

[DESCRIPTION]

[Title of Invention] PEPTIDE HAVING MESENCHYMAL STEM CELL MOBILIZING ACTIVITY

[Technical Field]

5 [0001]

The present application relates to peptides having an activity of mobilizing mesenchymal stem cells, compositions for mobilizing mesenchymal stem cells, and agents for treating diseases based on the mobilization of mesenchymal stem cells.

[Background Art]

10 [0002]

Mesenchymal stem cells contained in bone marrow fluid and the like have the ability to differentiate into various tissues (pluripotency) such as bone, cartilage, fat, muscle, nerve, and epithelium. In recent years, attempts have been widely made to perform regenerative medicine (cell transplantation therapy) using bone marrow-derived mesenchymal stem cells proliferated
15 by culture. However, collection of bone marrow blood containing mesenchymal stem cells is done with an invasive technique which inserts a thick needle into the iliac bone repeatedly, thereby placing a large burden on the donor. In addition, mesenchymal stem cells gradually lose their proliferative ability and pluripotency when subcultured continuously in vitro. Furthermore, culturing mesenchymal stem cells based on high quality control that guarantees the safety of in
20 vivo transplantation requires special culture equipment such as CPC (cell processing center), so the current situation is that it can be carried out only at a limited number of universities and companies.

[Citation List]

25 [Non-Patent Literature]

[0003]

[NPL 1] PNAS 2011 Apr 19; 108 (16): 6609-14

[Patent Literature]

[0004]

30 [PTL 1] WO2008/053892

[PTL 2] WO2009/133939

[PTL 3] WO2012/147470

[Summary]

35 [Technical Problem]

[0005]

An objective of the present application is to develop a new regenerative medicine technology that can overcome the problems of cell transplantation therapy.

[Solution to Problem]

[0006]

5 So far, based on their own research results, the present inventors have discovered an artificial sequence peptide “1r10” that has an activity of mobilizing mesenchymal stem cells into peripheral blood, and have filed a patent application on this peptide (PCT/JP2019/039232). This time, the present inventors synthesized a plurality of peptides each consisting of a partial sequence of the artificial sequence peptide “1r10” (hereinafter also referred to as “1r10 fragment peptides”),
10 investigated whether they have an activity of mobilizing mesenchymal stem cells into peripheral blood, and as a result, discovered that 1r10 fragment peptides having a specific sequence present the activity. Based on such findings, the present application provides peptides considered to show therapeutic effects on various diseases through mobilization of mesenchymal stem cells into peripheral blood.

15 [0006a]

 Therefore, in one aspect, the present disclosure relates to use of a peptide that is 29 amino acids or less in length and is selected from the following in manufacture of a medicament for treating a disease or pathological condition in a subject by mobilizing mesenchymal stem cells into peripheral blood:

20 (a) a peptide consisting of a portion of the amino acid sequence of SEQ ID NO: 1, and comprising the amino acid sequence of SEQ ID NO: 17 or 19;

 (b) a peptide consisting of a portion of an amino acid sequence resulting from substitution, deletion, insertion, or addition of one to five amino acids in the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19; and

25 (c) a peptide consisting of a portion of an amino acid sequence having a sequence identity of 90% or higher with the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19.,
 wherein the disease or pathological condition is selected from an inflammatory disease, an autoimmune disease, tissue damage, ischemia, necrosis, and a fibrotic disease.

30 [0006b]

 In another aspect, the present disclosure relates to use of a peptide that is 29 amino acids or less in length and is selected from the following in manufacture of a medicament for treating a disease selected from inflammatory bowel disease, atopic dermatitis, and cerebral infarction:

35 (a) a peptide consisting of a portion of the amino acid sequence of SEQ ID NO: 1, and comprising the amino acid sequence of SEQ ID NO: 17 or 19;

 (b) a peptide consisting of a portion of an amino acid sequence resulting from substitution,

deletion, insertion, or addition of one to five amino acids in the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19; and

(c) a peptide consisting of a portion of an amino acid sequence having a sequence identity of 90% or higher with the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19.

[0006c]

In another aspect, the present disclosure relates to a peptide that is 29 amino acids or less in length and is selected from the following:

(a) a peptide consisting of a portion of the amino acid sequence of SEQ ID NO: 1, and comprising the amino acid sequence of SEQ ID NO: 17 or 19;

(b) a peptide consisting of a portion of an amino acid sequence resulting from substitution, deletion, insertion, or addition of one to five amino acids in the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19; and

(c) a peptide consisting of a portion of an amino acid sequence having a sequence identity of 90% or higher with the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19.

