DESCRIPTION

TITLE OF THE INVENTION: PEPTIDE FOR INDUCING REGENERATION OF TISSUE, AND USE THEREOF

TECHNICAL FIELD

[0001] The present invention relates to a peptide for inducing regeneration of tissues, and uses thereof.

BACKGROUND ART

[0002] It has become even clearer that each of organs and tissues in the living bodies has tissue stem cells maintaining its structural and functional homeostasis. For example, the myocardial stem cells exist in the heart, the neural stem cells exist in the brain, and the epidermal stem cells and follicular stem cells exist in the skin, which supply myocardial cells, neural cells, epidermal cells, and follicular epithelial cells over the lifetime to maintain the structures and functions of the heart, the brain, and the skin. Meanwhile, the hematopoietic stem cells that differentiate into blood cells such as red blood cells, white blood cells, and platelets exist in the bone marrow.

These blood cells derived from the hematopoietic stem cells circulate all sorts of organs and tissues in the bodies through blood streams, and play some indispensable functions for life maintenance such as oxygen supply, immune responses, and hematostatis or recovery of damaged tissues. In other words, it is fair to say that the bone marrow hematopoietic stem cells contribute to the maintenance of homeostasis of all the tissues in

the live bodies via peripheral circulation, rather than the maintenance of homeostasis of the bone marrow or the bone tissues in which the bone marrow hematopoietic stem cells are localized.

[0003] In the recent years, it has been clarified that in addition to the hematopoietic stem cells, the mesenchymal stem cells that are differentiable into not only mesodermal tissues of bones, cartilages, adipose or the like, but also ectodermal tissues such as nerves and epidermides exist in the bone marrow; however, the existing significance in the live bodies has not yet been clarified in many ways. However, if the hematopoietic stem cells that maintain homeostasis of all the tissues and organs by supplying blood cells via the peripheral circulation exist in the bone marrow, there is similarly an expected possibility that the mesenchymal stem cells that exist in the bone marrow would also contribute to the maintenance of homeostasis of the tissues in the live bodies by providing cells that can differentiate into bones, cartilages, adipose, nerves, epithelia, or the like via the peripheral circulation to the tissues or organs in the live bodies in need thereof.

[0004] Currently, regenerative medicine has been actively developed, in which bone marrow mesenchymal stem cells are prepared by collection of the bone marrow blood, expanded by cell culture, and grafted to a damaged site of the intractable tissues or into the peripheral circulation blood to induce the regeneration of damaged tissues. The clinical applications of transplantation of the bone marrow mesenchymal stem cells have been already been underway in the regenerative medicine of cerebral infarction, myocardial infarction, intractable skin ulcer or the like. Further,

it has been clarified that the transplanted bone marrow mesenchymal stem cells exhibit an action of suppressing inflammations and immune responses and an action of suppressing fibrous scar formation locally in the live bodies, so that the clinical tests of the bone marrow mesenchymal stem cells transplantation therapy have been started as a new therapeutic method for graft versus host disease (GVHD), which is a serious side reaction after the bone marrow transplantation or transfusion, or for scleroderma, which is an autoimmune disease. However, the bone marrow blood containing the bone marrow mesenchymal stem cells is only collected by an invasive method in which thick needles are repeatedly pierced to the iliac bone. In addition, the bone marrow mesenchymal stem cells would gradually lose proliferation ability and pluripotency if the subculture is continued *ex vivo*. Further, the culture of the bone marrow mesenchymal stem cells based on the high-quality management that ensures safety of the *in vivo* transplantation would necessitate a specialized culturing equipment such as CPC (cell processing center), so that the cell culture is enabled at very limited universities or business enterprises at present. In other words, in order to make the regenerative medicine using the bone marrow mesenchymal stem cells available to many patients in the world suffering from intractable tissue damages, it is an urgent task to develop techniques for the regenerative medicine with the mesenchymal stem cells to be enabled in all sorts of medical facilities.

[0005] HMGB1 (High mobility group box 1: high mobility group box 1 protein) was identified about 30 years ago as a non-histone chromatin protein that controls the gene expression or repair of DNA by controlling

an intranuclear chromatin structure. The structure of the HMGB1 protein is constituted mainly by two DNA binding domains, in which a DNA binding domain at an N-terminal side is called an A-box, and a DNA binding domain at a C-terminal side is called a B-box. According to the past studies, it has been clarified that a domain that binds to TLR in the HMGB1 molecule and evokes an inflammatory reaction exists within the B-box.

[0006] It has been reported that the PDGFRα-positive cells are recruited in the blood from the bone marrow by administering mice generated with skin ulcer or cerebral infarction with a recombinant HMGB1 protein from tail vein, and further the cells are accumulated in the skin ulcer portion or the cerebral infarction portion, thereby strongly inducing the regeneration of skin ulcer or cerebral infarction. It has been already reported that the PDGFRα-positive cells in the bone marrow are mesenchymal stem cells that are differentiable into bones, cartilages, adipose, and further to nerves or epithelia. In other words, the PDGFRα-positive mesenchymal stem cells in the bone marrow are recruited to peripheral circulation by the HMGB1 administration, thereby making it possible to accumulate many of the mesenchymal stem cells in the damaged tissues in the live bodies without extracorporeally taking the cells, and subjecting them to a specialized culturing.

[0007] The regeneration-inducing medicine can be enabled with the bone marrow mesenchymal stem cells in all sorts of medical facilities by developing HMGB1 as a medicament for inducing regeneration of damaged tissues by the recruitment in blood of the bone marrow

mesenchymal stem cells in the live bodies. As a result, many of the disadvantages faced in the present regenerative medicine using the bone marrow mesenchymal stem cells would be overcome.

[0008] As mentioned above, the HMGB1 medicament is an epoch-making therapeutic agent which promotes the recruitment of the bone marrow mesenchymal stem cells in blood or the accumulation to damaged tissues, thereby inducing regeneration of tissues in the body. Regarding HMGB1, it has been already reported that not only a full length of HMGB1 protein but also fragments of the HMGB1 protein has a similar action.

PRIOR ART REFERENCES

PATENT PUBLICATIONS

[0009] Patent Publication 1: WO 2008/053892

Patent Publication 2: WO 2007/015546

Patent Publication 3: WO 2009/133939

Patent Publication 4: WO 2009/133943

Patent Publication 5: WO 2009/133940

Patent Publication 6: Japanese Unexamined Patent Publication No. 2005-537253

Patent Publication 7: WO 2012/147470

NON-PATENT PUBLICATIONS

[0010] Non-Patent Publication 1: Bustin et al., *Mol Cell Biol*, **19**:5237-5246, 1999

Non-Patent Publication 2: Hori et al., *J. Biol. Chem.*, **270**, 25752-

25761, 1995

Non-Patent Publication 3: Wang et al., *Science*, **285**:248-251, 1999

Non-Patent Publication 4: Muller et al., *EMBO J*, **20**:4337-4340, 2001

Non-Patent Publication 5: Wang et al., Science, **285**:248-251, 1999

Non-Patent Publication 6: Germani et al., *J Leukoc Biol.* Jan; **81**(1):41-5, 2007

Non-Patent Publication 7: Palumbo et al., *J. Cell Biol.*, 164:441-449, 2004

Non-Patent Publication 8: Merenmies et al., *J. Biol. Chem.*, **266**:16722-16729, 1991

Non-Patent Publication 9: Wu Y et al., *Stem cells*, **25**:2648-2659, 2007

Non-Patent Publication 10: Tamai et al., *Proc Natl Acad Sci USA.* 2011 Apr 4. [Epub ahead of print], **108**:6609-6614, 2011

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SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0011] An object to be solved by the present invention is to provide a peptide having activity of migrating bone marrow-derived stromal cells, in other words, a peptide for inducing regeneration of tissues.

