target for immunotherapy, because the use of such TAAs may minimize the well-described risk of immune escape of cancer cells attributable to deletion, mutation, or down-regulation of TAAs as a consequence of therapeutically driven immune selection.

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Summary ~~of Invention~~

[0004] The present ~~invention~~disclosure is based, in part, on the discovery of suitable targets of immunotherapy. Because TAAs are generally perceived for the immune system as "self" and therefore often have no immunogenicity, the discovery of appropriate targets is of extreme importance. As noted above, FOXM1 (SEQ ID NO: 34 encoded by the gene of GenBank Accession No. NM_202002.1 (SEQ ID NO: 33)) has been identified as up-regulated in tissues of cancers, such as acute myeloid leukemia (AML), bladder cancer, breast cancer, cervical cancer, cholangiocellular carcinoma, chronic myeloid leukemia (CML), colorectal cancer, esophageal cancer, gastric cancer, gastric cancer diffuse-type, liver cancer, non-small cell lung cancer (NSCLC), lymphoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal carcinoma, small cell lung cancer (SCLC), soft tissue tumor and testicular tumor. Thus, FOXM1 is a candidate target of immunotherapy.

The present ~~invention~~disclosure is based, at least in part, on the identification of specific epitope peptides of FOXM1, which possess the ability to induce cytotoxic T lymphocytes (CTLs) specific to FOXM1. As discussed in detail below, peripheral blood mononuclear cells (PBMCs) obtained from a healthy donor were stimulated using HLA-A*2402 binding candidate peptides derived from FOXM1. CTL lines with

specific cytotoxicity against HLA-A24 positive target cells pulsed with each of candidate peptides were then established. These results demonstrate that these peptides are HLA-A24 restricted epitope peptides that can induce potent and specific immune responses against cells expressing FOXM1. These results demonstrate that FOXM1 is strongly immunogenic and the epitopes thereof are effective targets for tumor immunotherapy.

[0005] Accordingly, it is an object of the present ~~invention~~disclosure to provide isolated peptides binding to HLA antigen, which is FOXM1 (SEQ ID NO: 34) or fragments thereof. The present peptides are expected to have CTL inducibility. They can be used to induce CTL ex vivo or can be administered to a subject for inducing immune responses against cancers such as AML, bladder cancer, breast cancer, cervical cancer, cholangiocellular carcinoma, CML, colorectal cancer, esophageal cancer, gastric cancer, gastric cancer diffuse-type, liver cancer, NSCLC, lymphoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal carcinoma, SCLC, soft tissue tumor and testicular tumor. Preferably, the peptides are nonapeptides or decapeptides, and more preferably, consist of the amino acid sequence selected from the group of SEQ ID NOs: 2, 7, 8, 16, 25, 30 and 31, show strong CTL inducibility.

The present ~~invention~~disclosure contemplates modified peptides, having an amino acid sequence of SEQ ID NOs: 2, 7, 8, 16, 25, 30 and 31, wherein one, two or more amino acid(s) is/are substituted or added, so long as the modified peptides retain the original CTL inducibility. In an aspect, there is provided an isolated peptide of less than 15 amino acids having cytotoxic T lymphocyte (CTL) inducibility, wherein the peptide comprises an amino acid sequence selected from the group consisting of: (i) an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 7, 8, 16, 25, 30 and 31; and (ii) an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 7, 8, 16, 25, 30 and 31, in which 1 or 2 amino acid(s) are substituted or added.

[0006] Further, the present ~~invention~~disclosure provides isolated polynucleotides encoding any of the peptides of the present invention. These polynucleotides can be used for inducing, or preparing antigen-expressing cells (APCs) with CTL inducibility or can be administered to a subject for inducing immune responses against cancers as well as the present peptides.