[0006d]

In another aspect, the present disclosure relates to a peptide selected from the following:

(1) the peptide consisting of the amino acid sequence from position 1 to position 27 of SEQ ID NO: 1 (SEQ ID NO: 2);

(2) the peptide consisting of the amino acid sequence from position 1 to position 26 of SEQ ID NO: 1 (SEQ ID NO: 3);

(3) the peptide consisting of the amino acid sequence from position 1 to position 25 of SEQ ID NO: 1 (SEQ ID NO: 4);

(4) the peptide consisting of the amino acid sequence from position 1 to position 24 of SEQ ID NO: 1 (SEQ ID NO: 5);

(5) the peptide consisting of the amino acid sequence from position 1 to position 23 of SEQ ID NO: 1 (SEQ ID NO: 6);

(6) the peptide consisting of the amino acid sequence from position 1 to position 19 of SEQ ID NO: 1 (SEQ ID NO: 7);

(7) the peptide consisting of the amino acid sequence from position 1 to position 18 of SEQ ID NO: 1 (SEQ ID NO: 8);

(8) the peptide consisting of the amino acid sequence from position 1 to position 16 of SEQ ID NO: 1 (SEQ ID NO: 9);

(9) the peptide consisting of the amino acid sequence from position 6 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 11);

(10) the peptide consisting of the amino acid sequence from position 11 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 12);

(11) the peptide consisting of the amino acid sequence from position 12 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 13);

5 (12) the peptide consisting of the amino acid sequence from position 13 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 14);

(13) the peptide consisting of the amino acid sequence from position 16 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 15);

10 (14) the peptide consisting of the amino acid sequence from position 17 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 16);

(15) the peptide consisting of the amino acid sequence from position 18 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 17); and

(16) the peptide consisting of the amino acid sequence from position 6 to position 16 of SEQ ID NO: 1 (SEQ ID NO: 19).

15 [0007]

Specifically, the present application provides the following:

[1]

A composition for use in mobilizing mesenchymal stem cells into peripheral blood, which comprises a peptide selected from the following:

20 (a) a peptide consisting of a portion of the amino acid sequence of SEQ ID NO: 1, and comprising the amino acid sequence of SEQ ID NO: 17 or 19;

(b) a peptide consisting of all or a portion of an amino acid sequence resulting from substitution, deletion, insertion, or addition of one to five amino acids in the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19; and

25 (c) a peptide consisting of all or a portion of an amino acid sequence having a sequence identity of 90% or higher with the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19.

[2]

30 A composition for use in treatment of a disease or pathological condition in a subject by mobilizing mesenchymal stem cells into peripheral blood, which comprises a peptide selected from the following:

(a) a peptide consisting of a portion of the amino acid sequence of SEQ ID NO: 1, and comprising the amino acid sequence of SEQ ID NO: 17 or 19;

35 (b) a peptide consisting of all or a portion of an amino acid sequence resulting from substitution, deletion, insertion, or addition of one to five amino acids in the amino acid

[CLAIMS]

1. Use of a peptide that is 29 amino acids or less in length and is selected from the following in
5 manufacture of a medicament for treating a disease or pathological condition in a subject by
mobilizing mesenchymal stem cells into peripheral blood:

(a) a peptide consisting of a portion of the amino acid sequence of SEQ ID NO: 1, and
comprising the amino acid sequence of SEQ ID NO: 17 or 19;

10 (b) a peptide consisting of a portion of an amino acid sequence resulting from
substitution, deletion, insertion, or addition of one to five amino acids in the amino acid
sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID
NO: 17 or 19; and

15 (c) a peptide consisting of a portion of an amino acid sequence having a sequence
identity of 90% or higher with the amino acid sequence of SEQ ID NO: 1, wherein the peptide
comprises the amino acid sequence of SEQ ID NO: 17 or 19,
wherein the disease or pathological condition is selected from an inflammatory disease, an
autoimmune disease, tissue damage, ischemia, necrosis, and a fibrotic disease.

20 2. The use of claim 1, wherein the disease or pathological condition is inflammatory bowel
disease.

3. The use of claim 1, wherein the disease or pathological condition is ulcerative colitis.

25 4. The use of claim 1, wherein the disease or pathological condition is atopic dermatitis.

5. The use of claim 1, wherein the disease or pathological condition is cerebral infarction.

30 6. Use of a peptide that is 29 amino acids or less in length and is selected from the following in
manufacture of a medicament for treating a disease selected from inflammatory bowel disease,
atopic dermatitis, and cerebral infarction:

(a) a peptide consisting of a portion of the amino acid sequence of SEQ ID NO: 1, and
comprising the amino acid sequence of SEQ ID NO: 17 or 19;

35 (b) a peptide consisting of a portion of an amino acid sequence resulting from
substitution, deletion, insertion, or addition of one to five amino acids in the amino acid
sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID
NO: 17 or 19; and

(c) a peptide consisting of a portion of an amino acid sequence having a sequence identity of 90% or higher with the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19.