MEANS TO SOLVE THE PROBLEMS

[0012] As a result of intensive studies, the present inventors have found out that a peptide having substitution of an amino acid of position 43 and/or position 44 in the peptide consisting of amino acids of position 1 to position 44 of the HMGB1 protein, and a peptide having substitution of an amino acid of position 43 and/or position 44 in the peptide consisting of the amino acids of position 2 to position 44 of the HMGB1 protein have the activity of migrating stromal cells derived from murine bone marrow, and the present invention has been perfected thereby.

[0013] Concretely, the present invention relates to:

(1) a peptide selected from the group consisting of:

a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403,

a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403, and having an activity of stimulating migration of cells,

a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 or an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in

SEQ ID NO: 403, and having an activity of stimulating migration of cells, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof;

(2) a peptide selected from the group consisting of:

a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283, 292 and 403,

a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283, 292 and 403, and having an activity of stimulating migration of cells, and

a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283 and 292, or an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells,

a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof;

(3) a peptide selected from the group consisting of:

a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 167 and 403,

a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 167 and 403, and having an activity of stimulating migration of cells, and

a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 167 or at an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells,

a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof;

(4) a peptide selected from the group consisting of:

a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 403,

a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2

to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 403, and having an activity of stimulating migration of cells, and

a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 or at an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof;

(5) a composition for use in stimulation of migration of PDGFRα-positive cells, containing a peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof as defined in any one of the above (1) to (4);

(6) a composition for use in recruitment of bone marrow mesenchymal stem cells from bone marrow to peripheral blood, containing a peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof as defined in any one of the above (1) to (4);

(7) a composition for use in regeneration of tissues, containing a peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof as defined in any one of the above (1) to (4); and

(8) a composition for use in stimulation of migration of bone marrow-derived stromal cells, containing a peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof as defined in any one of the above (1) to (4).

ADVANTAGEOUS EFFECTS OF THE INVENTION

[0014] The peptide of the present invention can be utilized as an active ingredient of, for example, a composition for use in stimulation of migration of PDGFRα-positive cells, a composition for use in recruitment of bone marrow mesenchymal stem cells from bone marrow to peripheral blood, a composition for use in regeneration of tissues, or a composition for use in stimulation of migration of bone marrow-derived stromal cells.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] [FIG. 1] FIG. 1 is a graph showing the results of the stability test of the peptides in plasma for six kinds of peptides (a peptide of position 2 to position 44 of human HMGB1 (2-44), and five kinds of peptides in which amino acids at position 43 or/and position 44 are modified (Peptide-1 to -5)). P1 to P5 mean the peptides of Peptide-1 to -5. The axis of ordinates is the remaining rate when the peptide immediately after the addition of the plasma was calculated as 100, and the axis of the abscissas is the time after the addition of the plasma. Here, the sample of 15 minutes or later after the addition of the plasma of the peptide of 2-44 was lower than the quantifiable lower limit (0.5 μg/mL), so that the remaining rate could not be plotted in FIG. 1.

[FIG. 2] FIG. 2 is a graph of the results of the measurements of the cell-migration activity of two kinds of peptides (a peptide of position 2 to position 44 of human HMGB1 (2-44), and a peptide in which the amino acids at position 43 and position 44 are modified (Peptide-6)). NC is a negative control.

[FIG. 3] FIG. 3 is a graph showing the results of the stability test in plasma of three kinds of peptides (a peptide of position 2 to position 44 of human HMGB1 (2-44), and two kinds of peptides in which amino acids at position 43 and position 44 are modified (Peptide-3 and -6)). The axis of ordinates is the remaining rate when the peptide immediately after the addition of the plasma was calculated as 100, and the axis of the abscissas is the time after the addition of the plasma.

MODES FOR CARRYING OUT THE INVENTION

[0016] The present invention provides a peptide as defined in any one of (a) to (c) given below:

(a) a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403;

(b) a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403, and having an activity of stimulating migration of cells; and

(c) a peptide comprising or consisting of an amino acid

sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 or an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells.

[0017] The present invention provides a composition for use in stimulation of migration of PDGFRα-positive cells or bone marrow-derived stromal cells, containing a peptide as defined in (a) to (c) given below:

(a) a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403;

(b) a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403, and having an activity of stimulating migration of cells; and

(c) a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 or an amino

acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells.

The composition for use in stimulation of migration of PDGFRα-positive cells or bone marrow-derived stromal cells of the present invention includes a reagent composition and a pharmaceutical composition. The reagent composition as used herein is also expressed as a reagent, and the pharmaceutical composition is also expressed as a medicament, a pharmaceutical agent, or a pharmaceutical composition.

[0018] The reagent composition for use in stimulation of migration of PDGFRα-positive cells or bone marrow-derived stromal cells of the present invention can be used as, for example, reagents that are necessary for basic researches and clinical researches in the developments of regenerative medicine and regeneration-inducing medicine. For example, cells are recruited in tissues in the live bodies in experimental animals by the use of the reagent composition, thereby making it possible to study the levels of tissue repair and tissue function reconstruction. Also, for example, the researches on inducing regeneration of tissues can be carried out by the recruitment of the cells *in vitro* by the use of the reagent composition.

[0019] In addition, the pharmaceutical composition for use in stimulation of migration of PDGFRα-positive cells or bone marrow-derived stromal cells of the present invention can be used as, for example, a medicament in the regenerative medicine and the regeneration-inducing medicine. For example, the tissues can be regenerated by the use of the pharmaceutical

composition. Also, for example, the pharmaceutical composition can prevent the lowering of the functions of tissues and organs by the decrease in the tissue stem cells as a so-called prophylactic medicament, or can delay the progress of aging changes as an anti-aging medicament.

[0020] Here, the composition for use in stimulation of migration of PDGFRα-positive cells or bone marrow-derived stromal cells as used herein is also expressed as an agent for use in stimulation of migration of PDGFRα-positive cells or bone marrow-derived stromal cells, a stimulation agent for cell migration, a composition for use in induction of cell migration, an agent for use in induction of cell migration, an inducing agent for cell migration, or an inducing agent of cells.

In the present invention the cell migration-stimulating activity means an activity of stimulating the cell migration. The cell migration-stimulating activity as used herein is also expressed as cell migration-inducing activity or cell-inducing activity.

[0021] The present invention provides a composition for use in recruitment of bone marrow mesenchymal stem cells from bone marrow to peripheral blood, containing a substance as defined in any one of the following (a) to (c):

(a) a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403;

(b) a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence

shown in any one of SEQ ID NOs: 1 to 399 and 403, and having an activity of stimulating migration of cells; and

(c) a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 or an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells.

The composition for use in recruitment of the bone marrow mesenchymal stem cells from bone marrow to peripheral blood of the present invention includes a reagent composition and a pharmaceutical composition.

[0022] The reagent composition for use in regeneration of tissues of the present invention can be used as, for example, reagents that are necessary for basic researches and clinical researches in the developments of regenerative medicine and regeneration-inducing medicine. In addition, the pharmaceutical composition for use in regeneration of tissues of the present invention can be used as, for example, a medicament in the regenerative medicine and the regeneration-inducing medicine. For example, the bone marrow cells are recruited to the peripheral circulation by the use of the pharmaceutical composition, so that the tissues can be regenerated. Also, for example, it is possible that the cells which are

recruited to the peripheral blood by utilizing the pharmaceutical composition are collected extracorporeally, concentrated, and administered to tissues to carry out the treatment. In the conventional methods, since the cells are collected from the bone marrow at the deep part in the body, the live bodies are subjected to invasiveness. However, when the pharmaceutical composition of the present invention is used, the bone marrow cells are collected from the peripheral blood at low invasion, which can be utilized in bone marrow cell transplantation or the like. Here, the composition for use in recruitment of the bone marrow mesenchymal stem cells from bone marrow to peripheral blood is also expressed as a composition for use in induction of the bone marrow mesenchymal stem cells from bone marrow to peripheral blood.

