[NPL 28] Allan VJ, and Schroer TA. Curr Opin Cell Biol 1999;11:476-82.
[NPL 29] Taniuchi K, et al. Cancer Res 2005;65:105-12.

Summary ~~of Invention~~

[0011] The present disclosure~~invention~~ is based in part on the discovery of new targets of immunotherapy. Because TAAs have often no immunogenicity, the discovery of appropriate targets is of extreme importance. In particular, the present disclosure~~invention~~ targets RAB6KIFL (SEQ ID NO: 2) encoded by the gene of GenBank Accession No. AF153329 or CR598555, also indicated by NM_005733 (SEQ ID NO: 1)), since RAB6KIFL has been identified as up-regulated in several cancers such as bladder cancer, breast cancer, cholangiocellular carcinoma, esophageal cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, prostate cancer, renal carcinoma and small cell lung cancer (SCLC). The present disclosure~~invention~~ provides a RAB6KIFL gene products containing epitope peptides that elicit surprisingly strong CTL response that is specific to the corresponding molecules. Peripheral blood mononuclear cells (PBMCs) obtained from a healthy donor were stimulated using the peptides of the present disclosure~~invention~~. The present disclosure~~invention~~ further provides established CTLs that specifically recognize HLA-A2 (A*0201) positive target cells pulsed with the respective peptides, and HLA-A2 (A*0201) restricted epitope peptides that can induce potent and specific immune responses against RAB6KIFL expressed on tumor. These results demonstrate that RAB6KIFL is strongly immunogenic and the epitopes thereof are effective targets for tumor immunotherapy.

[0012] Accordingly, it is an object of the present disclosure~~invention~~ to provide oligopeptides having CTL inducibility as well as an amino acid sequence selected from the group of SEQ ID NOs: 3, 4 and 5. In addition, in another embodiment of the present disclosure~~invention~~, one, two or several amino acids may be substituted, deleted, inserted and/or added, so long as the resulting modified oligopeptides retain the CTL inducibility of the original peptides.

[0012a] In an aspect, there is provided an isolated oligopeptide of less than 15 amino acids, wherein the oligopeptide is selected from the group consisting of: (a) an oligopeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 3, and 5; and (b) an oligopeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 3, and 5, in which 1 or 2 amino acids are substituted, deleted, inserted and/or added, and wherein the oligopeptide has cytotoxic T lymphocyte (CTL) inducibility.

[0012b] In another aspect, there is provided a polynucleotide encoding the oligopeptide as defined herein.

[0013] When administered to a subject, the present oligopeptides are presented on the surface of antigen-expressing cells and then induce CTLs targeting the respective peptides. Therefore, it is an object of the present disclosure~~invention~~ to provide antigen-presenting cells and exosomes that present any of the present peptides, as well as methods for inducing antigen-presenting cells.

[0013a] In another aspect, there is provided an exosome that presents on its surface a complex comprising the oligopeptide as defined herein, and an HLA antigen.

[0013b] In another aspect, there is provided an in vitro method for inducing an antigen-presenting cell, wherein the method comprises a step selected from the group consisting of: (a) contacting an antigen-presenting cell with the oligopeptide as defined herein, and (b) introducing a polynucleotide encoding the oligopeptide as defined herein into an antigen-presenting cell.

[0013c] In another aspect, there is provided an in vitro method for inducing a CTL, wherein the method comprises a step selected from the group consisting of: (a) contacting a CD8-positive T cell with an antigen-presenting cell and/or an exosome that presents the oligopeptide as defined herein on its surface, and (b) introducing a polynucleotide encoding a polypeptide that is capable of forming a T cell receptor (TCR) subunit binding to a complex of the oligopeptide as defined herein and an HLA antigen on an antigen-presenting cell surface, into a CD8-positive T cell.

[0013d] In another aspect, there is provided an isolated CTL, which targets the oligopeptide as defined herein.

[0013e] In another aspect, there is provided the isolated CTL, which is induced by using the oligopeptide as defined herein.

[0013f] In another aspect, there is provided an isolated antigen-presenting cell that presents on its surface a complex of an HLA antigen and the oligopeptide as defined herein.

[0014] An anti-tumor immune response is induced by the administration of the present RAB6KIFL oligopeptides or polynucleotides encoding the oligopeptides, as well as exosomes and antigen-presenting cells which present the RAB6KIFL oligopeptides. Therefore, it is yet another object of the present disclosure~~invention~~ to provide pharmaceutical agents or pharmaceutical composition containing the oligopeptides or polynucleotides

encoding them, as well as the exosomes and antigen-presenting cells as their active ingredients. The pharmaceutical agents or pharmaceutical compositions of the present disclosure~~invention~~ find use as vaccines.

