or down-regulation of TAAs as a consequence of therapeutically driven immune selection.

[0006] CDCA1, cell division cycle associated 1, was identified as a member of a class of genes that are coexpressed with cell cycle genes, such as CDC2, cyclin, topoisomerase II and the others (Walker et al., Curr Cancer Drug Targets 2001 May;1(1):73-83). CDCA1 in particular was found to be associated with centromeres of mitotic HeLa cells and was therefore considered a functional homologue of yeast Nuf2 (J Cell Biol 2001 Jan 22; 152(2):349-60).

[0007] In addition, through gene expression profile analysis using a genome-wide cDNA microarray containing 23,040 genes (Cancer Res 2006 Nov 1; 66(21):10339-48), CDCA1 has also been identified as a novel molecule up-regulated in breast cancer (WO2005/028676), bladder cancer (WO2006/085684), esophageal cancer (WO2007/013671), small cell lung cancer (SCLC) (WO2007/013665) and non-small cell lung cancer (NSCLC) (WO2005/089735), the contents of such disclosure being incorporated by reference herein. Expression of CDCA1 was particularly up-regulated in SCLC, NSCLC and tumor cell lines, though no expression was detected except testis among 23 normal tissues. Furthermore, down-regulation of CDCA1 expression by siRNA caused cell growth suppression in CDCA1 expressing lung cancer cell lines (WO2005/089735).

[0008] Taken together, this data suggests that CDCA1 is a novel, potentially universal on-coantigen. Accordingly, epitope peptides derived from CDCA1 may be applicable as cancer immunotherapeutics for the treatment of a wide array of cancers.

Summary

[0009] The present disclosure is based in part on the discovery of the suitable epitope peptides that may serve as targets of immunotherapy. Recognizing that CDCA1 are up-regulated in a number of cancer types, including breast cancer, bladder cancer, non-small cell lung cancer, small cell lung cancer and esophageal cancer, the present disclosure targets this cell division cycle associated 1 (CDCA1) (SEQ ID NO: 35 encoded by the gene of GenBank Accession No. NM_145697 (SEQ ID NO: 34)) for further analysis. In particular,CDCA1 gene products containing epitope peptides that elicit CTLs specific to the corresponding molecules were selected. Peripheral blood mononuclear cells (PBMCs) obtained from a healthy donor were stimulated using HLA-A*2402 binding candidate peptides derived from CDCA1. CTLs that specifically recognize HLA-A24 positive target cells pulsed with the respective candidate peptides were established, and HLA-A24 restricted epitope peptides that can induce potent and specific immune responses against CDCA1 were identified. These results demonstrate that CDCA1 is strongly immunogenic and the epitopes thereof are effective targets for

tumor immunotherapy.

[0010] Accordingly, it is an object of the present disclosure to provide peptides having CTL inducibility as well as an amino acid sequence selected from among SEQ ID NOs: 3, 4, 11, 14, 22 and 23. The present disclosure contemplates modified peptides, having an amino acid sequence of SEQ ID NOs: 3, 4, 11, 14, 22 or 23, wherein one, two or more amino acids are substituted, incorporated, deleted or added, so long as the modified peptides retain the original CTL inducibility.

[0010a] In one aspect, there is provided an isolated peptide having cytotoxic T lymphocyte (CTL) inducibility, wherein the peptide consists of an amino acid sequence selected from the group consisting of

(a) SEQ ID NO: 23, 3, 4, 11, 14 and 22; and

(b) SEQ ID NO: 23, 3, 4, 11, 14, and 22 wherein the second amino acid from the N-terminus of the amino acid sequence of the SEQ ID NOs is substituted with phenylalanine, tyrosine, methionine, or tryptophan, and/or

wherein the C-terminus of the amino acid sequence of the SEQ ID NOs is substituted with phenylalanine, leucine, isoleucine, tryptophan, or methionine.

[0011] When administered to a subject, the present peptides are presented on the surface of antigen-presenting cells or exosomes and then induce CTLs targeting the respective peptides. Therefore, it is an object of the present disclosure to provide antigen-presenting cells and exosomes presenting any of the present peptides, as well as methods for inducing antigen-presenting cells.

[0011a] In one aspect, there is provided an isolated polynucleotide encoding a peptide as described herein.

[0012] An anti-tumor immune response is induced by the administration of the present CDCA1 polypeptides or polynucleotide encoding the polypeptides, as well as exosomes and antigen-presenting cells which present the CDCA1 polypeptides. Therefore, it is an object of the present disclosure to provide pharmaceutical agents containing the polypeptides of the present disclosure or polynucleotides encoding them, as well as the exosomes and antigen-presenting cells containing such as their active ingredients. The pharmaceutical agents of the present disclosure find particular utility as vaccines.

[0012a] In one aspect, there is provided an *in vitro* method for inducing an antigen-presenting cell with high CTL inducibility by using a peptide as described herein, and/or a polynucleotide as described herein.

