both the initiation and elongation of DNA replication to ensure that chromosomal DNA is replicated only once per cell cycle (NPLs 16-19). CDC45L is highly conserved among all eukaryotes, and a targeted disruption of this gene causes embryonic lethality in mice (NPL 20). In adult humans, the vast majority of cells has differentiated and ceased cell division, and only a small population of cells is proliferating in some self-renewing tissues (NPL 21). Thus, while CDC45L is absent in long-term quiescent, terminally differentiated and senescent human cells, it is present throughout the cell cycle of proliferating cancer cells (NPL 18). Accordingly, CDC45L expression is tightly associated with proliferating cell populations, and thus is considered to be a promising candidate for a novel proliferation marker in cancer cell biology (NPLs 18, 22). However, the usefulness of CDC45L as a target for cancer immunotherapy has not yet been fully investigated.

Citation List

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Summary ~~of Invention~~

[0006] The present disclosure~~invention~~ is based, at least in part, on the discovery of peptides that may serves as targets of immunotherapy. Because TAAs are sometimes perceived by the immune system as "self" and therefore often have no immunogenicity, the discovery of appropriate targets is of extreme importance. As noted above, CDC45L (a typical amino acid sequence and gene sequence are shown in SEQ ID NO: 18 and SEQ ID NO: 17, respectively, and the sequences are also available from GenBank Accession No. NM_003504) has been identified as up-regulated in cancers, examples of which include, but are not limited to, testicular tumor, pancreatic cancer, bladder cancer, non-small cell lung cancer, small cell lung cancer, breast cancer, esophageal cancer, prostate cancer, chronic myeloid leukemia (CML), soft tissue tumor, gastric cancer, hepatobiliary cancer, and colorectal cancer. Thus, CDC45L is a candidate for the target of cancer/tumor immunotherapy.

[0007] The present disclosure~~invention~~ further relates to the identification of specific epitope peptides of the gene products of CDC45L that possess the ability to induce CTLs specific to CDC45L. As discussed in detail below, peripheral blood mononuclear cells (PBMCs) obtained from a healthy donor were stimulated using HLA-A*2402 or HLA-A*0201 binding candidate peptides derived from CDC45L. CTL lines were then established with specific cytotoxicity against the HLA-A24 or HLA-A2 positive target cells pulsed with each of candidate peptides. These results demonstrate that these peptides are HLA-A24 or HLA-A2 restricted epitope peptides that may induce potent and specific immune responses against cells expressing CDC45L. Further, the results indicate that CDC45L is strongly immunogenic and that the epitopes thereof are effective targets for caner/tumor immunotherapy.

[0008] Accordingly, it is an object of the present disclosure~~invention~~ to provide isolated peptides that bind to HLA antigen, particularly those derived from CDC45L (SEQ ID NO: 18) or an immunologically active fragments thereof. These peptides are expected to have CTL inducibility and, thus, can be used to induce CTL ex vivo or to be administered to a subject for inducing immune responses against cancers such as testicular tumor, pancreatic cancer, bladder cancer, non-small cell lung cancer, small cell lung cancer, breast cancer, esophageal cancer, prostate cancer, chronic myeloid leukemia (CML), soft tissue tumor, gastric cancer, hepatobiliary cancer, colorectal cancer and the like. Preferred peptides are nonapeptides or decapeptides, and more preferably, those having an amino acid sequence selected from among SEQ ID NOs: 1 to 16. Of these, the peptides having an amino sequence selected from among SEQ ID NOs: 2, 3, 4, 7 and 12 showed strong CTL inducibility and thus are most preferred. In one aspect, there is provided an isolated peptide of less than 15 amino acids that has cytotoxic T lymphocyte (CTL) inducibility, wherein said peptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOs: 4, 2, 3, 7 and 12; and (b) SEQ ID NOs: 4, 2, 3, 7 and 12, in which 1 or 2 amino acids are substituted and/or added.

[0009] The peptides of the present disclosure~~invention~~ encompass those wherein one, two or more amino acids are substituted deleted or added, so long as the resulting modified peptides retain the original CTL inducibility.