When administered to a subject, the present peptides are presented on the surface of APCs and then induce CTLs targeting the respective peptides. Therefore, ~~it is an aspect~~ there is~~of the present invention to~~ provided compositions or substances including any peptides or polynucleotides of the present invention for inducing CTL. Specifically, in an aspect, there is provided a composition for inducing CTL, wherein the composition comprises the peptide as defined above. In another aspect, there is provided a pharmaceutical composition which comprises the peptide as defined above. Furthermore, com-

positions or substances including any of the peptides or polynucleotides can be used for treating and/or for the prophylaxis of cancers, such as AML, bladder cancer, breast cancer, cervical cancer, cholangiocellular carcinoma, CML, colorectal cancer, esophageal cancer, gastric cancer, gastric cancer diffuse-type, liver cancer, NSCLC, lymphoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal carcinoma, SCLC, soft tissue tumor and testicular tumor, and/or for preventing post-operative recurrence thereof. Thus, it is yet another object of the present ~~invention~~disclosure to provide pharmaceutical compositions or substances for treating and/or for the pro-

phylaxis of cancers, and/or for preventing postoperative recurrence thereof, which include any of the peptides or polynucleotides of the present ~~invention~~disclosure. Instead of or in addition to the present peptides or polynucleotides, the present pharmaceutical compositions or substances may include, as the active ingredients, APCs or exosomes which present any of the present peptides.

The peptides or polynucleotides of the present ~~invention~~disclosure may be used to induce APCs which present on its surface a complex of an HLA antigen and the present peptide, for example, by contacting APCs derived from a subject with the present peptide or introducing a polynucleotide encoding the present peptide into APCs. Such APCs have high CTL inducibility against the target peptides and are useful for cancer immunotherapy. Therefore, it is another object of the present ~~invention~~disclosure to provide methods for inducing APCs with CTL inducibility as well as APCs obtained by the methods. In an aspect, there is provided a method for inducing an antigen-presenting cell (APC) with CTL inducibility, wherein the method comprises contacting an APC with the peptide as defined above in vitro or ex vivo.

[0007] It is a further object of the present ~~invention~~disclosure to provide a method for inducing CTL, which includes the step of co-culturing CD8-positive cells with APCs or exosomes presenting a peptide of the present invention on its surface or the step of introducing a gene that includes a polynucleotide encoding a T cell receptor (TCR) subunit binding to the present peptide. The CTLs obtainable by the present methods also find use in treating and/or preventing cancers, such as AML, bladder cancer, breast cancer, cervical cancer, cholangiocellular carcinoma, CML, colorectal cancer, esophageal cancer, gastric cancer, gastric cancer diffuse-type, liver cancer, NSCLC, lymphoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal carcinoma, SCLC, soft tissue tumor and testicular tumor. Therefore, it is another object of the present ~~invention~~disclosure to provide CTLs obtainable by the present methods. In an aspect, there is provided a method for inducing CTL comprising at least one of the following steps: (a) co-culturing a CD8-positive T cell with an APC, which presents on its surface a complex of an HLA antigen and the peptide as defined above; and (b) co-culturing a CD8-positive T cell with an exosome, which presents on its surface a complex of an HLA antigen and the peptide as defined above.

[0008] Moreover, a further object of the present ~~invention~~disclosure is to provide methods for inducing immune response against cancers, which methods include the step of administering substances or compositions containing FOXM1 or fragments thereof, polynucleotides encoding FOXM1 or the fragments thereof, or exosomes or APCs presenting FOXM1 or the fragments thereof.

The present ~~invention~~disclosure may be applied to any diseases related to FOXM1 overexpression including cancer, such as AML, bladder cancer, breast cancer, cervical cancer,

cholangiocellular carcinoma, CML, colorectal cancer, esophageal cancer, gastric cancer, gastric cancer diffuse-type, liver cancer, NSCLC, lymphoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal carcinoma, SCLC, soft tissue tumor and testicular tumor.

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

Claims

[Claim 1] An isolated peptide binding to an HLA antigen and having cytotoxic T lymphocytes (CTL) inducibility, wherein the peptide consists of the amino acid sequence of SEQ ID NO: 34 or is an immunologically active fragment thereof.

[Claim 2] The isolated peptide of claim 1, wherein the HLA antigen is HLA-A24.

[Claim 3] The isolated peptide of claim 1 or 2, which comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 7, 8, 16, 25, 30 and 31.

[Claim 4] The isolated peptide of claim 2 or 3 which is a nonapeptide or decapeptide.