[0012b] In another aspect, there is provided an isolated antigen-presenting cell that presents a peptide as described herein on its surface.

[0012c] In yet another aspect, there is provided an *in vitro* method for inducing a CTL by using:

(a) a peptide as described herein;

(b) a polynucleotide described herein;

(c) an antigen-presenting cell and/or an exosome that presents a peptide as described herein on its surface;

(d) a polynucleotide encoding a polypeptide that is capable of forming a T cell receptor (TCR) subunit recognizing a complex of a peptide as described herein and an HLA antigen; or

(e) combinations thereof.

[0012d] In one aspect, there is provided an isolated CTL which targets any one of the peptides as described herein.

[0012e] In one aspect, there is provided an isolated CTL that is induced by using the method as described herein.

[0012f] In one aspect, there is provided a pharmaceutical agent comprising an active ingredient selected from the group consisting of:

(a) at least one peptide as described herein;

(b) at least one polynucleotide as described herein;

(c) an antigen-presenting cell and/or an exosome that presents at least one peptide as described herein on its surface;

(d) a CTL as described herein; and

(e) combinations thereof,

in combination with a pharmacologically acceptable carrier for use selected from the group consisting of:

(i) treatment of a cancer;

(ii) prophylaxis of a cancer;

(iii) prevention of postoperative recurrence of a cancer; and

(iv) combinations thereof.

[0012g] In another aspect, there is provided a composition comprising

(a) a peptide as described herein;

(b) a polynucleotide as described herein;

(c) an antigen-presenting cell and/or an exosome that presents a peptide as described herein on its surface;

(d) a CTL as described herein; or

(e) combinations thereof,

for use in inducing an immune response against cancer.

[0013] It is a further object of the present disclosure to provide methods for the treatment and/or prophylaxis of (i.e., preventing) cancers (tumors), and/or prevention of post-operative recurrence thereof, as well as methods for inducing CTLs, methods for inducing anti-tumor immunity, which methods include the step of administering the CDCA1 polypeptides, polynucleotides encoding CDCA1 polypeptides, exosomes or the antigen-presenting cells presenting CDCA1 polypeptides or the pharmaceutical agents of the disclosure. In addition, the CTLs of the disclosure also find use as vaccines against cancer. Examples of cancers contemplated by the present disclosure include, but are not limited to breast cancer, bladder cancer, esophageal cancer, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

[0014] In addition to the above, other objects and features of the disclosure will become more fully apparent when the following detailed description is read in conjunction with the accompanying figures and examples. However, it is to be understood that both the foregoing summary and the following detailed description are of exemplified embodiments, and not restrictive of the disclosure or other alternate embodiments of the disclosure. In particular, while the disclosure is described herein with reference to a number of specific embodiments, it will be appreciated that the description is illustrative of the disclosure and is not constructed as limiting of the

disclosure. Various modifications and applications may occur to those who are skilled in the art, without departing from the spirit and the scope of the disclosure, as described by the appended claims. Likewise, other objects, features, benefits and advantages of the present disclosure will be apparent from this summary and certain embodiments described below, and will be readily apparent to those skilled in the art. Such objects, features, benefits and advantages will be apparent from the above in conjunction with the accompanying examples, data, figures and all reasonable inferences to be drawn therefrom, alone or with consideration of the references incorporated herein.

Brief Description of Drawings

[0015] 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.

[fig. 1] Figure 1 is composed of a series of photographs, (a) to (g), depicting the results of an IFN-gamma ELISPOT assay on CTLs that were induced with peptides derived from CDCA1. The CTLs in well numbers #8 stimulated with CDCA1-A24-10-119 (SEQ ID NO: 3) (a), #1 with CDCA1-A24-10-335 (SEQ ID NO: 4) (b), #1 with CDCA1-A24-10-48 (SEQ ID NO: 11) (c), #4 with CDCA1-A24-10-5 (SEQ ID NO: 14) (d), #2 with CDCA1-A24-9-8 (SEQ ID NO: 22) (e) and #2 with CDCA1-A24-9-56 (SEQ ID NO: 23) (f) showed potent IFN-gamma production as compared with the control, respectively. In contrast, no specific IFN-gamma production against peptide-pulsed target cells was detected in the CTLs stimulated with CDCA1-A24-10-74 (SEQ ID NO: 2) (g). The cells in the wells denoted with a rectangular box were expanded to establish CTL lines. In the figures, "+"indicates the IFN-gamma production against target cells pulsed with the appropriate peptide, and "-"indicates the IFN-gamma production against target cells not pulsed with any peptides.

