ANTI-MUTATED KRAS T CELL RECEPTORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/084,654, filed November 26, 2014 and U.S. Provisional Patent Application No. 62/171,321, filed June 5, 2015, each of which is incorporated by reference in its entirety herein.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 231,164 Byte ASCII (Text) file named "722261_ST25.txt," dated November 20, 2015.

BACKGROUND OF THE INVENTION

[0003] Some cancers may have very limited treatment options, particularly when the cancer becomes metastatic and unresectable. Despite advances in treatments such as, for example, surgery, chemotherapy, and radiation therapy, the prognosis for many cancers, such as, for example, pancreatic, colorectal, lung, endometrial, ovarian, and prostate cancers, may be poor. Accordingly, there exists an unmet need for additional treatments for cancer.

SUMMARY

[0004] In one aspect, the present disclosure refers to an isolated or purified T cell receptor (TCR) having antigenic specificity for a mutated epitope presented in the context of an HLA-A11 molecule, the mutated epitope (a) comprising VVVGADGVGK (SEQ ID NO: 2) or (b) consisting of VVVGAVGVGK (SEQ ID NO: 33) or VVGAVGVGK (SEQ ID NO: 35)., wherein the TCR comprises (a) an α chain complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 3, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 4, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 5, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 6, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a β chain

CDR3 comprising the amino acid sequence of SEQ ID NO: 8; (b) an α chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 125, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 126, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 127, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 128, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 129, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 130; (c) an α chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 137, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 138, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 139, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 140, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 141, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 142; (d) an α chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 149, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 150, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 151, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 152, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 153, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 154; or (e) an α chain CDR1 comprising the amino acid sequence of SEQ ID NO: 149, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 150, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 207, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 152, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 153, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 154. In another aspect, the present disclosure refers to an isolated or purified protein comprising (a) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 3-5 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 6-8; (b) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 125-127 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 128-130; (c) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 137-139 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 140-142; (d) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 149-151 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 152-154; or (e) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 149, 150, and 207 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 152-154. In another aspect, there is disclosed an isolated or purified nucleic

acid comprising a nucleotide sequence encoding the TCR as disclosed herein, the polypeptide as disclosed herein, or the protein according as disclosed herein. In a further aspect, the present disclosure refers to a recombinant expression vector comprising the nucleic acid as disclosed herein. In yet another aspect, the present disclosure refers to an isolated host cell comprising the recombinant expression vector as disclosed herein. In one aspect, the present disclosure refers to a population of cells comprising at least one host cell as disclosed herein. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the TCR as disclosed herein, the polypeptide as disclosed herein, the protein as disclosed herein, the nucleic acid as disclosed herein, the recombinant expression vector as disclosed herein, the host cell as disclosed herein, or the population as disclosed herein, and a pharmaceutically acceptable carrier. In yet another aspect, the present disclosure refers to use of the host cell as disclosed herein or the population of cells as disclosed herein in the manufacture of a medicament for the treatment of cancer in a mammal. In a further aspect, the present disclosure refers to a method of detecting the presence of cancer in a mammal, the method comprising contacting a sample comprising one or more cells from the mammal with the host cell as disclosed herein or the population of cells as disclosed herein, wherein the TCR, polypeptide, or protein is expressed from the host cell or the population of cells, thereby forming a complex between the TCR, polypeptide, and protein and a cancer antigen, and detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal. In one example, there is disclosed an isolated or purified T cell receptor (TCR) having antigenic specificity for a mutated epitope, the mutated epitope (a) comprising VVVGADGVGK (SEQ ID NO: 2) or (b) consisting of VVVGAVGVGK (SEQ ID NO: 33) or VVGAVGVGK (SEQ ID NO: 35).

[0005] Further disclosed herein are related polypeptides and proteins, as well as related nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions relating to the TCRs of the invention.

[0006] Methods of detecting the presence of cancer in a mammal and methods of treating or preventing cancer in a mammal are further provided by the invention.