[Claim 5] The isolated peptide of claim 4, which consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 7, 8, 16, 25, 30 and 31, wherein 1, 2, or several amino acid(s) are inserted, substituted, deleted or added.

[Claim 6] The peptide of claim 4 or 5 having one or both of the following characteristics:
(a) the second amino acid from the N-terminus is selected from the group of phenylalanine, tyrosine, methionine and tryptophan; and
(b) the C-terminal amino acid is selected from the group of phenylalanine, leucine, isoleucine, tryptophan and methionine.

[Claim 7] An isolated polynucleotide encoding a peptide of any of claims 1 to 6.

[Claim 8] A composition for inducing CTL, wherein the composition comprises one or more peptides of any one of claims 1 to 6, or one or more polynucleotide(s) of claim 7.

[Claim 9] A pharmaceutical composition for the treatment and/or prophylaxis of cancers, and/or the prevention of postoperative recurrence thereof, wherein the composition comprises one or more peptide(s) of any one of claims 1 to 6, or one or more polynucleotide(s) of claim 7.

[Claim 10] The pharmaceutical composition of claim 9, which is formulated for the administration to a subject whose HLA antigen is HLA-A24.

[Claim 11] The pharmaceutical composition of claim 9 or 10, which is formulated for treating cancer.

[Claim 12] A method for inducing an antigen-presenting cell (APC) with CTL inducibility, wherein the method comprises one of the following steps:
(a) contacting an APC with a peptide of any one of claims 1 to 6 in vitro, ex vivo or in vivo; and

(b) introducing a polynucleotide encoding a peptide of any one of claims 1 to 6 into an APC.

[Claim 13] A method for inducing CTL by any of the methods comprising at least one of the following steps:
(a) co-culturing CD8-positive T cells with APCs, which presents on its surface a complex of an HLA antigen and a peptide of any one of claims 1 to 6;
(b) co-culturing CD8-positive T cells with exosomes, which presents on its surface a complex of an HLA antigen and a peptide of any one of claims 1 to 6; and
(c) introducing a gene that comprises a polynucleotide encoding a T cell receptor (TCR) subunit polypeptide binding to a peptide of any one of claims 1 to 6 into a T cell.

[Claim 14] An isolated APC that presents on its surface a complex of an HLA antigen and a peptide of any one of claims 1 to 6.

[Claim 15] The APC of claim 14, which is induced by the method of claim 12.

[Claim 16] An isolated CTL that targets a peptide of any one of claims 1 to 6.

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

[Claim 18] A method of inducing immune response against cancer in a subject comprising administering to the subject a composition comprising a peptide of any one of claims 1 to 6, an immunologically active fragment thereof, or a polynucleotide encoding the peptide or the fragment.

CLAIMS:

1. An isolated peptide of less than 15 amino acids having cytotoxic T lymphocyte (CTL) inducibility, wherein the peptide comprises an amino acid sequence selected from the group consisting of: (i) an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 7, 8, 16, 25, 30 and 31; and (ii) an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 7, 8, 16, 25, 30 and 31, in which 1 or 2 amino acid(s) are substituted or added.

2. The isolated peptide of claim 1 which is a nonapeptide or decapeptide.

3. The peptide of claim 1 having one or both of the following characteristics: (a) the second amino acid from the N-terminus is selected from the group consisting of phenylalanine, tyrosine, methionine and tryptophan; and (b) the C-terminal amino acid is selected from the group consisting of phenylalanine, leucine, isoleucine, tryptophan and methionine.

4. A composition for inducing CTL, wherein the composition comprises the peptide of claim 1.

5. A pharmaceutical composition which comprises the peptide of claim 1.

6. A method for inducing an antigen-presenting cell (APC) with CTL inducibility, wherein the method comprises contacting an APC with the peptide of claim 1 in vitro or ex vivo.

7. A method for inducing CTL comprising at least one of the following steps: (a) co-culturing a CD8-positive T cell with an APC, which presents on its surface a complex of an HLA antigen and the peptide of claim 1; and (b) co-culturing a CD8-positive T cell with an exosome, which presents on its surface a complex of an HLA antigen and the peptide of claim 1.