The present disclosure~~invention~~ also provides isolated polynucleotides encoding any one of the peptides of the present disclosure~~invention~~. These polynucleotides can be used to induce APCs with CTL inducibility and can be administered to a subject for inducing immune responses against cancers much like the present peptides.

[0010] When administered to a subject, the present peptides are preferably presented on the surface of APCs so as to induce CTLs targeting the respective peptides. Accordingly, it is a further object of the present disclosure~~invention~~ to provide compositions or agents that induce CTL, such compositions or substances including one or more peptides or polynucleotides of the present disclosure~~invention~~. In a second aspect, there is provided a composition for inducing a CTL, wherein the composition comprises one or more peptide(s) as defined above. The present disclosure~~invention~~ further contemplates compositions or agents including one or more peptides or polynucleotides of the present disclosure~~invention~~ formulated for the treatment and/or prophylaxis of cancers as well as the prevention of postoperative recurrence thereof, such cancers including, but not limited to, testicular tumor, pancreatic cancer, bladder cancer, non-small cell lung cancer, small cell lung cancer, breast cancer, esophageal cancer, prostate cancer, chronic myeloid leukemia (CML), soft tissue tumor, gastric cancer, hepatobiliary cancer, and colorectal cancer. Thus, the present disclosure~~invention~~ also provides pharmaceutical compositions or agents for the treatment and/or prophylaxis of cancers, and/or the prevention of postoperative recurrence thereof, such pharmaceutical compositions or agents including one or more of the peptides or polynucleotides of the present disclosure~~invention~~. In a third aspect, there is provided a pharmaceutical composition for the treatment of cancers in which CDC45L is overexpressed, wherein the composition comprises one or more peptide(s) as defined above. In addition to and/or instead of the aforementioned peptide or polynucleotide, the pharmaceutical compositions or agents of the present disclosure~~invention~~ may optionally include as active ingredients APCs or exosomes that present one or more of the present peptides of the present disclosure~~invention~~.

[0011] The peptides and polynucleotides of the present disclosure~~invention~~ can induce APCs that present on their surface a complex of an HLA antigen and a present peptide, for example, by contacting APCs derived from a subject with a peptide of the present disclosure~~invention~~ or by introducing a polynucleotide encoding such a peptide into APCs. Such APCs have high CTL inducibility against target peptides and find use in cancer immunotherapy. Therefore, the present disclosure~~invention~~ encompasses the methods for inducing APCs with CTL inducibility and the APCs obtained by such methods. In a fourth aspect, there is provided a method for inducing an antigen-presenting cell (APC) with CTL inducibility, wherein the method comprises a step of contacting an APC with the peptide as defined above in vitro.

[0012] The present disclosure~~invention~~ also provides a method for inducing CTL that includes the step of co-culturing CD8 positive cells with APCs or exosomes presenting a peptide of the present disclosure~~invention~~ on its surface. Alternatively, the method may include the step of introducing a gene that includes a polynucleotide coding for a T cell receptor (TCR) subunit polypeptide capable of binding to a peptide of the present disclosure~~invention~~. In a fifth aspect, there is provided an in vitro method for inducing a CTL, wherein the method comprises a step of co-culturing a CD8 positive T cell with an APC that presents on its surface a complex of an HLA antigen and the peptide as defined above. The CTLs obtained by such methods can find use in the treatment and/or prevention of cancers, examples of which include, but are not limited to, testicular tumor, pancreatic cancer, bladder cancer, non-small cell lung cancer, small cell lung cancer, breast cancer,

esophageal cancer, prostate cancer, chronic myeloid leukemia (CML), soft tissue tumor, gastric cancer, hepatobiliary cancer, and colorectal cancer. Therefore, the present disclosure~~invention~~ encompasses the CTLs obtained by the present methods.

