Document 1).

RELATED ART DOCUMENTS

PATENT DOCUMENT

[0009]

Patent Document 1: International Publication No. WO 2020/045547

NON PATENT DOCUMENTS

[0010]

Non-Patent Document 1: Circulation. 2016; 133: 1484-1497

Non-Patent Document 2: Bull N Y Acad Med., 1938; 14: 231-251

Non-Patent Document 3: Am J Physiol Endocrinol Metab., 2009; 296: E1183-E1194

Non-Patent Document 4: Front Immunol., 2016; 7: 613

Non-Patent Document 5: Peptides, 2008; 29: 2243-2249

Non-Patent Document 6: J Cardiovasc Pharmacol., 2010; 56: 413-419

Non-Patent Document 7: Nat Commun., 2018; 9; Article number 2704

Non-Patent Document 8: Ann Intern Med., 2020; 172(9): 629-632

Non-Patent Document 9: Semin Respir Crit Care Med., 2006; 27: 600-612

Non-Patent Document 10: Lymphat Res Biol., 2009; 7: 197-203

Non-Patent Document 11: Lymphat Res Biol., 2014; 12: 238-250

Non-Patent Document 12: Blood, 2012; 119: 5931-5942

Non-Patent Document 13: Lymphat Res Biol., 2010; 8: 199-207

Non-Patent Document 14: Am J Physiol - Heart Circ Physiol., 2008; 295: 2113-2127

Non-Patent Document 15: PLoS One., 2020; 15: e0237810

Non-Patent Document 16: Pulm Pharmacol Ther., 2012 Aug; 25: 281-285

Non-Patent Document 17: Stem Cells Transl Med. 2017; 6(10): 1905-1916

SUMMARY

PROBLEMS TO BE SOLVED BY THE DISCLOSURE

[0011]

An object of the present disclosure is to provide a fibroblast having lymphangiogenesis ability and a pharmaceutical composition including the fibroblast.

[0011a]

In one aspect, provided herein is a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX.

[0011b]

In another aspect, provided herein is the use of any one of the pharmaceutical compositions described herein in the manufacture of a medicament for treating fibrosis.

[0011c]

In another aspect, provided herein is the use of any one of the pharmaceutical compositions described herein in the manufacture of a medicament for amelioration of a condition of reduced lymphangiogenesis ability.

[0011d]

In another aspect, provided herein is the use of any one of the pharmaceutical compositions described herein in the manufacture of a medicament for amelioration of a disorder of homeostasis in a tissue fluid.

[0011e]

In another aspect, provided herein is the use of any one of the pharmaceutical compositions described herein in the manufacture of a medicament for reduction of edema.

[0011f]

In another aspect, provided herein is the use of any one of the pharmaceutical

compositions described herein in the manufacture of a medicament for amelioration of a disorder of transportability of lipid and/or vitamin.

[0011g]

In another aspect, provided herein is the use of any one of the pharmaceutical compositions described herein in the manufacture of a medicament for activation of an immunological surveillance mechanism.

[0011h]

In another aspect, provided herein is a method for producing a fibroblast highly expressing ADM, comprising contacting TNF-α and IL-4 with a fibroblast and culturing the fibroblast contacted, under a condition where ADM is capable of being highly expressed.

[0011i]

In another aspect, provided herein is a fibroblast highly expressing ADM, obtained by any one of the methods described herein.

[0011j]

In another aspect, provided herein is a cell population of fibroblasts comprising the fibroblast described herein.

[0011k]

In another aspect, provided herein is a fibroblast highly expressing ADM.

[0011l]

In another aspect, provided herein is a cell population of fibroblasts comprising any one of the fibroblasts described herein.

[0011m]

In another aspect, provided herein is a cell population comprising a CD106-positive pulmonary fibroblast, wherein the proportion (based on the number of cells) of the CD106-positive pulmonary fibroblast in the total fibroblast contained in the cell population is more than 18.01%.

[0011n]

In another aspect, provided herein is a pharmaceutical composition comprising any one of the fibroblasts described herein, or any one of the cell populations described herein.