[0023] The present invention provides a composition for use in regeneration of tissues, containing a substance as defined in any one of the following (a) to (c):

(a) a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403;

(b) a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403, and having an activity of stimulating migration of cells; and

(c) a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino

acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 or an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells.

The composition for use in regeneration of tissues of the present invention includes a reagent composition and a pharmaceutical composition.

[0024] The reagent composition for use in regeneration of tissues of the present invention can be used as, for example, reagents that are necessary for basic researches and clinical researches in the developments of regenerative medicine and regeneration-inducing medicine. In addition, the pharmaceutical composition for use in regeneration of tissues of the present invention can be used as, for example, a medicament in the regenerative medicine and the regeneration-inducing medicine.

[0025] Here, the composition for use in regeneration of tissues as used herein is also expressed as a composition for use in induction or promotion of regeneration of tissues, an agent for use in induction or promotion of regeneration of tissues, a tissue regeneration-inducing agent or a tissue regeneration-promoting agent. In addition, the regeneration of tissues includes tissue repair.

[0026] The composition for use in regeneration of tissues of the present invention can be administered or added to any sites. In other words, the

composition can exhibit its effects even when administered to any of tissues such as tissues in need of regeneration, tissues different from the tissues in need of regeneration, in blood, or the like. For example, when the composition is administered or added, the cells are recruited to a site to be administered or to be added or a tissue in a vicinity thereof, thereby inducing or promoting the regeneration of tissues. Also, for example, when the composition is administered or added to a damaged tissue site or a vicinity thereof, the cells are recruited in the damaged tissues, thereby inducing or promoting the regeneration of tissues. In addition, for example, when the composition is administered or added to a tissue different from the tissues in need of regeneration, the bone marrow cells are recruited from the bone marrow to the tissues in need of regeneration via the peripheral circulation, thereby inducing or promoting the regeneration of tissues. Here, the "peripheral circulation" is also called "blood circulation" or "peripheral circulation bloodstream."

[0027] The tissues in need of regeneration include damaged tissues, necrotic tissues, tissues after surgery, tissues with reduced function, fibrotic tissues, aged tissues, diseased tissues, and the like. Examples include live body skin tissues and tissues from internal biopsy (surgery) (brain, lungs, heart, liver, stomach, small intestine, large intestine, pancreas, kidneys, urinary bladders, spleens, uterus, testis, blood, etc.).

[0028] The administration to the tissues different from the tissues in need of regeneration means administration to a site other than a site in need of regeneration (site different from the site in need of regeneration). Therefore, the "tissues different from the tissues in need of regeneration"

can be expressed as a site different from the tissues in need of regeneration, a site different from a site in need of regeneration, a site away from the tissues in need of regeneration, a site away from a site in need of regeneration, a site distal from a site in need of regeneration, a site distal from the tissues in need of regeneration, a distal site, or a distal tissue. In other words, the composition of the present invention is effectively used in regeneration of tissues (brain, heart, etc.) that are difficult to be directly administered with a pharmaceutical agent from outside of the body.

[0029] The cells recruited to the tissues in need of regeneration differentiate into various cells to contribute to functional regeneration of the tissues in need of regeneration and to maintenance of functions or enhancement of functions of the tissues. In the present invention, the tissues in need of regeneration include tissues damaged by various pathologies caused by ischemic, hypoperfusive or hypoxic conditions, trauma, burns, inflammation, autoimmunity, genetic abnormalities, and the like, without being limited to these causes.

[0030] The tissues in the present invention are not particularly limited so long as they are tissues into which the bone marrow-derived cells can differentiate, which include, for example, all the tissues in the live bodies, such as skin tissues, bone tissues, cartilage tissues, muscle tissues, adipose tissues, cardiomuscular tissues, nervous system tissues, pulmonary tissues, digestive tract tissues, hepatic, biliary, and pancreatic tissues, and urogenital organs. In addition, it is made possible to carry out the treatment of inducing functional tissue regeneration in not only a cutaneous disease such as intractable skin ulcers, skin wounds,

hydroa/bullous disease, or alopecia, but also in tissues in need of regeneration of cerebral infarction, myocardial infarction, bone fracture, pulmonary infarction, gastric ulcer, enteritis, or the like by the use of the above composition. The animal species to be administered with the above composition is not particularly limited, and includes mammals, birds, fish, and the like. The mammals include human or non-human animals, including, for example, human, mice, rats, monkeys, pigs, dogs, rabbits, hamsters, guinea pigs, horses, sheep, whales, and the like, but not particularly limited thereto.

[0031] In addition, the tissues different from the tissues in need of regeneration include blood tissues, muscular tissues, subcutaneous tissues, intradermal tissues, abdominal cavity, and the like.

[0032] The neural tissues include central nervous tissues, but not limited thereto. Also, the composition for use in regeneration of neural tissues can be used, for example, in the treatment of cerebral infarction, cerebral hemorrhage, brain contusion or the like, but not limited thereto. In addition, the composition for use in regeneration of bone tissues can be used, for example, in the treatment of bone fracture, but not limited thereto. Also, the composition for use in regeneration of skin tissues can be used, for example, in the treatment of skin ulcers, insufficient suture closure of surgical wounds, burns, cuts, bruises, skin erosion, abrasions, or the like, but not limited thereto.

[0033] In addition, in the present invention, the cells that are stimulated to migrate or the cells that are recruited from bone marrow to peripheral blood include undifferentiated cells and cells in different differentiation

stages, but not limited thereto. Also, in the present invention, the cells that are stimulated to migrate or the cells that are recruited from bone marrow to peripheral blood include stem cells, non-stem cells, and the like, but not limited thereto. The stem cells include circulatory stem cells or non-circulatory stem cells. The non-circulatory stem cells include tissue stem cells that reside in the tissues. The circulatory stem cells include circulatory stem cells in blood.

[0034] Also, the cells that are stimulated to migrate or the cells that are recruited from bone marrow to peripheral blood include bone marrow-derived cells or hematopoietic stem cells, but not limited thereto. The "hematopoietic stem cells" as used herein are stem cells that can differentiate into blood cells such as red blood cells, platelets, mast cells, and dendritic cells, as well as white blood cells such as neutrophils, eosinophils, basophils, lymphocytes, monocytes, and macrophages. The markers thereof have been known to be CD34-positive, CD133-positive in human, CD34-negative, c-Kit-positive, Sca-1-positive, lineage marker-negative in mice. In addition, the hematopoietic stem cells have the feature that when cultured in a culture dish, it is difficult to culture alone, so that it is necessary to be co-cultured with stromal cells.

[0035] The term "bone marrow cells" as used herein means cells that are present in the bone marrow, while the term "bone marrow-derived cells" means "bone marrow cells" recruited or taken out from bone marrow to outside the bone marrow. The term "bone marrow cells" includes cells containing tissue progenitor cell population that are present in the bone marrow. In addition, the term "bone marrow-derived cells" may be cells

containing mesoangioblasts, or may be cells excluding the mesoangioblasts.