[0013] It is yet another object of the present disclosure~~invention~~ to provide methods for inducing an immune response against cancer in a subject in need thereof, such methods including the step of administering compositions or agents including the CDC45L polypeptides of the present disclosure~~invention~~ or an immunologically active fragment thereof, polynucleotides encoding the CDC45L polypeptides of the present disclosure~~invention~~, or exosomes or the APCs presenting such CDC45L polypeptides. In a sixth aspect, there is provided a diagnostic kit comprising the peptide as defined above.

[0014] Specifically, the present disclosure~~invention~~ provides the following [1] to [22];

[1] An isolated peptide binding to an HLA antigen and having cytotoxic T lymphocytes (CTL) inducibility, wherein the peptide is derived from a polypeptide consisting of the amino acid sequence of SEQ ID NO: 18 or an immunologically active fragment thereof,

[2] The isolated peptide of [1], wherein the HLA antigen is HLA-A24 or A2,

[3] The isolated peptide of [1] or [2], wherein said peptide comprises an amino acid sequence selected from the group consisting of:

(a) SEQ ID NOs: 4, 2, 3, 7 and 12; and

(b) SEQ ID NOs: 4, 2, 3, 7 and 12, wherein 1, 2, or several amino acids are substituted, inserted, deleted and/or added,

[4] The isolated peptide of any one of [1] to [3], wherein the peptide has one or both of the following characteristics:

(a) the second amino acid from N-terminus is or is modified to be an amino acid selected from the group consisting of phenylalanine, tyrosine, methionine and tryptophan; and

(b) the C-terminal amino acid is or is modified to be an amino acid selected from the group consisting of phenylalanine, leucine, isoleucine, tryptophan and methionine,

[5] The isolated peptide of any one of [1] to [3], wherein the peptide has one or both of the following characteristics:

(a) the second amino acid from the N-terminus is or is modified to be an amino acid selected from the group consisting of leucine and methionine; and

(b) the C-terminal amino acid is or is modified to be an amino acid selected from the group consisting of valine and leucine,

[6] The isolated peptide of any one of [1] to [5], wherein the peptide is nonapeptide or decapeptide,

[7] An isolated polynucleotide encoding the peptide of any one of [1] to [6],

[8] A composition for inducing CTL, wherein the composition comprises one or more of the peptide(s) set forth in any one of [1] to [6], or one or more of the polynu-

[22] A diagnostic kit comprising any of the peptides of [1] to [6], the nucleotide of [7] or the antibody of [19].

[0015] The applicability of the present disclosure~~invention~~ extends to any of a number diseases relating to or arising from CDC45L overexpression, such as cancer, examples of which include, but are not limited to, testicular tumor, pancreatic cancer, bladder cancer, non-small cell lung cancer, small cell lung cancer, breast cancer, esophageal cancer, prostate cancer, chronic myeloid leukemia (CML), soft tissue tumor, gastric cancer, hepatobiliary cancer, and colorectal cancer.

[0016] In addition to the above, other objects and features of the present disclosure~~invention~~ 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 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~~. In particular, while the present disclosure~~invention~~ is described herein with reference to a number of specific embodiments, it will be appreciated that the description is illustrative of the present disclosure~~invention~~ and is not constructed as limiting of the present disclosure~~invention~~. Various modifications and applications may occur to those who are skilled in the art, without departing from the spirit and the scope of the present disclosure~~invention~~, as described by the appended claims. Likewise, other objects, features, benefits and advantages of the present disclosure~~invention~~ 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

[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 that follows.

[Fig. 1a-d]

Figure 1 is composed of a series of photographs, A to F, depicting the results of CDC45L mRNA analyses expressed in human normal tissues, cancer cell lines and cancer tissues. Parts A, B: RT-PCR and Northern blot analysis of CDC45L mRNA expressed in various normal tissues. Part C: RT-PCR analysis of CDC45L mRNA expressed in various cancer cell lines. Part D: RT-PCR analysis of CDC45L mRNA expressed in lung cancer tissues and adjacent normal lung tissues.

[0018]

[Fig. 1e-f]Part E: RT-PCR analysis of CDC45L mRNA expressed in various cancer cell