[0014a] In another aspect, there is provided a pharmaceutical composition for use in treating and/or prophylaxis of cancer, and/or preventing postoperative recurrence thereof, wherein the composition comprises a pharmaceutically acceptable carrier and one or more oligopeptides as defined herein, or a polynucleotide encoding the oligopeptide.

[0014b] In another aspect, there is provided the oligopeptide as defined herein for use in a method for inducing an antigen-presenting cell.

[0014c] In another aspect, there is provided the oligopeptide as defined herein for use in a method for inducing a CTL.

[0014d] In another aspect, there is provided a vaccine for use in a method of inducing immune response against cancer in a subject, wherein the vaccine comprises at least one active ingredient selected from the group consisting of: (a) one or more oligopeptides as defined herein; (b) one or more polynucleotides encoding the oligopeptide as defined herein; (c) one or more isolated CTLs as defined herein; (d) one or more isolated antigen-presenting cells as defined herein.

[0014e] In another aspect, there is provided a pharmaceutical composition for use in inducing a CTL, wherein the composition comprises a pharmaceutically acceptable carrier and one or more oligopeptide(s) as defined herein, a polynucleotide encoding the oligopeptide, or an isolated antigen-presenting cell as defined herein.

[0014f] In another aspect, there is provided the use of an active ingredient selected from the group consisting of: (a) one or more oligopeptides as defined herein; (b) one or more polynucleotides encoding the oligopeptide as defined herein as in an expressible form; (c) one or more antigen-presenting cells presenting the oligopeptide as defined herein; and (d) one or more CTLs that is capable of binding to a complex of the oligopeptide as defined herein and an HLA antigen on an antigen-presenting cell surface, in manufacturing a pharmaceutical composition or agent for treating cancer.

[0015] Moreover, it is a further object of the present disclosure~~invention~~ to provide methods for the treatment and/or prophylaxis of (i.e., prevention) cancers (tumors), and/or prevention of postoperative recurrence thereof, as well as methods for inducing CTLs, methods for inducing anti-tumor immunity, such methods including the step of administering the RAB6KIFL oligopeptides, polynucleotides encoding RAB6KIFL oligopeptides, exosomes or the antigen-presenting cells presenting RAB6KIFL polypeptides or the pharmaceutical agents of the present disclosure~~invention~~. In addition, the CTLs of the present disclosure~~invention~~ also find use as vaccines against cancer. Examples of target cancers include, but are not limited to bladder cancer, breast cancer, cholangiocellular carcinoma, esophageal cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, prostate cancer, renal carcinoma and small cell lung cancer (SCLC).

[0016] It is to be understood that both the foregoing summary of the present disclosure~~invention~~ and the following detailed description are of exemplified embodiments, and not restrictive of the present disclosure~~invention~~ or other alternate embodiments of the present disclosure~~invention~~.

Brief Description of Drawings

[0017] Various aspects and applications of the present invention will become apparent to the skilled artisan upon consideration of the brief description of the figures and the detailed description of the present invention and its preferred embodiments which follows:

[0018] [fig.1]Figure 1 depicts markedly and frequently enhanced expression of RAB6KIFL mRNA in pancreatic cancer tissues as based on a cDNA microarray analysis. A depicts a list of up-regulated genes in pancreatic cancer cells. These genes were overexpressed in cancer cells in comparison to their normal counterparts. The expression of RAB6KIFL mRNA in pancreatic cancer cells was markedly enhanced in all of 6 pancreatic cancer patients. B depicts the relative expression ratio of RAB6KIFL gene in normal tissues based on a cDNA microarray analysis. RAB6KIFL gene was faintly expressed only in the testis and thymus. C depicts the expression level of the RAB6KIFL gene was also enhanced in many lung and bladder cancers as well as pancreatic cancer based on the previous cDNA microarray analysis.
[fig.2]Figure 2 depicts the analyses of RAB6KIFL mRNA expressed in human normal tissues, cancer cell lines, and cancer tissues. A depicts the expression of RAB6KIFL mRNA was investigated in various normal tissues by using RT-PCR analysis. RAB6KIFL mRNA was faintly expressed only in testis. B depicts the RT-PCR analysis of the RAB6KIFL expression in various cancer cell lines. C depicts the RT-

Claims

[Claim 1] An isolated oligopeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 4 and 5.

[Claim 2] The oligopeptide of claim 1, wherein 1, 2, or several amino acids are substituted, deleted, inserted and/or added, wherein the oligopeptide has cytotoxic T lymphocyte (CTL) inducibility.