[0036] The tissue progenitor cells are defined as undifferentiated cells having a unidirectional differentiability into specified tissue cells other than the blood system, and include undifferentiated cells having differentiability into mesenchymal tissues, epithelial tissues, neural tissues, parenchymatous organs, and vascular endothelia mentioned above.

[0037] The terms "bone marrow cells" and "bone marrow-derived cells" are hematopoietic stem cells and differentiated cells derived therefrom such as white blood cells, red blood cells, platelets, osteoblasts, and fibrocytes, or are stem cells which are represented by cells which have been hitherto called bone marrow mesenchymal stem cells, bone marrow mesenchymal stromal cells, bone marrow pluripotent stromal cells, or bone marrow pluripotent stem cells. The term "bone marrow stem cells" as used herein means stem cells existing in the bone marrow, and on the other hand, the term "bone marrow-derived stem cells" means "bone marrow stem cells" that are recruited or taken out from the bone marrow to outside of the bone marrow. In the present invention, the cells that are stimulated to migrate or the cells that are recruited from bone marrow to peripheral blood include "bone marrow-derived stem cells," but not limited thereto. The "bone marrow cells" and the "bone marrow-derived cells" can be isolated by collection from bone marrow (collection of bone marrow cells), or peripheral blood collection. The hematopoietic stem cells are non-adherent cells, and some of the "bone marrow cells" and the "bone marrow-derived cells" are obtained as adherent cells by means of a cell culture of a monocyte fraction in blood obtained by collection from bone

marrow (collection of bone marrow cells), or peripheral blood collection.

[0038] In addition, the "bone marrow cells" and the "bone marrow-derived cells" include mesenchymal stem cells, and preferably have a potential to differentiate into osteoblasts (which can be specified by observing calcium deposition when inducing differentiation), chondrocytes (which can be specified by Alcian blue staining-positive, safranin-O staining positive, etc.), adipocytes (which can be specified by Sudan III staining positive), and further mesenchymal cells such as fibroblasts, smooth muscle cells, stromal cells, tendon cells, further neural cells, epithelial cells (e.g., epidermal keratinocytes and intestinal epithelial cells expressing cytokeratin family), and vascular endothelial cells. The differentiated cells are not limited to the above cells, and also include the potential to differentiate into cells of parenchymatous organs such as liver, kidneys, and pancreas.

[0039] The term "bone marrow stromal cells" as used herein refer to cells other than the hematopoietic stem cells and the blood cells derived therefrom among the cells that exist in the bone marrow, which are collected from the bone marrow and capable of being cultured and proliferated as adherent cells on a culture dish. The bone marrow stromal cells or the bone marrow-derived stromal cells that are taken outside of the bone marrow include cells having pluripotency (bone marrow pluripotent stromal cells or bone marrow-derived pluripotent stromal cells). In addition, the bone marrow-derived stromal cells may be established as a cell line. Examples of the bone marrow-derived stromal cells in cell line include ST2 cells (Ogawa et al., *EMBO J* 1988; 7:1337-43), and the like.

The ST2 cells are bone marrow-derived pluripotent stromal cell lines having a differentiating ability into osteoblasts and adipocytes.

[0040] The term "bone marrow mesenchymal stem cells" as used herein is used interchangeably with the terms "bone marrow mesenchymal stromal cells," "bone marrow pluripotent stromal cells," and "bone marrow pluripotent stem cells." The "bone marrow mesenchymal stem cells" as used herein refer to cells that exist in the bone marrow, which are collected directly from the bone marrow, or indirectly from other tissues (blood, skin, adipose, and other tissues), and can be cultured and proliferated as adherent cells on a culture dish (made of plastic or glass). The cells have the characteristics of having a potential to differentiate into mesenchymal tissues such as bones, cartilages, and adipose (mesenchymal stem cells), or into skeletal muscles, heart muscles, and further neural tissues, and epithelial tissues (pluripotent stem cells), and can be obtained by collection of bone marrow cells.

[0041] On the other hand, the "bone marrow-derived mesenchymal stem cells," the "bone marrow-derived mesenchymal stromal cells," the "bone marrow-derived pluripotent stromal cells," or the "bone marrow-derived pluripotent stem cells" that are recruited from bone marrow to outside the bone marrow are cells which can be obtained by collection of peripheral blood, or further by collection from mesenchymal tissues such as adipose, epithelial tissues such as skins, or neural tissues such as brain.

[0042] In addition, these cells also have the characteristics of having a potential to differentiate into, for example, epithelial tissues such as keratinocytes constituting the skins, or tissues of the nervous system

constituting the brain, when the cells are administered to a damaged site of live bodies immediately after collection or after once being adhered onto a culture dish.

[0043] The bone marrow mesenchymal stem cells, the bone marrow mesenchymal stromal cells, the bone marrow pluripotent stromal cells, and the bone marrow pluripotent stem cells, or these cells that are recruited from the bone marrow to outside the bone marrow preferably have a potential to differentiate into osteoblasts (which can be specified by observing calcium deposition when inducing differentiation), chondrocytes (which can be specified by Alcian blue staining-positive, safranin-O staining positive, etc.), adipocytes (which can be specified by Sudan III staining positive), and, for example, mesenchymal cells such as fibroblasts, smooth muscle cells, skeletal muscle cells, stromal cells, and tendon cells; neural cells, pigment cells, epidermal cells, hair follicle cells (expressing cytokeratin family, hair keratin family, etc.), epithelial cells (e.g., epidermal keratinocytes and intestinal epithelial cells expressing cytokeratin family), and endothelial cells, and further have a potential to differentiate into cells of parenchymatous organs such as liver, kidneys, and pancreas, but the differentiated cells are not limited to the above cells.

[0044] Human bone marrow cells and human bone marrow-derived cells include, but are not limited to, cells that can be obtained by collection from bone marrow (collection of bone marrow cells), peripheral blood collection, or collection of adipose, and can be obtained as adherent cells by direct culture or by culturing an isolated monocyte fraction. Markers for the human bone marrow cells or the human bone marrow-derived cells (e.g.,

bone marrow mesenchymal stem cells) include all or part(s) of PDGFRα-positive, PDGFRβ-positive, Lin-negative, CD45-negative, CD44-positive, CD90-positive, CD29-positive, Flk-1-negative, CD105-positive, CD73-positive, CD90-positive, CD71-positive, Stro-1-positive, CD106-positive, CD166-positive, CD31-negative, CD271-positive, and CD11b-negative, but not limited thereto.

[0045] In addition, murine bone marrow cells and murine bone marrow-derived cells include, but are not limited to, cells that can be obtained by collection from bone marrow (collection of bone marrow cells), peripheral blood collection, or collection of adipose, and can be obtained as adherent cells by direct culture or by culturing an isolated monocyte fraction. Markers for the murine bone marrow cells or murine marrow-derived cells (e.g., bone marrow mesenchymal stem cells) include all or part(s) of CD44-positive, PDGFRα-positive, PDGFRβ-positive, CD45-negative, Lin-negative, Sca-1-positive, c-kit-negative, CD90-positive, CD29-positive, Flk-1-negative, CD271-positive, and CD11b-negative, but not limited thereto.

[0046] In the present invention, the cells that are stimulated to migrate or the cells that are recruited from bone marrow to peripheral blood include PDGFRα-positive cells, but not limited thereto. In addition, the markers other than PDGFRα include all or part(s) of CD29-positive, CD44-positive, CD90-positive, CD271-positive, CD11b-negative, and Flk-1-negative, but not limited thereto. The PDGFRα-positive cells include, but are not limited to, PDGFRα-positive bone marrow-derived cells, PDGFRα-positive bone marrow-derived mesenchymal stem cells, tissue cells

residing in the PDGFRα-positive tissues (including, e.g., fibroblasts, etc.), PDGFRα-positive bone marrow-derived cells obtained as adherent cells by cell culture of a monocyte fraction in blood obtained by collection from bone marrow (collection of bone marrow cells) or by peripheral blood collection, or the like.