[0011o]

In another aspect, provided herein is the use of the pharmaceutical composition described herein in the manufacture of a medicament for treating a pulmonary disease.

[0011p]

In another aspect, provided herein is the use of the pharmaceutical composition described herein in the manufacture of a medicament for amelioration of a condition of reduced lymphangiogenesis ability.

MEANS FOR SOLVING THE PROBLEMS

[0012]

The present inventors have made studies in order to solve the above problems, have found that a fibroblast contacted with TNF-α and IL-4 significantly enhances the gene expression level(s) of ADM and/or HHEX, and have completed the present disclosure.

[0013]

In other words, the present disclosure includes the following first example (Disclosure A).

(A1) A pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX.

(A2) The pharmaceutical composition according to (A1), wherein the fibroblast is an adult-derived fibroblast.

(A3) The pharmaceutical composition according to (A1) or (A2), wherein gene expression level(s) of ADM and/or HHEX in the fibroblast are/is 1.20 times or

higher as compared with a control fibroblast.

(A4) The pharmaceutical composition according to any of (A1) to (A3), for treating fibrosis.

(A5) The pharmaceutical composition according to any of (A1) to (A4), for amelioration of a condition of lymphangiogenesis ability reduced.

(A6) The pharmaceutical composition according to any of (A1) to (A5), for amelioration of a disorder of homeostasis in a tissue fluid.

(A7) The pharmaceutical composition according to any of (A1) to (A6), for reduction of edema.

(A8) The pharmaceutical composition according to any of (A1) to (A7), for amelioration of a disorder of transportability of lipid and/or vitamin.

(A9) The pharmaceutical composition according to any of (A1) to (A8), for activation of an immunological surveillance mechanism.

(A10) The pharmaceutical composition according to any of (A1) to (A9), wherein the pharmaceutical composition is an injectable composition.

(A11) The pharmaceutical composition according to any of (A1) to (A9), wherein the fibroblast is constructed as a planar or three-dimensional cellular tissue.

(A12) The pharmaceutical composition according to any of (A1) to (A11), wherein the fibroblast is a cardiac fibroblast.

[0014] The present disclosure includes the following second example (Disclosure B).

(B1) A method for treating fibrosis in a subject, the method comprising administrating or transplanting a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX, to the subject.

(B2) A method for ameliorating a condition of lymphangiogenesis ability reduced, in a subject, the method comprising administrating or transplanting a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX, to the subject.

(B3) A method for ameliorating a disorder of homeostasis in a tissue fluid, in a subject, the method comprising administrating or transplanting a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX, to the subject.

(B4) A method for reducing edema in a subject, the method comprising administrating or transplanting a pharmaceutical composition comprising a fibroblast

highly expressing ADM and/or HHEX, to the subject.

(B5) A method for ameliorating a disorder of transportability of lipid and/or vitamin, in a subject, the method comprising administrating or transplanting a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX, to the subject.

(B6) A method for activating an immunological surveillance mechanism in a subject, the method comprising administrating or transplanting a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX, to the subject.

(B7) A method for treating organ failure in a subject, the method comprising administrating or transplanting a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX, to the subject.

[0015] The present disclosure includes the following third example (Disclosure C).

(C1) Use of a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX, as an injection for administration to a failed organ tissue and/or its peripheral region, or a fibrotic tissue and/or its peripheral region.

(C2) Use of a pharmaceutical composition comprising a fibroblast highly expressing ADM and/or HHEX, as a transplantation material for transplantation to a failed organ tissue and/or its peripheral region, or a fibrotic tissue and/or its peripheral region.

[0016] The present disclosure includes the following fourth example (Disclosure D).

(D1) A method for producing a fibroblast highly expressing ADM, the method comprising:

contacting TNF-α and IL-4 with a fibroblast; and

culturing the fibroblast contacted, under a condition where ADM is capable of being highly expressed.

(D2) The method according to (D1), wherein the fibroblast highly expresses VEGF-C.

(D3) The method according to (D1) or (D2), wherein the fibroblast is CD106-positive.

(D4) The method according to (D3), comprising selecting or concentrating a fibroblast highly expressing ADM, by use of an anti-CD106 antibody.

