by normal cells, but are broadly upregulated by a variety of different cancers secondary to genomic damage. MIC is an important ligand for the NKG2D receptor on cytotoxic lymphocytes, specifically NK cells, CD8 T cells and gamma-delta T cells. Expression of MIC targets such cells for elimination by the immune system. However, many tumors are found to escape this important immune surveillance pathway by shedding MIC from the cell surface, a process in which the MIC alpha3 domain is unfolded by the disulfide isomerase ERp5 rendering it sensitive to cleavage by matrix metalloproteases such as ADAM 10 and ADAM 17. Shed MIC causes downregulation of the NKG2D receptor on NK cells and CD8 T cells. Proteolytic cleavage thus turns an immune-stimulatory protein into an immunosuppressive substance.

[0007] Thus a need exists for compounds to inhibit MICA shedding.

SUMMARY OF THE INVENTION

[0007a] In one aspect, the present invention provides a vaccine composition comprising, as an immunogenic component, comprising or consisting of:

a. a MIC alpha 3-domain peptide; or

b. a MIC alpha 3-domain peptide comprising or consisting of an amino acid sequence that is at least 90% identical to SEQ ID NO: 3 or SEQ ID NO: 4

wherein the MIC alpha 3-domain is present in an amount effective to elicit an immune response against the MIC alpha 3-domain.

[0007b] In another aspect, the present invention provides a fusion protein comprising a monomeric ferritin subunit protein joined to a MIC alpha 3-domain protein to form a monomeric ferritin subunit protein joined to a MIC alpha 3-domain protein construct, and wherein the monomeric ferritin subunit protein comprises a domain that allows the fusion protein to self-assemble into nanoparticles.

[0007c] In yet another aspect, the present invention provides a nanoparticle comprising the fusion protein disclosed herein.

[0007d] In yet another aspect, the present invention provides a vaccine composition comprising the nanoparticle disclosed herein.

[0007e] In yet another aspect, the present invention provides use of a vaccine composition disclosed herein in the manufacture of a medicament for treating cancer in a subject.

[0007f] In yet another aspect, the present invention provides use of a vaccine comprising cells that express MIC alpha-3 domain in the manufacture of a medicament for treating cancer.

[0007g] In yet another aspect, the present invention provides use of a replicating or non-replicating virus in the manufacture of a medicament for treating cancer where an immune response against MIC is to be induced by use of the replicating or non-replicating virus.

[0008] Disclosed are vaccine compositions including as an immunogenic component, an effective amount of a peptide including the MIC alpha 3-domain. By effective amount means an amount effective to elicit an immune response against the MIC alpha 3-domain.

[0009] The MIC alpha 3-domain is a MICA or MICB alpha 3-domain. Optionally, the MIC alpha 3-domain is non glycosylated. Preferably, the peptide includes amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4. Also disclosed is that the vaccine composition comprises a plurality of peptides. Also disclosed is that the peptide is conjugated to a carrier protein.

[00010] Also disclosed is a fusion protein having a monomeric ferritin subunit protein joined to a MIC alpha 3-domain protein. The monomeric ferritin subunit protein has a domain that allows the fusion protein to self-assemble into nanoparticles. In a preferred example, the monomeric subunit is a Helicobacter pylori ferritin protein. Optionally, the fusion protein is further conjugated to a CpG oligonucleotide.

[00011] Also disclosed is a nanoparticle including the fusion protein according to the disclosure. The nanoparticle includes a plurality of MIC alpha 3-domain peptides.

[00012] Also disclosed is a vaccine composition comprising the nanoparticle according to the disclosure. The vaccine composition can further comprise GM-CSF.

[00013] Also disclosed is method of treating cancer in a subject by administering to a subject a vaccine composition according to the disclosure. Optionally, the vaccine composition contains GM-CSF. The subject has tested positive for shed MIC in their serum. The vaccine composition is administered as part of a therapeutic regimen. A therapeutic regimen includes for example, radiation therapy, targeted therapy, immunotherapy, or chemotherapy. Optionally, the subject is further administered one or more vaccines specific for an antigen other than a MIC alpha 3-domain antigen.

[00014] Also disclosed is a method for treating cancer by administering to the subject a vaccine comprising cells that express MIC alpha-3 domain. Also disclosed is a method for treating cancer where an immune response against MIC is induced by use of a replicating or non-replicating virus.

[00015] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety. In cases of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples described herein are illustrative only and are not intended to be limiting.

[00016] Other features and advantages of the invention will be apparent from and encompassed by the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[00017] **Figures 1A** is a schematic that demonstrates the interaction between NKG2D homodimer and MICA. The MICA-alpha3 domain is identified for reference. From: Nat Immunol. 2001 May;2(5):443-51. Complex structure of the activating immunoreceptor NKG2D and its MHC class I-like ligand MICA.

We Claim:

1. A vaccine composition comprising, as an immunogenic component, comprising or consisting of:

a. a MIC alpha 3-domain peptide; or

b. a MIC alpha 3-domain peptide comprising or consisting of an amino acid sequence that is at least 90% identical to SEQ ID NO: 3 or SEQ ID NO: 4

wherein the MIC alpha 3-domain is present in an amount effective to elicit an immune response against the MIC alpha 3-domain.

2. The vaccine composition of claim 1, wherein the MIC alpha 3-domain is a MICA or MICB alpha 3-domain.

3. The vaccine composition of claim 1 or 2, wherein the vaccine composition comprises a plurality of peptides.

4. The vaccine composition of any one of claims 1-3, further comprising a TLR agonist.

5. A fusion protein comprising a monomeric ferritin subunit protein joined to a MIC alpha 3-domain protein to form a monomeric ferritin subunit protein joined to a MIC alpha 3-domain protein construct, and wherein the monomeric ferritin subunit protein comprises a domain that allows the fusion protein to self-assemble into nanoparticles.

6. The fusion protein of claim 5, wherein the monomeric subunit is a monomeric subunit of a Helicobacter pylori ferritin protein.

7. A nanoparticle comprising the fusion protein of claim 5 or 6.

8. A vaccine composition comprising the nanoparticle of claim 7.

9. Use of a vaccine composition of any one of claims 1-4 or 8 in the manufacture of a medicament for treating cancer in a subject.

10. The use of claim 9, wherein the vaccine composition is to be administered as part of a therapeutic regimen.

11. The use of claim 10, wherein the therapeutic regimen is radiation therapy, targeted therapy, immunotherapy, or chemotherapy.

12. The use of any one of claims 9-11, wherein said subject has tested positive for shed MIC in their serum.

13. The use of any one of claims 9-12, wherein one or more vaccines specific for an antigen other than a MIC alpha 3-domain antigen is to be administered to the subject.

14. Use of a vaccine comprising cells that express MIC alpha-3 domain in the manufacture of a medicament for treating cancer.

15. Use of a replicating or non-replicating virus in the manufacture of a medicament for treating cancer where an immune response against MIC is to be induced by use of the replicating or non-replicating virus.