CLAIM(S):

1. An isolated or purified T cell receptor (TCR) having antigenic specificity for a mutated epitope presented in the context of an HLA-A11 molecule, the mutated epitope (a) comprising VVVGADGVGK (SEQ ID NO: 2) or (b) consisting of VVVGAVGVGK (SEQ ID NO: 33) or VVGAVGVGK (SEQ ID NO: 35), wherein the TCR comprises:

(a) an α chain complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 3, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 4, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 5, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 6, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8;

(b) an α chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 125, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 126, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 127, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 128, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 129, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 130;

(c) an α chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 137, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 138, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 139, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 140, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 141, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 142;

(d) an α chain CDR 1 comprising the amino acid sequence of SEQ ID NO: 149, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 150, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 151, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 152, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 153, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 154; or

(e) an α chain CDR1 comprising the amino acid sequence of SEQ ID NO: 149, an α chain CDR2 comprising the amino acid sequence of SEQ ID NO: 150, an α chain CDR3 comprising the amino acid sequence of SEQ ID NO: 207, a β chain CDR1 comprising the amino acid sequence of SEQ ID NO: 152, a β chain CDR2 comprising the amino acid sequence of SEQ ID NO: 153, and a β chain CDR3 comprising the amino acid sequence of SEQ ID NO: 154.

2. The isolated or purified TCR of claim 1, comprising:

(a) an α chain variable region comprising the amino acid sequence of SEQ ID NO: 9 and a β chain variable region comprising the amino acid sequence of SEQ ID NO: 10;

(b) an α chain variable region comprising the amino acid sequence of SEQ ID NO: 131 and a β chain variable region comprising the amino acid sequence of SEQ ID NO: 132;

(c) an α chain variable region comprising the amino acid sequence of SEQ ID NO: 143 and a β chain variable region comprising the amino acid sequence of SEQ ID NO: 144;

(d) an α chain variable region comprising the amino acid sequence of SEQ ID NO: 155 and a β chain variable region comprising the amino acid sequence of SEQ ID NO: 156; or

(e) an α chain variable region comprising the amino acid sequence of SEQ ID NO: 208 and a β chain variable region comprising the amino acid sequence of SEQ ID NO: 156.

3. The isolated or purified TCR of claim 1 or 2, further comprising:

(a) an α chain constant region comprising the amino acid sequence of SEQ ID NO: 13 and a β chain constant region comprising the amino acid sequence of SEQ ID NO: 14;

(b) an α chain constant region comprising the amino acid sequence of SEQ ID NO: 135 and a β chain constant region comprising the amino acid sequence of SEQ ID NO: 136;

(c) an α chain constant region comprising the amino acid sequence of SEQ ID NO: 147 and a β chain constant region comprising the amino acid sequence of SEQ ID NO: 148; or

(d) an α chain constant region comprising the amino acid sequence of SEQ ID NO: 159 and a β chain constant region comprising the amino acid sequence of SEQ ID NO: 160.

4. The isolated or purified TCR of any one of claims 1-3, comprising:

(a) an α chain comprising the amino acid sequence of SEQ ID NO: 11 and a β chain comprising the amino acid sequence of SEQ ID NO: 12;

(b) an α chain comprising the amino acid sequence of SEQ ID NO: 133 and a β chain comprising the amino acid sequence of SEQ ID NO: 134;

(c) an α chain comprising the amino acid sequence of SEQ ID NO: 145 and a β chain comprising the amino acid sequence of SEQ ID NO: 146;

(d) an α chain comprising the amino acid sequence of SEQ ID NO: 157 and a β chain comprising the amino acid sequence of SEQ ID NO: 158; or

(e) an α chain comprising the amino acid sequence of SEQ ID NO: 209 and a β chain comprising the amino acid sequence of SEQ ID NO: 158.

5. The TCR of any one of claims 1-4, having antigenic specificity for the mutated epitope comprising VVVGADGVGK (SEQ ID NO: 2).

6. The TCR of any one of claims 1-4, having antigenic specificity for the mutated epitope consisting of VVVGAVGVGK (SEQ ID NO: 33) or VVGAVGVGK (SEQ ID NO: 35).

