virus that specifically replicates in cancer cells, but leave normal cells unharmed. However, there have been challenges in designing viruses that selectively replicate in cancer cells. Thus, there is a need for additional viruses that selectively replicate in cancer cells.

SUMMARY

[0005] Provided herein is an adenovirus comprising an E1A polypeptide comprising one or more modifications, an E4orf6/7 polypeptide comprising one or more modifications, or an E4orf1 polypeptide comprising one or more modifications or a combination thereof. Compositions and kits comprising the modified adenoviruses are also provided. Further, provided is a method of treating a proliferative disorder in a subject comprising administering to the subject an adenovirus comprising an E1A polypeptide comprising one or more modifications, an E4orf6/7 polypeptide comprising one or more modifications, or an E4orf1 polypeptide comprising one or more modifications or a combination thereof.

[0005a] In one embodiment, there is provided a recombinant adenovirus comprising:

(i) an E1A polypeptide comprising a deletion or substitution in an Rb-binding site;

(ii) a deletion of one or both of the E4orf6/7 exons; and

(iii) adenovirus E1A and E4 promoters,

wherein the recombinant adenovirus selectively replicates in Rb-deficient cells.

[0005b] In one embodiment, there is provided a recombinant adenovirus, comprising:

(i) an E1A polypeptide comprising a deletion or substitution in an Rb-binding site;

(ii) an E4orf1 polypeptide comprising a deletion in the C-terminal region, or a deletion of all of the E4orf1 gene; and

(iii) adenovirus E1A and E4 promoters,

wherein the recombinant adenovirus selectively replicates in Rb-deficient cells.

[0005c] In one embodiment, there is provided a pharmaceutical composition comprising the recombinant adenovirus as described herein and a pharmaceutically acceptable carrier.

[0005d] In one embodiment, there is provided the use of the adenovirus described herein or the pharmaceutical composition described herein, in the manufacture of a medicament for treating a proliferative disorder in a subject.

[0006] The details of one or more embodiments are set forth in the accompanying drawings and the description below. Other features, objects, and advantages will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

[0007] Figure 1 is a schematic showing the general rationale of oncolytic viral cancer therapy.

[0008] Figure 2 is a schematic showing the structural features of adenovirus (Ad) and a map of the adenovirus genome with transcriptional units in boxes and labeled genes.

[0009] Figure 3 are images of immunoblots of cell lysates from infected primary small airway epithelial cells and tumor cells infected with wild type Ad5 and the "RB/p16/E2F pathway" selective viruses. Tumor and primary human cells were infected with either

WHAT IS CLAIMED IS:

1. A recombinant adenovirus comprising:

(i) an E1A polypeptide comprising a deletion or substitution in an Rb-binding site;

(ii) a deletion of one or both of the E4orf6/7 exons; and

(iii) adenovirus E1A and E4 promoters,

wherein the recombinant adenovirus selectively replicates in Rb-deficient cells.

2. The recombinant adenovirus of claim 1, wherein the E1A polypeptide comprises two Rb-binding sites and the E1A polypeptide comprises a deletion or substitution in both Rb-binding sites.

3. The recombinant adenovirus of claim 1 or claim 2, wherein the E1A polypeptide comprises a deletion of an LXCXE motif.

4. The recombinant adenovirus of claim 3, wherein the E1A polypeptide comprises a deletion of amino acid residues 122-126, a deletion of amino acid residues 2-11, or both.

5. The recombinant adenovirus of any one of claims 1-4, wherein the E1A polypeptide comprises a substitution at residue Y47, a substitution at residue C124, or both.

6. The recombinant adenovirus of claim 5, wherein the substitution at residue Y47 is a Y47H substitution, or the substitution at residue C124 is a C124G substitution, or both.

7. The recombinant adenovirus of any one of claims 1-6, wcomprising a deletion of one of the E4orf6/7 exons.

8. The recombinant adenovirus of any one of claims 1-7, further comprising:

an E4orf1 polypeptide comprising a deletion in the C-terminal region; or

a deletion of all of the E4orf1 gene.

9. The recombinant adenovirus of claim 8, wherein the E4orf1 polypeptide comprises a deletion in the C-terminal region.

10. The recombinant adenovirus of claim 9, wherein the E4orf1 polypeptide comprises a deletion of the last four amino acids in the C-terminal region.

11. The recombinant adenovirus of claim 9, wherein the E4orf1 polypeptide comprises a deletion of residues 125-128.

12. A recombinant adenovirus, comprising:

(i) an E1A polypeptide comprising a deletion or substitution in an Rb-binding site;

(ii) an E4orf1 polypeptide comprising a deletion in the C-terminal region, or a deletion of all of the E4orf1 gene; and

(iii) adenovirus E1A and E4 promoters,

wherein the recombinant adenovirus selectively replicates in Rb-deficient cells.

13. The recombinant adenovirus of claim 12, wherein the E1A polypeptide comprises two Rb-binding sites and the E1A polypeptide comprises a deletion or substitution in both Rb-binding sites.

14. The recombinant adenovirus of claim 12 or claim 13, wherein the E1A polypeptide comprises a deletion of an LXCXE motif.

15. The recombinant adenovirus of claim 14, wherein the E1A polypeptide comprises a deletion of amino acid residues 122-126, a deletion of amino acid residues 2-11, or both.

16. The recombinant adenovirus of any one of claims 12-15, wherein the E1A polypeptide comprises a substitution at residue Y47, a substitution at residue C124, or both.

17. The recombinant adenovirus of claim 16, wherein the substitution at residue Y47 is a Y47H substitution, or the substitution at residue C124 is a C124G substitution, or both.

18. The recombinant adenovirus of any one of claims 12-17, wherein the E4orf1 polypeptide comprises a deletion in the C-terminal region.

19. The recombinant adenovirus of claim 18, wherein the E4orf1 polypeptide comprises a deletion of the last four amino acids in the C-terminal region.

20. The recombinant adenovirus of claim 18, wherein the E4orf1 polypeptide comprises a deletion of residues 125-128.

21. A pharmaceutical composition comprising the recombinant adenovirus of any one of claims 1-20 and a pharmaceutically acceptable carrier.