comprising a TCR-a region and a TCR-b region, wherein the TCR-a region comprises a CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:21, 22, and 23, respectively and the TCR-b region comprises a CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:28, 29, and 30, respectively.

2. The TCR of claim 1, wherein the TCR-a region comprises the amino acid sequence of SEQ ID NO:19 or an amino acid sequence with at least 70% sequence identity to SEQ ID NO:19 and the TCR-b region comprises the amino acid sequence of SEQ ID NO:26 or an amino acid sequence with at least 70% sequence identity to SEQ ID NO:26.

3. The TCR of claim 1 or 2, wherein the TCR is a single chain TCR, wherein the TCR-a region and the TCR-b region are on different polypeptides, or wherein the TCR-a region and the TCR-b region are on the same polypeptide.

4. A polypeptide comprising the TCR of any one of claims 1-3, wherein the polypeptide is bi-specific.

5. A fusion protein comprising the TCR or polypeptide of any one of claims 1-4 and a CD3 binding region and wherein the CD3 binding region comprises a CD3-specific fragment antigen binding (Fab), single chain variable fragment (scFv), single domain antibody, or single chain antibody.

6. The polypeptide, fusion protein, or TCR of any one of claims 1-5, wherein the polypeptide further comprises a signal peptide or wherein the polypeptide comprises a signal peptide comprising the amino acid sequence of one of SEQ ID NOs:20, 27, 6, or 13 or an amino acid sequence with at least 80% identity to one of SEQ ID NOs:20, 27, 6, or 13.

7. One or more nucleic acid(s) encoding for the TCR, fusion protein, or polypeptide of any one of claims 1-6.

8. A cell comprising the TCR, fusion protein, or polypeptide of any one of claims 1-6 or the nucleic acid of claim 7.

9. The cell of claim 8, wherein the cell comprises a stem cell, a progenitor cell, an immune cell, a natural killer (NK) cell, a hematopoietic stem or progenitor cell, a T cell, a cell differentiated from mesenchymal stem cells (MSCs), an induced pluripotent stem cell (iPSC), a cell isolated or derived from peripheral blood mononuclear cell (PBMCs), a cell isolated from a cancer patient, and/or a T cell selected from a cytotoxic T lymphocyte (CTL), a $CD8^+$ T cell, a $CD4^+$ T cell, an invariant NK T (iNKT) cell, a gamma-delta T cell, a NKT cell, a regulatory T cell, or a $CD4^+$ regulatory cell.

10. A composition comprising the polypeptide, fusion protein, or TCR of any one of claims 1-6, the nucleic acid(s) of claim 7, or the cell of claim 8 or 9.

11. A method of making an engineered cell comprising transferring the nucleic acid of 7 into a cell.

12. Use of the composition of claim 10 in the manufacture of a medicament for treating or preventing cancer in a subject or for stimulating an immune response in a subject, wherein the cancer is a Hormad1-expressing cancer.

13. The use of claim 12, wherein the subject is a human, the subject has been diagnosed with cancer, the cancer comprises a cancer that is positive for expression of a peptide SEQ ID NO: 2, wherein the peptide-specific T cells are autologous or allogeneic; and/or wherein treating comprises one or more of reducing tumor size; increasing the overall survival rate; reducing the risk of recurrence of the cancer; reducing the risk of progression; and/or increasing the chance of progression-free survival, relapse-free survival, and/or recurrence-free survival.

14. The use of 12 or 13, wherein the cancer comprises leukemia, lung cancer, skin cancer, a solid tumor, adenocarcinoma, and/or squamous cell carcinoma.

15. The composition of claim 14 for use in therapy.