[0047] The composition of the present invention may contain a substance other than at least one member of the peptides as defined in any one of the above (a) to (c). In the composition of the present invention, the substance other than at least one member of the peptides as defined in the above (a) to (c) is not particularly limited so long as the substance does not inhibit the activity of stimulating cell migration, the activity of recruiting the cells, or the activity of promoting tissue regeneration. For example, the composition of the present invention may contain, in addition to at least one member of the peptides as defined in the above (a) to (c), related molecule(s) enhancing the function(s) of the peptides as defined in the above (a) to (c), molecule(s) suppressing the actions other than the expected effects of the peptides as defined in the above (a) to (c), factors controlling proliferation or differentiation of cells, and other factors enhancing and maintaining the functions of these factors or cells.

[0048] The human HMGB1 protein in the present invention means a protein consisting of the amino acid sequence shown in SEQ ID NO: 401 as a human-derived HMGB1 protein. In addition, a peptide consisting of an amino acid sequence of position 1 to position 44 of the HMGB1 protein means a peptide consisting of the amino acid sequence shown in SEQ ID NO: 402.

[0049] The activity of stimulating cell migration of the peptide can be confirmed by, for example, a method described in Examples, or a method disclosed in WO 2012/147470, but not limited thereto.

[0050] The stability of the peptide in plasma can be confirmed by, for example, a method described in Examples, but not limited thereto.

[0051] The peptide of the present invention can be exemplified by the peptides consisting of the following amino acid sequences, but not limited to the followings.

(1) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSKP (SEQ ID NO: 1)

(2) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSPK (SEQ ID NO: 2)

(3) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSPP (SEQ ID NO: 3)

(4) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSKA (SEQ ID NO: 4)

(5) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSKE (SEQ ID NO: 5)

(6) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAA (SEQ ID NO: 6)

(7) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAC (SEQ ID NO: 7)

(8) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAD (SEQ ID NO: 8)

(9) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE

FSAE (SEQ ID NO: 9)

(10) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAF (SEQ ID NO: 10)

(11) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAG (SEQ ID NO: 11)

(12) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAH (SEQ ID NO: 12)

(13) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAI (SEQ ID NO: 13)

(14) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAK (SEQ ID NO: 14)

(15) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAL (SEQ ID NO: 15)

(16) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAM (SEQ ID NO: 16)

(17) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAN (SEQ ID NO: 17)

(18) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAP (SEQ ID NO: 18)

(19) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAQ (SEQ ID NO: 19)

(20) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAR (SEQ ID NO: 20)

(21) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAS (SEQ ID NO: 21)

(22) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAT (SEQ ID NO: 22)

(23) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAV (SEQ ID NO: 23)

(24) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAW (SEQ ID NO: 24)

(25) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSAY (SEQ ID NO: 25)

(26) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCA (SEQ ID NO: 26)

(27) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCC (SEQ ID NO: 27)

(28) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCD (SEQ ID NO: 28)

(29) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCE (SEQ ID NO: 29)

(30) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCF (SEQ ID NO: 30)

(31) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCG (SEQ ID NO: 31)

(32) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCH (SEQ ID NO: 32)

(33) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCI (SEQ ID NO: 33)

(34) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE

FSCK (SEQ ID NO: 34)

(35) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCL (SEQ ID NO: 35)

(36) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCM (SEQ ID NO: 36)

(37) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCN (SEQ ID NO: 37)

(38) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCP (SEQ ID NO: 38)

(39) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCQ (SEQ ID NO: 39)

(40) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCR (SEQ ID NO: 40)

(41) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCS (SEQ ID NO: 41)

(42) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCT (SEQ ID NO: 42)

(43) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCV (SEQ ID NO: 43)

(44) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCW (SEQ ID NO: 44)

(45) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSCY (SEQ ID NO: 45)

(46) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDA (SEQ ID NO: 46)

(47) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDC (SEQ ID NO: 47)

(48) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDD (SEQ ID NO: 48)

(49) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDE (SEQ ID NO: 49)

(50) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDF (SEQ ID NO: 50)

[0052] (51) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDG (SEQ ID NO: 51)

(52) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDH (SEQ ID NO: 52)

(53) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDI (SEQ ID NO: 53)

(54) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDK (SEQ ID NO: 54)

(55) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDL (SEQ ID NO: 55)

(56) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDM (SEQ ID NO: 56)

(57) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDN (SEQ ID NO: 57)

(58) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDP (SEQ ID NO: 58)

(59) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE

FSDQ (SEQ ID NO: 59)

(60) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDR (SEQ ID NO: 60)

(61) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDS (SEQ ID NO: 61)

(62) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDT (SEQ ID NO: 62)

(63) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDV (SEQ ID NO: 63)

(64) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDW (SEQ ID NO: 64)

(65) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSDY (SEQ ID NO: 65)

(66) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEA (SEQ ID NO: 66)

(67) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEC (SEQ ID NO: 67)

(68) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSED (SEQ ID NO: 68)

(69) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEE (SEQ ID NO: 69)

(70) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEF (SEQ ID NO: 70)

(71) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEG (SEQ ID NO: 71)

(72) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEH (SEQ ID NO: 72)

(73) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEI (SEQ ID NO: 73)

(74) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEK (SEQ ID NO: 74)

(75) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEL (SEQ ID NO: 75)

(76) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEM (SEQ ID NO: 76)

(77) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEN (SEQ ID NO: 77)

(78) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEP (SEQ ID NO: 78)

(79) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEQ (SEQ ID NO: 79)

(80) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSER (SEQ ID NO: 80)

(81) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSES (SEQ ID NO: 81)

(82) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSET (SEQ ID NO: 82)

(83) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEV (SEQ ID NO: 83)

(84) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE

FSEW (SEQ ID NO: 84)

(85) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSEY (SEQ ID NO: 85)

(86) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFA (SEQ ID NO: 86)

(87) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFC (SEQ ID NO: 87)

(88) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFD (SEQ ID NO: 88)

(89) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFE (SEQ ID NO: 89)

(90) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFF (SEQ ID NO: 90)

(91) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFG (SEQ ID NO: 91)

(92) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFH (SEQ ID NO: 92)

(93) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFI (SEQ ID NO: 93)

(94) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFK (SEQ ID NO: 94)

(95) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFL (SEQ ID NO: 95)

(96) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFM (SEQ ID NO: 96)

(97) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFN (SEQ ID NO: 97)

(98) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFP (SEQ ID NO: 98)

(99) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFQ (SEQ ID NO: 99)

(100) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFR (SEQ ID NO: 100)

[0053] (101) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFS (SEQ ID NO: 101)

(102) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFT (SEQ ID NO: 102)

(103) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFV (SEQ ID NO: 103)

(104) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFW (SEQ ID NO: 104)

(105) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSFY (SEQ ID NO: 105)

(106) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGA (SEQ ID NO: 106)

(107) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGC (SEQ ID NO: 107)

(108) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGD (SEQ ID NO: 108)

(109) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK

HPDASVNFSE FSGE (SEQ ID NO: 109)

(110) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGF (SEQ ID NO: 110)

(111) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGG (SEQ ID NO: 111)

(112) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGH (SEQ ID NO: 112)

(113) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGI (SEQ ID NO: 113)