[Claim 3] The oligopeptide of claim 2, wherein the oligopeptide has at least one substitution selected from the group consisting of:
(a) the second amino acid from the N-terminus is leucine or methionine, and
(b) the C-terminal amino acid is valine or leucine.

[Claim 4] A pharmaceutical agent for treating and/or prophylaxis of cancer, and/or preventing postoperative recurrence thereof, wherein the agent comprises a pharmaceutically acceptable carrier and one or more oligopeptides of any one of claims 1 to 3, or a polynucleotide encoding the oligopeptide.

[Claim 5] The pharmaceutical agent of claim 4, which is formulated for the administration to a subject whose HLA antigen is HLA-A2.

[Claim 6] The pharmaceutical agent of claim 4, wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, cholangiocellular carcinoma, esophageal cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, prostate cancer, renal carcinoma and small cell lung cancer (SCLC).

[Claim 7] The pharmaceutical agent of claim 4, which is a vaccine.

[Claim 8] An exosome that presents on its surface a complex comprising the oligopeptide of any one of claims 1 to 3, and an HLA antigen.

[Claim 9] The exosome of claim 8, wherein the HLA antigen is HLA-A2.

[Claim 10] A method for inducing an antigen-presenting cell by using the oligopeptide of any one of claims 1 to 3.

[Claim 11] The method of claim 10, wherein the method comprising the step selected from the group consisting of:
(a) contacting an antigen-presenting cell with the oligopeptide of any one of claims 1 to 3, and
(b) introducing a polynucleotide encoding the oligopeptide of any one of claims 1 to 3 into an antigen-presenting cell.

[Claim 12] A method for inducing a CTL by using the oligopeptide of any one of claims 1 to 3.

[Claim 13] The method of claim 12, wherein the method comprising the step selected from the group consisting of:
(a) contacting a CD8-positive T cell with an antigen-presenting cell and/or an exosome that present the oligopeptide of any one of claims 1 to 3 on its surface, and
(b) introducing a polynucleotide encoding a polypeptide that is capable of forming a T cell receptor (TCR) subunit binding to a complex of the oligopeptide of any one of claims 1 to 3 and an HLA antigen on an antigen-presenting cell surface, into a CD8-positive T cell.

[Claim 14] An isolated CTL, which targets the oligopeptide of any one of claims 1 to 3.

[Claim 15] The CTL of claims 14, which is capable of binding to a complex of the oligopeptide of any one of claims 1 to 3 and an HLA antigen on an antigen-presenting cell surface.

[Claim 16] The isolated CTL, which is induced by using the oligopeptide of any one of claims 1 to 3.

[Claim 17] The CTL of claim 16, which is induced by the method of claim 13.

[Claim 18] An isolated antigen-presenting cell that presents on its surface a complex of an HLA antigen and the oligopeptide of any one of claims 1 to 3.

[Claim 19] The antigen-presenting cell of claim 18, which is induced by the method of claim 10 or 11.

[Claim 20] A method of inducing immune response against cancer in a subject, which comprising the step of administering to said subject a vaccine comprising at least one active ingredient selected from the group consisting of:
(a) one or more oligopeptides of any one claims 1 to 3, or an immunologically active fragment thereof;
(b) one or more polynucleotides encoding the oligopeptide of any one of claims 1 to 3, or an immunologically active fragment thereof;
(c) one or more isolated CTLs of any one of claims 14 to 17;
(d) one or more isolated antigen-presenting cells of claim 18 or 19.

[Claim 21] A pharmaceutical agent for inducing a CTL, wherein the agent comprises a pharmaceutically acceptable carrier and one or more oligopeptide(s) of any one of claims 1 to 3, a polynucleotide encoding the oligopeptide, or an isolated antigen-presenting cell of claim 18 or 19.

~~[Claim 22] Use of an active ingredient selected from the group consisting of :~~

(a) one or more oligopeptides of any one of claims 1 to 3;
(b) one or more polynucleotides encoding the oligopeptide of any one of claims 1 to 3 as in an expressible form;
(c) one or more antigen-presenting cells presenting the oligopeptide of any one of claims 1 to 3; and
(d) one or more CTLs that is capable of binding to a complex of the oligopeptide of any one of claims 1 to 3 and an HLA antigen on an antigen-presenting cell surface,
in manufacturing a pharmaceutical composition or agent for treating cancer.