(D5) The method according to any of (D1) to (D4), wherein the fibroblast is a pulmonary fibroblast.

(D6) A fibroblast highly expressing ADM, obtained by the method according to any of (D1) to (D5).

(D7) A cell population of fibroblast comprising the fibroblast according to (D6).

[0017] The present disclosure includes the following fifth example (Disclosure E).

(E1) A fibroblast highly expressing ADM.

(E2) The fibroblast according to (E1), wherein the fibroblast highly expresses VEGF-C.

(E3) The fibroblast according to (E1) or (E2), wherein the fibroblast is CD106-positive.

(E4) The fibroblast according to any of (E1) to (E3), wherein gene expression level(s) of VEGF-C and/or ADM in the fibroblast are/is 1.20 times or higher as compared with a control fibroblast.

(E5) The fibroblast according to any of (E1) to (E4), wherein the fibroblast is a pulmonary fibroblast.

(E6) A cell population of fibroblast comprising the fibroblast according to any of (E1) to (E5).

(E7) A cell population comprising a CD106-positive pulmonary fibroblast, wherein the proportion (based on the number of cells) of the CD106-positive

pulmonary fibroblast in the total fibroblast contained in the cell population is more than 18.01%.

[0018] The present disclosure includes the following sixth example (Disclosure F).

(F1) A pharmaceutical composition comprising the fibroblast according to any of (D6) and (E1) to (E5) or the cell population according to any of (D7) and (E6) to (E7).

(F2) The pharmaceutical composition according to any of (F1), for treating a pulmonary disease.

(F3) The pharmaceutical composition according to (F2), wherein the pulmonary disease is pulmonary fibrosis or interstitial pneumonia.

(F4) The pharmaceutical composition according to (F1), for amelioration of a condition of lymphangiogenesis ability reduced.

(F5) The pharmaceutical composition according to any of (F1) to (F4), wherein the pharmaceutical composition is an injectable composition.

(F6) The pharmaceutical composition according to any of (F1) to (F4), wherein the fibroblast or the cell population is constructed as a planar or three-dimensional cellular tissue.

[0019] The present disclosure includes the following seventh example (Disclosure G).

(G1) A method for treating a pulmonary disease in a subject, the method comprising administrating or transplanting the fibroblast according to any of (D6) and (E1) to (E5), the cell population according to any of (D7) and (E6) to (E7) or the pharmaceutical composition according to (F1), to the subject.

(G2) The method according to (G1), wherein the pulmonary disease is pulmonary fibrosis or interstitial pneumonia.

(G3) A method for ameliorating a condition of lymphangiogenesis ability reduced, in

a subject, the method comprising administrating or transplanting the fibroblast according to any of (D6) and (E1) to (E5), the cell population according to any of (D7) and (E6) to (E7) or the pharmaceutical composition according to (F1), to the subject.

[0020]

The present disclosure includes the following eighth example (Disclosure H).

(H1) Use of the fibroblast according to any of (D6) and (E1) to (E5), the cell population according to any of (D7) and (E6) to (E7), or the pharmaceutical composition according to (F1), as an injection for administration to a lung tissue and/or its peripheral region.

(H2) Use of the fibroblast according to any of (D6) and (E1) to (E5), the cell population according to any of (D7) and (E6) to (E7) or the pharmaceutical composition according to (F1), as a transplantation material for transplantation to a lung tissue and/or its peripheral region.

EFFECT OF THE INVENTION

[0021] The present disclosure can provide a pharmaceutical composition including a fibroblast having lymphangiogenesis ability, namely, a pharmaceutical composition including a cell highly expressing ADM and/or HHEX, and also can provide a procedure for treating fibrosis, a procedure for ameliorating a condition of lymphangiogenesis ability reduced, and procedures for modulating homeostasis of a tissue fluid, transport of lipid and/or vitamin, and immunological surveillance, and for treating organ failure, by use of the pharmaceutical composition. The present disclosure can also provide a fibroblast highly expressing ADM, and a procedure for treating a pulmonary disease by use of the cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022]