(114) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGK (SEQ ID NO: 114)

(115) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGL (SEQ ID NO: 115)

(116) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGM (SEQ ID NO: 116)

(117) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGN (SEQ ID NO: 117)

(118) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGP (SEQ ID NO: 118)

(119) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGQ (SEQ ID NO: 119)

(120) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGR (SEQ ID NO: 120)

(121) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGS (SEQ ID NO: 121)

(122) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGT (SEQ ID NO: 122)

(123) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGV (SEQ ID NO: 123)

(124) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGW (SEQ ID NO: 124)

(125) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSGY (SEQ ID NO: 125)

(126) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHA (SEQ ID NO: 126)

(127) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHC (SEQ ID NO: 127)

(128) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHD (SEQ ID NO: 128)

(129) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHE (SEQ ID NO: 129)

(130) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHF (SEQ ID NO: 130)

(131) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHG (SEQ ID NO: 131)

(132) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHH (SEQ ID NO: 132)

(133) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHI (SEQ ID NO: 133)

(134) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK

HPDASVNFSE FSHK (SEQ ID NO: 134)

(135) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHL (SEQ ID NO: 135)

(136) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHM (SEQ ID NO: 136)

(137) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHN (SEQ ID NO: 137)

(138) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHP (SEQ ID NO: 138)

(139) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHQ (SEQ ID NO: 139)

(140) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHR (SEQ ID NO: 140)

(141) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHS (SEQ ID NO: 141)

(142) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHT (SEQ ID NO: 142)

(143) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHV (SEQ ID NO: 143)

(144) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHW (SEQ ID NO: 144)

(145) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSHY (SEQ ID NO: 145)

(146) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSIA (SEQ ID NO: 146)

(147) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSIC (SEQ ID NO: 147)

(148) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSID (SEQ ID NO: 148)

(149) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSIE (SEQ ID NO: 149)

(150) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSIF (SEQ ID NO: 150)

[0054] (151) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSIG (SEQ ID NO: 151)

(152) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSIH (SEQ ID NO: 152)

(153) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSII (SEQ ID NO: 153)

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(360) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWA (SEQ ID NO: 360)

(361) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWC (SEQ ID NO: 361)

(362) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWD (SEQ ID NO: 362)

(363) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWE (SEQ ID NO: 363)

(364) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWF (SEQ ID NO: 364)

(365) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWG (SEQ ID NO: 365)

(366) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWH (SEQ ID NO: 366)

(367) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWI (SEQ ID NO: 367)

(368) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWK (SEQ ID NO: 368)

(369) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWL (SEQ ID NO: 369)

(370) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWM (SEQ ID NO: 370)

(371) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWN (SEQ ID NO: 371)

(372) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWP (SEQ ID NO: 372)

(373) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWQ (SEQ ID NO: 373)

(374) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWR (SEQ ID NO: 374)

(375) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWS (SEQ ID NO: 375)

(376) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWT (SEQ ID NO: 376)

(377) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWV (SEQ ID NO: 377)

(378) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWW (SEQ ID NO: 378)

(379) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSWY (SEQ ID NO: 379)

(380) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYA (SEQ ID NO: 380)

(381) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYC (SEQ ID NO: 381)

(382) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYD (SEQ ID NO: 382)

(383) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYE (SEQ ID NO: 383)

(384) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK

HPDASVNFSE FSYF (SEQ ID NO: 384)

(385) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYG (SEQ ID NO: 385)

(386) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYH (SEQ ID NO: 386)

(387) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYI (SEQ ID NO: 387)

(388) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYK (SEQ ID NO: 388)

(389) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYL (SEQ ID NO: 389)

(390) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYM (SEQ ID NO: 390)

(391) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYN (SEQ ID NO: 391)

(392) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYP (SEQ ID NO: 392)

(393) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYQ (SEQ ID NO: 393)

(394) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYR (SEQ ID NO: 394)

(395) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYS (SEQ ID NO: 395)

(396) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYT (SEQ ID NO: 396)

(397) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYV (SEQ ID NO: 397)

(398) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYW (SEQ ID NO: 398)

(399) MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSYY (SEQ ID NO: 399)

(400) GKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSPP (SEQ ID NO: 403)

[0059] The peptide of the present invention further includes a peptide having substitution of an amino acid at position 43 or/and position 44 of the peptide shown in the above SEQ ID NOs: 1 to 399 with a non-naturally occurring amino acid, and a peptide having substitution of an amino acid at position 42 or/and position 43 of the peptide shown in the above SEQ ID NO: 403 with a non-naturally occurring amino acid.

[0060] The peptide of the present invention may have a conservative substitution of an amino acid or amino acids in the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5. The conservative substitution refers to substitution with another amino acid having a structure or properties chemically similar to those of the original amino acid, without undergoing substantial changes in the functions of the peptide. Examples of the conservative substitution include mutual substitutions between aspartic acid and glutamic acid which are acidic amino acids; mutual substitutions between lysine, arginine, and histidine which are basic amino acids; mutual substitutions between serine, threonine, asparagine, and glutamine which are hydrophilic amino acids;

and the like. For example, a peptide of SEQ ID NO: 167 is a product in which glutamic acid (E) at position 44 of the peptide of SEQ ID NO: 5 is substituted with aspartic acid (D), which is considered to have a function equivalent to that of the peptide of SEQ ID NO: 5. Further, peptides shown in SEQ ID NOs: 126, 128, 129, 138, 248, 254, 280, 282, 283 and 292 also have a conservative substitution of the amino acid in the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, which are considered to have the function equivalent to that of any one of the peptide of SEQ ID NOs: 1 to 5. In one embodiment, the peptide of the present invention has the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283, 292 and 403. In one more preferred embodiment, the peptide of the present invention has the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 167 and 403, and in one even more preferred embodiment, the peptide of the present invention has the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 403, from the viewpoint that the peptide is expected to have the above function more surely.

[0061] Therefore, one of preferred embodiments of the peptide defined in the above (a) is a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283, 292 and 403, one of more preferred embodiment is a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 167 and 403, and one of even more preferred embodiment is a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 403.

[0062] Further, one of preferred embodiments of the peptide defined in the above (b) is a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283, 292 and 403, and having an activity of stimulating migration of cells, one of more preferred embodiment is a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 167 and 403, and having an activity of stimulating migration of cells, and one of even more preferred embodiment is a peptide consisting of an amino acid sequence having addition of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 403, and having an activity of stimulating migration of cells.

[0063] Further, one of preferred embodiments of the peptide as defined in the above (c) is a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an

amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283 and 292 or an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells, one of more preferred embodiments is a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 167 or an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells, and one of even more preferred embodiments is a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids, e.g., 2 to 40 amino acids, 2 to 30 amino acids, 2 to 20 amino acids, 2 to 10 amino acids, 2 to 5 amino acids, or 4, 3, or 2 amino acids, at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 or an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells.

[0064] The term "derivative" of the peptide of the present invention means a peptide having substantially the same biological function or activity as

the peptide of the present invention, in other words, the activity of stimulating migration of cells. The C-terminal of the derivative of the peptide may be any one of a carboxyl group, a carboxylate, an amide, or an ester. For example, the derivative includes a modified peptide obtained by addition of a modifying group, a mutant peptide obtained by altering an amino acid residue, and the like.

The modifying group includes functional groups showing fluorescent properties, functional groups not involved in the formation of conformation of a peptide, and the like. In addition, the modifying group may be an amino acid residue (for example, β-alanine etc.) other than an amino acid residue constituting the naturally occurring peptide of the present invention. The functional group showing fluorescent properties includes eosin, fluorescein isothiocyanate (FITC) and the like. The functional groups not involved in the formation of conformation of a peptide include spacer groups represented by β-alanine residues, and the like. It is preferable that the functional group is present at a terminal. Further, a peptide modified with polyethylene glycol (PEG) is also included in the "derivative."