~~[Claim 23] A polynucleotide encoding the oligopeptide of any one of claims 1 to 3.~~

CLAIMS

1. An isolated oligopeptide of less than 15 amino acids, wherein the oligopeptide is selected from the group consisting of:

   (a) an oligopeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 3, and 5; and

   (b) an oligopeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 3, and 5, in which 1 or 2 amino acids are substituted, deleted, inserted and/or added, and wherein the oligopeptide has cytotoxic T lymphocyte (CTL) inducibility.

2. The oligopeptide of claim 1, wherein the oligopeptide has at least one substitution selected from the group consisting of:

   (a) the second amino acid from the N-terminus is leucine or methionine, and

   (b) the C-terminal amino acid is valine or leucine.

3. The oligopeptide of claim 1, consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 3, and 5.

4. A pharmaceutical composition for use in treating and/or prophylaxis of cancer, and/or preventing postoperative recurrence thereof, wherein the composition comprises a pharmaceutically acceptable carrier and one or more oligopeptides of any one of claims 1 to 3, or a polynucleotide encoding the oligopeptide.

5. The pharmaceutical composition for use as in claim 4, which is formulated for the administration to a subject whose HLA antigen is HLA-A2.

6. The pharmaceutical composition for use as in claim 4, wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, cholangiocellular carcinoma, esophageal cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, prostate cancer, renal carcinoma and small cell lung cancer (SCLC).

7. The pharmaceutical composition for use as in claim 4, which is a vaccine.

8. An exosome that presents on its surface a complex comprising the oligopeptide of any one of claims 1 to 3, and an HLA antigen.

9. The exosome of claim 8, wherein the HLA antigen is HLA-A2.

10. The oligopeptide of any one of claims 1 to 3 for use in a method for inducing an antigen-presenting cell.

11. An in vitro method for inducing an antigen-presenting cell, wherein the method comprises a step selected from the group consisting of:

   (a) contacting an antigen-presenting cell with the oligopeptide of any one of claims 1 to 3, and

   (b) introducing a polynucleotide encoding the oligopeptide of any one of claims 1 to 3 into an antigen-presenting cell.

12. The oligopeptide of any one of claims 1 to 3 for use in a method for inducing a CTL.

13. An in vitro method for inducing a CTL, wherein the method comprises a step selected from the group consisting of:

    (a) contacting a CD8-positive T cell with an antigen-presenting cell and/or an exosome that presents the oligopeptide of any one of claims 1 to 3 on its surface, and

    (b) introducing a polynucleotide encoding a polypeptide that is capable of forming a T cell receptor (TCR) subunit binding to a complex of the oligopeptide of any one of claims 1 to 3 and an HLA antigen on an antigen-presenting cell surface, into a CD8-positive T cell.

14. An isolated CTL, which targets the oligopeptide of claim 1 or 2.

15. The CTL of claim 14, which is capable of binding to a complex of the oligopeptide of any one of claims 1 to 3 and an HLA antigen on an antigen-presenting cell surface.

16. The isolated CTL, which is induced by using the oligopeptide of any one of claims 1 to 3.

17. The CTL of claim 16, which is induced by the method of claim 13.

18. An isolated antigen-presenting cell that presents on its surface a complex of an HLA antigen and the oligopeptide of any one of claims 1 to 3.

19. The antigen-presenting cell of claim 18, which is induced by using the oligopeptide of claim 10 or by the method of claim 11.

20. A vaccine for use in a method of inducing immune response against cancer in a subject, wherein the vaccine comprises at least one active ingredient selected from the group consisting of:

    (a) one or more oligopeptides of any one of claims 1 to 3;

    (b) one or more polynucleotides encoding the oligopeptide of any one of claims 1 to 3;

    (c) one or more isolated CTLs of any one of claims 14 to 17;

    (d) one or more isolated antigen-presenting cells of claim 18 or 19.

21. A pharmaceutical composition for use in inducing a CTL, wherein the composition comprises a pharmaceutically acceptable carrier and one or more oligopeptide(s) of any one of claims 1 to 3, a polynucleotide encoding the oligopeptide, or an isolated antigen-presenting cell of claim 18 or 19.

22. Use of an active ingredient selected from the group consisting of:

(a) one or more oligopeptides of any one of claims 1 to 3;

(b) one or more polynucleotides encoding the oligopeptide of any one of claims 1 to 3 as in an expressible form;

(c) one or more antigen-presenting cells presenting the oligopeptide of any one of claims 1 to 3; and

(d) one or more CTLs that is capable of binding to a complex of the oligopeptide of any one of claims 1 to 3 and an HLA antigen on an antigen-presenting cell surface,
in manufacturing a pharmaceutical composition or agent for treating cancer.

23. A polynucleotide encoding the oligopeptide of any one of claims 1 to 3.