- 5 7. The use of any one of claims 1-6, wherein the peptide is selected from the following:
 - (1) the peptide consisting of the amino acid sequence from position 1 to position 27 of SEQ ID NO: 1 (SEQ ID NO: 2);
 - (2) the peptide consisting of the amino acid sequence from position 1 to position 26 of SEQ ID NO: 1 (SEQ ID NO: 3);
 - 10 (3) the peptide consisting of the amino acid sequence from position 1 to position 25 of SEQ ID NO: 1 (SEQ ID NO: 4);
 - (4) the peptide consisting of the amino acid sequence from position 1 to position 24 of SEQ ID NO: 1 (SEQ ID NO: 5);
 - (5) the peptide consisting of the amino acid sequence from position 1 to position 23 of
 - 15 SEQ ID NO: 1 (SEQ ID NO: 6);
 - (6) the peptide consisting of the amino acid sequence from position 1 to position 19 of SEQ ID NO: 1 (SEQ ID NO: 7);
 - (7) the peptide consisting of the amino acid sequence from position 1 to position 18 of SEQ ID NO: 1 (SEQ ID NO: 8);
 - 20 (8) the peptide consisting of the amino acid sequence from position 1 to position 16 of SEQ ID NO: 1 (SEQ ID NO: 9);
 - (9) the peptide consisting of the amino acid sequence from position 6 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 11);
 - (10) the peptide consisting of the amino acid sequence from position 11 to position 30
 - 25 of SEQ ID NO: 1 (SEQ ID NO: 12);
 - (11) the peptide consisting of the amino acid sequence from position 12 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 13);
 - (12) the peptide consisting of the amino acid sequence from position 13 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 14);
 - 30 (13) the peptide consisting of the amino acid sequence from position 16 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 15);
 - (14) the peptide consisting of the amino acid sequence from position 17 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 16);
 - (15) the peptide consisting of the amino acid sequence from position 18 to position 30
 - 35 of SEQ ID NO: 1 (SEQ ID NO: 17); and
 - (16) the peptide consisting of the amino acid sequence from position 6 to position 16 of

SEQ ID NO: 1 (SEQ ID NO: 19).

8. A peptide that is 29 amino acids or less in length and is selected from the following:

(a) a peptide consisting of a portion of the amino acid sequence of SEQ ID NO: 1, and comprising the amino acid sequence of SEQ ID NO: 17 or 19;

(b) a peptide consisting of a portion of an amino acid sequence resulting from substitution, deletion, insertion, or addition of one to five amino acids in the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19; and

(c) a peptide consisting of a portion of an amino acid sequence having a sequence identity of 90% or higher with the amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of SEQ ID NO: 17 or 19.

9. A peptide selected from the following:

(1) the peptide consisting of the amino acid sequence from position 1 to position 27 of SEQ ID NO: 1 (SEQ ID NO: 2);

(2) the peptide consisting of the amino acid sequence from position 1 to position 26 of SEQ ID NO: 1 (SEQ ID NO: 3);

(3) the peptide consisting of the amino acid sequence from position 1 to position 25 of SEQ ID NO: 1 (SEQ ID NO: 4);

(4) the peptide consisting of the amino acid sequence from position 1 to position 24 of SEQ ID NO: 1 (SEQ ID NO: 5);

(5) the peptide consisting of the amino acid sequence from position 1 to position 23 of SEQ ID NO: 1 (SEQ ID NO: 6);

(6) the peptide consisting of the amino acid sequence from position 1 to position 19 of SEQ ID NO: 1 (SEQ ID NO: 7);

(7) the peptide consisting of the amino acid sequence from position 1 to position 18 of SEQ ID NO: 1 (SEQ ID NO: 8);

(8) the peptide consisting of the amino acid sequence from position 1 to position 16 of SEQ ID NO: 1 (SEQ ID NO: 9);

(9) the peptide consisting of the amino acid sequence from position 6 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 11);

(10) the peptide consisting of the amino acid sequence from position 11 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 12);

(11) the peptide consisting of the amino acid sequence from position 12 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 13);

(12) the peptide consisting of the amino acid sequence from position 13 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 14);

(13) the peptide consisting of the amino acid sequence from position 16 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 15);

5 (14) the peptide consisting of the amino acid sequence from position 17 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 16);

(15) the peptide consisting of the amino acid sequence from position 18 to position 30 of SEQ ID NO: 1 (SEQ ID NO: 17); and

10 (16) the peptide consisting of the amino acid sequence from position 6 to position 16 of SEQ ID NO: 1 (SEQ ID NO: 19).