[0065] The term "pharmaceutically acceptable salt" of the peptide of the present invention includes physiologically acceptable salts with acids or bases, and particularly acid-added salts are preferred. As the salt as mentioned above, a salt with an inorganic acid such as hydrochloric acid, phosphoric acid, hydrobromic acid, or sulfuric acid, a salt with an organic acid such as acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic

acid, methanesulfonic acid, or benzenesulfonic acid, or the like is used.

[0066] The term "solvate" of the peptide of the present invention or the above salt includes those in which any number of solvent molecules are coordinated to the peptide of the present invention, and preferably a hydrate.

[0067] The present invention provides the peptide as described above. In the synthesis of the peptide in the present invention, the peptide can be chemically synthesized according to any of the methods of the peptide liquid phase synthesis methods and the peptide solid phase synthesis methods. In the present invention, the peptide synthesized according to the peptide solid phase synthesis method is preferred. The peptide solid phase synthesis method is one of the generally employed methods when peptides are chemically synthesized, which can be, for example, carried out as follows: Using as a solid phase beads of polystyrene polymer gel having a diameter of 0.1 mm or so of which surfaces are modified with amino groups, an amino acid chain is extended one by one by dehydration reaction therefrom. When an intended sequence of the peptide is prepared, the peptide is cut out from the solid phase surface, to obtain an intended substance.

According to the solid phase synthesis method, it is made possible to perform the synthesis of ribosomal peptide which is difficult to synthesize in bacteria, introduction of a non-naturally occurring amino acid such as D-form or heavy atom substituted compound, modification of peptide and protein main chain, or the like. When a long peptide chain of from 70 to exceeding 100 peptides is synthesized in the solid phase method,

the peptide chains can be synthesized by binding two peptide chains using a native chemical ligation method.

[0068] The method for administration of a composition of the present invention includes oral administration or parenteral administration, and specific methods of the parenteral administration include injection administration, transnasal administration, transpulmonary administration, transdermal administration, and the like, but not limited thereto. As examples of the injection administration, for example, a composition of the present invention can be administered systemically or locally (e.g., subcutaneously, intradermally, epidermally, to eyeball or palpebral conjunctiva, to nasal cavity mucosa, to oral cavity and gastrointestinal mucosa, to vaginal or intrauterine mucosa, to a damaged site, etc.) by intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection or the like.

[0069] In addition, the method for administration of a composition of the present invention includes, for example, intravascular administration (intraarterial administration, intravenous administration, etc.), blood administration, intramuscular administration, subcutaneous administration, intradermal administration, and intraperitoneal administration, but not limited thereto.

[0070] In addition, the site of administration is not limited, which includes a tissue site in need of regeneration or its neighborhood region, a site different from the tissue in need of regeneration, or a site distal and different from the tissue in need of regeneration. For example, the site of administration includes blood (intraarterially, intravenously, etc.), muscles,

subcutaneous site, intradermal site and intraperitoneal site, but not limited thereto.

[0071] In addition, the method for administration can be appropriately selected depending upon age and symptoms of the patients. When the peptide of the present invention is administered, for example, a dose within a range of from 0.0000001 mg to 1,000 mg per 1 kg body weight per single administration can be selected. Alternatively, for example, a dose within a range of from 0.00001 to 100,000 mg/body per patient can be selected. When cells that secrete the peptide of the present invention or a vector for genetic therapy into which a DNA encoding the peptide is inserted is administered, the peptide can be administered such that the amount of the peptide is within the above range. However, the pharmaceutical composition of the present invention is not limited to these doses.

[0072] The pharmaceutical composition of the present invention can be formulated in accordance with conventional methods (e.g., Remington's Pharmaceutical Science, latest edition, Mark Publishing Company, Easton, U.S.A), which may together contain a pharmaceutically acceptable carrier or additives. Examples of the carriers and additives include, for example, surfactants, excipients, colorants, perfumes, preservatives, stabilizers, buffers, suspending agents, isotonic agents, binders, disintegrants, lubricants, fluidity promoters, flavoring agents, and the like, but not limited thereto, and other conventionally used carriers can be appropriately used. Specific examples include light anhydrous silicic acid, lactose, crystalline celluloses, mannitol, starches, carmellose calcium, carmellose

sodium, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl acetal diethylaminoacetate, polyvinyl pyrrolidone, gelatin, medium-chained fatty acid triglyceride, polyoxyethylene hydrogenated castor oil 60, white sugar, carboxymethyl cellulose, corn starch, inorganic salts, and the like.

[0073] Here, all the prior art references cited in the present specification will be incorporated herein by reference.

EXAMPLES

[0074] The present invention will be further illustrated by means of the following Examples, without intending to limit the present invention to the following Examples.

[0075] Example 1

Synthesis of Various Kinds of HMGB1 Peptides

A peptide consisting of the amino acids at position 2 to position 44 of human HMGB1 (2-44) and each of the five kinds of peptides having substitution of an amino acid sequence at position 43 and/or position 44 in the peptide at position 1 to position 44 of human HMGB1 (Peptide-1 to -5) were synthesized by a solid phase method.

2-44 GKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSKK (SEQ ID NO: 400)

Peptide-1 MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSKP (SEQ ID NO: 1)

Peptide-2 MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSPK (SEQ ID NO: 2)

Peptide-3 MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSPP (SEQ ID NO: 3)

Peptide-4 MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSKA (SEQ ID NO: 4)

Peptide-5 MGKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSKE (SEQ ID NO: 5)

[0076] Example 2

Measurements of Cell-Migration Activity

Cells of murine bone marrow-derived stromal cell line ST2 (RCB0224, RIKEN BioResource Research Center) were removed from a dish using TrypLE Express (Thermo Fisher Scientific), and collected by centrifugation at 25°C and 1,500 rpm for 5 minutes. The cell pellets were prepared into a concentration of 7×10^5 cells/mL with RPMI 1640 / 10% FBS / 1% PenStrep (Gibco), and seeded at 70 μL/insert well on a 24-well plate set with a culture insert (Nippon Genetics Co., Ltd.). After 24 hours, the culture insert was taken out, and the cells were washed once with RPMI 1640. Each of the peptide samples (a peptide of position 2 to position 44 of human HMGB1 (2-44), and the five kinds of modified peptides Peptide-1 to -5 prepared in Example 1), each prepared at 10 μM with an assay medium (RPMI 1640 / 0.1% FBS) was added in an amount of 550 μL, and the cells were further cultured overnight. As a negative control (NC), only the assay medium was added. After the culture, the cells were fixed, stained with DiffQuik, and photographed. The degree of cell migration of each group from the photographed images was evaluated with five levels of scores (-, ±, +, ++, +++). In addition, each of the

peptide samples was subjected to three test runs under the same conditions.

[0077] Results

The presence or absence of the migration activity of the peptide of position 2 to position 44 of human HMGB1 (2-44), the five kinds of modified peptides Peptide-1 to -5 prepared in Example 1, and NC was ascertained. As a result, all of the five kinds of modified peptides were found to have migration activity (Table 1).

[Table 1]

Table 1

	1st Run	2nd Run	3rd Run
NC	−	±	−
2−44	+++	+++	+++
Peptide−1	+++	+	+++
Peptide−2	+++	++	+++
Peptide−3	+	+	+
Peptide−4	++	+	+++
Peptide−5	++	++	++

[0078] Example 3

Stability of Peptides in Plasma

Whole blood collected from Crl : CD (SD) rats using an anti-coagulant EDTA-2K was centrifuged to obtain a blank plasma. The plasma obtained was stored on ice, and used only on the day of the stability test.