[fig. 2] Figure 2 is composed of a series of line graphs, (a) to (g), representing the results of an IFN-gamma ELISA assay on CTL lines established with CDCA1-A24-10-119 (SEQ ID NO: 3) (a), CDCA1-A24-10-335 (SEQ ID NO: 4) (b), CDCA1-A24-10-48 (SEQ ID NO: 11) (c), CDCA1-A24-10-5 (SEQ ID NO: 14) (d), CDCA1-A24-9-8 (SEQ ID NO: 22) (e) and CDCA1-A24-9-56 (SEQ ID NO: 23) (f) in the above IFN-gamma ELISA assay. The results demonstrate that CTL lines established by stimulation with each peptide showed potent IFN-gamma production as compared with the control. In contrast, no specific IFN-gamma production against peptide-pulsed target cells was observed in the CTL line established with CDCA1-A24-10-74 (SEQ ID NO: 2) (g). In the figures, "+"indicates the IFN-gamma production against target cells pulsed with the appropriate peptide, and "-"indicates the IFN-gamma production

CLAIMS

1. An isolated peptide having cytotoxic T lymphocyte (CTL) inducibility, wherein the peptide consists of an amino acid sequence selected from the group consisting of
   (a) SEQ ID NO: 23, 3, 4, 11, 14 and 22; and
   (b) SEQ ID NO: 23, 3, 4, 11, 14, and 22 wherein the second amino acid from the N-terminus of the amino acid sequence of the SEQ ID NOs is substituted with phenylalanine, tyrosine, methionine, or tryptophan, and/or
   wherein the C-terminus of the amino acid sequence of the SEQ ID NOs is substituted with phenylalanine, leucine, isoleucine, tryptophan, or methionine.

2. The isolated peptide of claim 1, wherein the peptide consists of an amino acid sequence selected from the group consisting of SEQ ID NO: 23, 3, 4, 11, 14 and 22.

3. An isolated polynucleotide encoding a peptide of claims 1 or 2.

4. An in vitro method for inducing an antigen-presenting cell with high CTL inducibility by using a peptide as set forth in claim 1 or 2, and/or a polynucleotide as set forth in claim 3.

5. The method of claim 4, wherein said method comprises one or both of the following steps:
   (a) contacting an antigen-presenting cell with a peptide as set forth in claim 1 or 2, and
   (b) introducing a polynucleotide as set forth in claim 3 into an antigen-presenting cell.

6. An isolated antigen-presenting cell that presents a peptide as set forth in claim 1 or 2 on its surface.

7. The antigen-presenting cell of claim 6, wherein said cell is induced by the method of claim 4 or 5.

8. An in vitro method for inducing a CTL by using:
   (a) a peptide as set forth in claim 1 or 2;
   (b) a polynucleotide as set forth in claim 3;
   (c) an antigen-presenting cell and/or an exosome that presents a peptide as set

forth in claim 1 or 2 on its surface;

(d) a polynucleotide encoding a polypeptide that is capable of forming a T cell receptor (TCR) subunit recognizing a complex of a peptide as set forth in claim 1 or 2 and an HLA antigen; or

(e) combinations thereof.

9. The method of claim 8, wherein said method comprises at least one step selected from the group consisting of:

(a) contacting a CD 8-positive T cell with an antigen-presenting cell and/or an exosome that presents a peptide as set forth in claim 1 or 2 on its surface, and

(b) introducing a polynucleotide encoding a polypeptide that is capable of forming a T cell receptor (TCR) subunit recognizing a complex of a peptide as set forth in claim 1 or 2 and an HLA antigen into a CD8-positive T cell.

10. An isolated CTL which targets any one of the peptides of claim 1 or 2.

11. An isolated CTL that is induced by using the method of claim 8 or 9.

12. A pharmaceutical agent comprising an active ingredient selected from the group consisting of:

(a) at least one peptide as set forth in claim 1 or 2;

(b) at least one polynucleotide as set forth in claim 3;

(c) an antigen-presenting cell and/or an exosome that presents at least one peptide as set forth in claim 1 or 2 on its surface;

(d) a CTL as set forth in claim 10 or 11; and

(e) combinations thereof,

in combination with a pharmacologically acceptable carrier for use selected from the group consisting of:

(i) treatment of a cancer;

(ii) prophylaxis of a cancer;

(iii) prevention of postoperative recurrence of a cancer; and

(iv) combinations thereof.

13. A composition comprising

(a) a peptide as set forth in claim 1 or 2;

(b) a polynucleotide as set forth in claim 3;

(c) an antigen-presenting cell and/or an exosome that presents a peptide as set forth in claim 1 or 2 on its surface;

(d) a CTL as set forth in claim 10 or 11; or
(e) combinations thereof,
for use in inducing an immune response against cancer.

14. The pharmaceutical agent for use according to claim 12, wherein said pharmaceutical agent is a vaccine.

15. The pharmaceutical agent for use of claim 12, the composition for use of claim 13 or the vaccine for use of claim 14, which is formulated for the administration to a subject whose HLA antigen is HLA-A24.