EXTRACELLULAR VESICLES FOR TARGETED THERAPIES AGAINST MYELOID-DERIVED SUPPRESSOR CELLS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Application No. 62/747,982, filed October 19, 2018, which is hereby incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] This application contains a sequence listing filed in electronic form as an ASCII.txt file entitled “321501-2360 Sequence Listing_ST25” created on October 16, 2019. The content of the sequence listing is incorporated herein in its entirety.

BACKGROUND

[0003] Myeloid-derived suppressor cells (MDSCs) play a fundamental role in a number of physiological and pathological processes, including cancer, wound healing and tissue repair. MDSCs, for example, enable tumor/cancer progression by shielding tumor cells from the host's immune system and/or anti-cancer therapies, and by promoting tumor cell dissemination/spreading. As such, therapeutic approaches need to be developed to selectively target MDSCs and modulate their activity.

SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a fusion protein comprising ICAM1 and an exosomal or lysosomal transmembrane protein.

[0003b] In another aspect of the present disclosure, there is provided a cell comprising a nucleic acid encoding the fusion protein disclosed herein.

[0003c] In a further aspect of the present disclosure, there is provided a method of producing an extracellular vesicle, comprising culturing the cell disclosed herein under conditions suitable for vesicle secretion, and isolating extracellular vesicles secreted by the cell.

[0003d] In another aspect of the present disclosure, there is provided a use of an extracellular vesicle disclosed herein in the manufacture of a medicament for treating cancer in a subject.

[0003e] In a further aspect of the present disclosure, there is provided an extracellular vesicle disclosed herein for use in treating cancer in a subject.

[0004] Disclosed herein is a nanocarrier system to effectively target MDSCs and deliver therapeutic cargo. These nanocarriers are based on designer extracellular vesicles

(EVs), which can be autologous (i.e., derived from cells from the same patient) or allogeneic (i.e., derived from cells from a donor) in nature. Cells naturally produce EVs. However to avoid an immune response, cells from the immune system can be used, such as antigen presenting cells (e.g. dendritic cells) or macrophages.

[0005] The disclosed ICAM-decorated EVs can be used to target myeloid cells in many different conditions, such as cancer and autoimmune diseases. The decoration cais in some examples achieved by transfecting ICAM-expressing vectors into the “donor” cells or tissues. Alternatively, donor cells and tissues can be used that inherently have high levels of ICAM expression.

[0006] Designer EVs can therefore be obtained after transfection of cells in vitro, or tissues in vivo, using different transfection techniques (e.g. bulk electroporation, nano-electroporation, tissue nano-transfection, viral transfection, sonoporation, nanoparticles, microparticles, chemical transfection). Loading with therapeutic cargo and/or decoration with

MDSC-targeting ligands can be achieved by transfecting the cells with, for example, plasmid DNA encoding ICAM1. ICAM1-based targeting allows for selective EV/cargo delivery to MDSCs within minutes.

[0007] Once collected, these EVs can be further modified via electroporation (to add more cargo), biochemical or chemical functionalization to include contrast agents (for diagnostics) or additional targeting or tracing proteins/elements. The EVs could also be further modified with lipid-permeable drugs/chemicals that can enter the EVs via a concentration gradient to further modify the cargo (e.g., to add a pharmacological agent in addition to the genetic cargo).

[0008] The therapeutic cargo could be varied depending on whether myelosuppresor activity is to be enhanced or tamed, depending on the condition that is being treated. For example, loading ICAM1-decorated EVs with miR146a, for example, could be used to counter MDSC activity within the tumor niche. In addition to nucleic acid-based therapeutic cargo, ICAM1-decorated EVs can be loaded with membrane-permeable pharmacological compounds (e.g., Ibrutinib), which can diffuse into the EVs via a concentration gradient. In some examples, the cargo is an imaging agent, such as a contrast agent, for diagnostic imaging.

[0009] The details of one or more examples of the present disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the present disclosure will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

[0010] FIG. 1 is a schematic representation of production of ICAM1-decorated EVs to target MDSCs. EVs are made by delivering plasmids encoding for ICAM1 and therapeutic cargo (for nucleic acid-based therapeutics) into autologous or allogeneic cells (in vitro or in vivo). The cell machinery process these plasmids to then enable the production of designer EVs decorated with ICAM1 and loaded with the nucleic acid of interest.

[0011] FIG. 2 is a schematic representation of surface-decorated EVs loaded with pharmacotherapeutic cargo for example, Ibrutinib, a membrane-permeable pharmacological compound that inhibits brutontyrosine kinase (BTK).

[0012] FIG. 3 illustrates ICAM1-decorated EVs can be used to target MDSCs and Tumor associated macrophages (TAMs) within the tumor microenvironment to counter their immunosuppressive activity and facilitate the treatment of the tumor.

[0013] FIG. 4A shows ICAM1-decorated EVs were preferentially internalized by MDSCs or macrophages (e.g.,TAMs) and not cancer cells (A549) after 15min of incubation

WHAT IS CLAIMED IS:

1. A fusion protein comprising ICAM1 and an exosomal or lysosomal transmembrane protein.
2. The extracellular vesicle comprising the fusion protein of claim 1.
3. The extracellular vesicle of claim 2, further comprising a therapeutic cargo.
4. The extracellular vesicle of claim 3, wherein the therapeutic cargo comprises miR146a.
5. The extracellular vesicle of claim 3 or 4, wherein the therapeutic cargo comprises Ibrutinib.
6. A cell comprising a nucleic acid encoding the fusion protein of claim 1.
7. The cell of claim 6, further comprising a nucleic acid encoding a therapeutic RNA.
8. A method of producing an extracellular vesicle, comprising culturing the cell of claim 6 or 7 under conditions suitable for vesicle secretion, and isolating extracellular vesicles secreted by the cell.
9. The method of claim 8, further comprising loading the extracellular vesicle with a therapeutic drug.
10. Use of an extracellular vesicle of any one of claims 3 to 5 in the manufacture of a medicament for treating cancer in a subject.
11. The use of claim 10, wherein the subject has circulating myeloid-derived suppressor cells (MDSCs).
12. An extracellular vesicle of any one of claims 3 to 5 for use in treating cancer in a subject.
13. The extracellular vesicle for use of claim 12, wherein the subject has circulating myeloid-derived suppressor cells (MDSCs).