COMPOSITIONS AND METHODS FOR VIRAL VECTORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/331,903, filed on April 18, 2022; the disclosure of which is hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The disclosure relates generally to HSV-1 vectors, and, more particularly, the invention relates to replication defective HSV-1 vectors and their use to deliver one or more genes encoding transgenic proteins that stimulate immune destruction of tumors.

BACKGROUND

[0003] Developments in immuno-oncology have provided new therapies directed to treating cancers that have evaded successful treatment because the cancers have evolved mechanisms for evading a subject's immune system. However, despite the significant advances made to date in treating various cancers with immune-stimulating therapies such as checkpoint inhibitors and CAR T cells, significant numbers of patients remain unresponsive to immunotherapy treatment. Furthermore, solid tumors may be harder to treat using immune-oncologic methods, given the complexity of the tumor microenvironment (TME) of a solid tumor, which contains epithelial cells, endothelial cells, mesenchymal cells, stromal cells, cancer cells and immune cells. In certain solid tumors, the cancer cells influence of the activity or inactivity of the immune cells in the TME.

[0004] Viral vectors have been developed to deliver therapeutics to cells. However, many such vectors exhibit insufficient persistence in target cells, preventing sufficient expression of therapeutics. Furthermore, many existing vectors cause non-specific inflammation and tissue damage that makes delivery unsafe. Accordingly, despite the advances made to date, there is still a need for methods and compositions that can stimulate immune activity against tumor cells which, either alone or in combination with other cancer drugs, may be effective in treating a tumor in a given subject.

SUMMARY

[0005] The disclosure is based, in part, upon the discovery that HSV-1 vectors comprising an alteration (such as a gene deletion) that prevents expression of one or more functional

results in one or more of (a) delayed oncolysis; (b) increased immunogenicity; and (c) increased immune activation.

[0007a] In another aspect, provided herein is a method of expressing a polypeptide in a subject comprising administering to the subject a vector as described herein.

[0007b] In another aspect, provided herein is a method of preparing a vector as described herein, the method comprising incubating cells transfected with: (a) a first nucleic acid molecule comprising: (i) a portion of HSV genome but does not encode functional ICP4 and ICP47 proteins; and (ii) a sequence that encodes a marker element, wherein the sequence that encodes the marker element is flanked by a first homology region (HR1) and a second homology region (HR2); and (b) a second nucleic acid molecule comprising a sequence that encodes a therapeutic polypeptide, wherein the sequence encoding the therapeutic polypeptide is flanked by a first homology region (HR1) and a second homology region (HR2), wherein HR1 is homologous to HR1 and HR2 is homologous to HR2 such that the sequence encoding the therapeutic polypeptide is integrated into the first nucleic acid molecule via homologous recombination.

[0007c] In another aspect, provided herein is the use of a therapeutically effective amount of a vector as described herein in the manufacture of a medicament for reducing the size of a tumor in a subject in need thereof, wherein a therapeutically effective amount of the vector is to be administered to the subject in need thereof to reduce the size of the tumor, and wherein the vector comprises a nucleic acid encoding a therapeutic polypeptide that functions to reduce the size of the tumor.

[0007d] In another aspect, provided herein is a vector comprising a herpes simplex virus (HSV) genome, wherein the vector comprises an alteration that prevents expression of one or more functional ICP4 and ICP47 proteins, and wherein the vector encodes one or more therapeutic polypeptides that support NK cell survival in a tumor microenvironment (TME).

[0007e] In another aspect, provided herein is a vector as described herein, for use in therapy.

[0008] In certain embodiments, the vector comprises a nucleic acid sequence encoding one or more therapeutic polypeptides. In certain embodiments, the therapeutic polypeptide can have one or more of the following attributes:

(a) targets the stroma of a tumor;

(b) supports T cell (*e.g.*, CAR T cell) and/or NK cell survival in a tumor microenvironment;

(c) induces tertiary lymphoid structures (TLS) in a tumor bed; and/or

(d) promotes phagocytic innate immune surveillance.

[0009] In certain embodiments, the therapeutic polypeptide targets the stroma of a tumor by degrading an extracellular matrix protein. Examples of such therapeutic polypeptides include without limitation, hyaluronidase (SEQ ID NO: 6), MMP-9 (SEQ ID NO: 7), or an inhibitor of lysyl oxidase. In certain embodiments, the therapeutic polypeptide targets the stroma of a tumor by activating local endothelium to increase T cell infiltration. Examples of such therapeutic polypeptides include without limitation a proinflammatory cytokine, *e.g.*, TNF (SEQ ID NO: 11), IL-1β (SEQ ID NO: 8), IL-6 (SEQ ID NO: 9), or IL-18 (SEQ ID NO: 18).

[0010] In certain embodiments, the therapeutic polypeptide supports T cell survival in the tumor microenvironment by enhancing recruitment of T cells to a site of a tumor. Examples of such therapeutic polypeptides include, without limitation, CCL19 (SEQ ID NO: 12) or CCL21 (SEQ ID NO: 13). In certain embodiments, the therapeutic polypeptide supports T cell survival in the tumor microenvironment by supporting T cell function. Examples of such therapeutic polypeptide include without limitation a T cell trophic factor, *e.g.*, a T cell trophic factor selected from IL-7 (SEQ ID NO: 14), IL-12 (SEQ ID NO: 15 and 16), IL-15 (SEQ ID NO: 17), IL-18 SEQ ID NO: 18), and IFNγ (SEQ ID NO: 19).

[0011] Depending upon the circumstances, for example, the indication to be treated, the T cell is a CAR T cell. In such an embodiment, the therapeutic polypeptide can comprise soluble TGFβRII (SEQ ID NO: 20 or SEQ ID NO: 21). Alternatively, the therapeutic polypeptide comprises an antigen recognized by the CAR T cell, *e.g.*, mesothelin. Alternatively or in addition, the therapeutic polypeptide can comprise a co-stimulatory molecule, *e.g.*, a co-stimulatory molecule selected from CD40L (SEQ ID NO: 22) and OX40L (SEQ ID NO: 23).