7. An isolated or purified polypeptide comprising a functional portion of the TCR of any one of claims 1-4, wherein the functional portion comprises:

(i) the amino acid sequences of SEQ ID NOs: 3-8;

(ii) the amino acid sequences of SEQ ID NOs: 125-130;

(iii) the amino acid sequences of SEQ ID NOs: 137-142;

(iv) the amino acid sequences of SEQ ID NOs: 149-154; or

(v) the amino acid sequences of SEQ ID NOs: 149-150, 207, and 152-154.

8. An isolated or purified polypeptide comprising a functional portion of the TCR of any one of claims 1-4, wherein the functional portion comprises:

(i) the amino acid sequence of both SEQ ID NOs: 9 and 10;

(ii) the amino acid sequence of both SEQ ID NOs: 131 and 132;

(iii) the amino acid sequence of both SEQ ID NOs: 143 and 144;

(iv) the amino acid sequence of both SEQ ID NOs: 155 and 156; or

(v) the amino acid sequence of both SEQ ID NOs: 208 and 156.

9. An isolated or purified polypeptide comprising a functional portion of the TCR of any one of claims 1-4, wherein the functional portion comprises:

(i) the amino acid sequence of both SEQ ID NOs: 11 and 12;

(ii) the amino acid sequence of both SEQ ID NOs: 133 and 134;

(iii) the amino acid sequence of both SEQ ID NOs: 145 and 146;

(iv) the amino acid sequence of both SEQ ID NOs: 157 and 158; or

(v) the amino acid sequence of both SEQ ID NOs: 209 and 158.

10. An isolated or purified protein comprising:

(a) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 3-5 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 6-8;

(b) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 125-127 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 128-130;

(c) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 137-139 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 140-142;

(d) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 149-151 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 152-154; or

(e) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 149, 150, and 207 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 152-154.

11. The isolated or purified protein according to claim 10, comprising:

(a) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 9 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 10;

(b) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 131 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 132;

(c) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 143 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 144;

(d) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 155 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 156; or

(e) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 208 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 156.

12. The isolated or purified protein of claim 10 or 11, comprising:

(a) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 11 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 12;

(b) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 133 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 134;

(c) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 145 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 146;

(d) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 157 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 158; or

(e) a first polypeptide chain comprising the amino acid sequence of SEQ ID NO: 209 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NO: 158.

13. An isolated or purified nucleic acid comprising a nucleotide sequence encoding the TCR according to any one of claims 1-6, the polypeptide according to any one of claims 7-9, or the protein according to any one of claims 10-12.

14. A recombinant expression vector comprising the nucleic acid according to claim 13.

15. An isolated host cell comprising the recombinant expression vector of claim 14.

16. The host cell according to claim 15, wherein the cell is human.

17. A population of cells comprising at least one host cell of claim 15 or 16.

18. A pharmaceutical composition comprising the TCR according to any one of claims 1-6, the polypeptide according to any one of claims 7-9, the protein according to any one of claims 10-12, the nucleic acid according to claim 13, the recombinant expression vector of claim 14, the host cell of claim 15 or 16, or the population of cells of claim 17, and a pharmaceutically acceptable carrier.

19. Use of the host cell of claim 15 or 16 or the population of cells of claim 17 in the manufacture of a medicament for the treatment of cancer in a mammal.

20. A method of detecting the presence of cancer in a mammal, the method comprising

contacting a sample comprising one or more cells from the mammal with the host cell of claim 15 or 16 or the population of cells of claim 17, wherein the TCR, polypeptide, or protein is expressed from the host cell or the population of cells, thereby forming a complex between the TCR, polypeptide, and protein and a cancer antigen, and

detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal.

21. The use of claim 19 or the method of claim 20, wherein the cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.

22. The use of claim 19 or 21 or the method of claim 20 or 21, wherein host cell is a peripheral blood lymphocyte.

23. The use of claim 19 or 21 or the method of claim 20 or 21, wherein population of cells comprises peripheral blood lymphocytes.

24. The method of claim 20, wherein the sample comprises whole cells, lysates thereof, or a fraction of the whole cell lysates.