Each of the six kinds of peptides used in Example 2 was prepared into a solution at 375 μg/mL with distilled water from a stock solution in which each peptide was dissolved in a 0.1% aqueous TFA solution at 1 mg/mL. Sixteen microliters of the solution was added to 1,184 μL of the

blank plasma to prepare a sample for the stability test (assay concentration: 5 μg/mL). The sample for stability test was allowed to stand on ice, and 50 μL (at each time point, 3 samples) was collected immediately after the addition, and 1, 3, 5, 15, 30, and 60 minutes after the addition. To 50 μL of the collected sample were added 250 μL of 270 mmol/L citric acid solution / 130 mmol/L EDTA-2K aqueous solution (4:1, v/v), 25 μL of a 0.1% aqueous TFA solution, and 25 μL of IS solution (4 μg/mL aqueous 0.1% TFA solution of a compound in which nine carbon atoms and one nitrogen atom of phenylalanine at position 18, position 38, and position 41 in the peptide of position 1 to position 44 of human HMGB1 are each substituted with a stable isotope), and mixed. To the mixture was added 350 μL of methanol and mixed, and further 100 μL of acetonitrile was added thereto and mixed, and the mixture was once frozen with dry ice. The frozen mixture was thawed at room temperature, and the supernatant obtained by centrifugation was transferred to a separate container and stirred to be used as a sample for the measurement.

[0079] The samples for the measurement were introduced into high-performance liquid chromatograph-tandem quadrupolar mass spectrometer to detect the monitor ions peculiar to each of the peptides. From separately prepared samples of which concentrations were known, a calibration curve was drawn in a concentration range of from 0.1 to 10 μg/mL, and an inverse regression was obtained from peak areas of chromatograms obtained by measurements of each sample to obtain a peptide concentration in the samples. The peptide concentration at each time point was averaged, and a remaining rate (%) which was calculated by defining

one immediately after the addition as 100 was plotted against the time after the addition (FIG. 1).

Results

As a result of the stability test in rat plasma (on ice) of the peptide at position 2 to position 44 of human HMGB1 (2-44) and the five kinds of peptides in which the amino acids at position 43 and position 44 were modified (Peptide-1 to -5), 2-44 were equal to or lower than the quantifiable lower limit (0.5 μg/mL) for the sample at 15 minutes or more later of the addition. On the other hand, it was confirmed that the five kinds of the modified peptides Peptide-1 to -5 all were stable as compared to 2-44 (FIG. 1).

[0080] Example 4

Synthesis of HMGB1 Peptide

A peptide consisting of a sequence given below having substitution of two amino acids at a C-terminal in the peptide of position 2 to position 44 of human HMGB1 (2-44) (Peptide-6) was synthesized by a solid phase method.

Peptide-6 GKGDPKKPR GKMSSYAFFV QTCREEHKKK HPDASVNFSE FSPP (SEQ ID NO: 403)

[0081] Example 5

Measurements of Cell-Migration Activity

Cells of murine bone marrow-derived stromal cell line ST2 (RCB0224, RIKEN BioResource Research Center) were removed from a dish using 2.5g/L - Trypsin/1mmol/L - EDTA Solution (nacalai tesque), and collected by centrifugation at 25°C and 200 g for 3 minutes. The cell

pellets were prepared into a concentration of 8.6×10^5 cells/mL with RPMI 1640 / 10% FBS / 1% PenStrep (nacalai tesque), and seeded at 70 μL/insert well on a 24-well plate set with a culture insert (Nippon Genetics Co., Ltd.). After 18 hours, the culture insert was taken out, and the cells were washed once with RPMI 1640. Each of the peptide samples (the peptide of position 2 to position 44 of human HMGB1 (2-44), and the modified peptide Peptide-6 prepared in Example 4), each prepared at 20 μM with an assay medium (RPMI 1640 / 0.1% FBS) was added in an amount of 1,000 μL, and the cells were cultured for additional 20 hours. As a negative control (NC), only the assay medium was added. Immediately after the addition of the assay medium and after 20 hours of culture, the cells were photographed. From the photographed image, the degree of cell migration of each group was evaluated as a proportion (%) of the area occupied by the cells migrated to the region at 20 hours relative to the area of blank region prepared by the culture insert (region in which the cells do not exist at the time point of addition of the assay medium).

Results

The presence or absence of the migration activity of the peptide at position 2 to position 44 of human HMGB1 (2-44), the modified peptide prepared in Example 4 (Peptide-6) and NC was ascertained. As a result, the modified peptide (Peptide-6) was found to have the same level of migration activity as the peptide at position 2 to position 44 of human HMGB1 (2-44) (FIG. 2).

[0082] Example 6

Stability of Peptides in Plasma

A 5 mL tube previously charged with 60 μL of a 10% EDTA-2K was charged with 3 mL of whole blood collected from Crl : CD (SD) rats, and the contents were allowed to stand at room temperature for 30 minutes, and then centrifuged at 4°C and at 3,000 rpm (1600 × g) for 10 minutes. The supernatant was collected to be used as a blank plasma. The plasma obtained was stored on ice and only used on the day of the stability test.

Each of the peptide at position 2 to position 44 of human HMGB1 (2-44), the modified peptide prepared in Example 1 (Peptide-3), and the modified peptide prepared in Example 4 (Peptide-6) was prepared into a solution at 375 μg/mL with distilled water from a stock solution in which each peptide was dissolved in a 0.1% aqueous TFA solution at 1 mg/mL. Eight microliters of the solution was added to 592 μL of the blank plasma to prepare a sample for the stability test (assay concentration: 5 μg/mL). The sample for stability test was allowed to stand on ice, and 50 μL was collected immediately after the addition, and 30 and 60 minutes after the addition. To 50 μL of the collected sample were added 250 μL of 270 mmol/L citric acid solution / 130 mmol/L EDTA-2K aqueous solution (4:1, v/v), and 50 μL of a 0.1% aqueous TFA solution, and mixed. To the mixture was added 350 μL of methanol and mixed, and further 100 μL of acetonitrile was added thereto and mixed, and the mixture was once frozen with dry ice. After 5 to 60 minutes, the frozen sample was thawed at room temperature, and the supernatant obtained by centrifugation at 4°C and at 14,000 × g for 3 minutes was collected in an amount of 400 μL, dried and solidified with a centrifugal concentrator (Spin Dryer Light VC-36R, manufactured by TAITEC CORPORATION), and dissolved in 200 μL of a

1% TFA / 2% ACN Buffer, and filtrated with a filter (0.22 μm) to obtain samples for the measurement.

The samples for the measurement were introduced into high-performance liquid chromatograph-single quadrupolar mass spectrometer to detect the monitor ions peculiar to each of the peptides. From separately prepared samples of which concentrations were known, a calibration curve was drawn in a concentration range of from 0.1 to 10 μg/mL, and an inverse regression was obtained from peak areas of chromatograms obtained by measurements of each sample to obtain a peptide concentration in the samples. For the peptide concentration at each time point, a remaining rate (%) which was calculated by defining one immediately after the addition as 100 was plotted against the time after the addition (FIG. 3).

Results

As a result of the stability test in rat plasma (on ice), 2-44 showed to be equal to or lower than the quantifiable lower limit (0.5 μg/mL) at a time point of 30 minutes after the addition. On the other hand, it was confirmed that both of Peptide-3 and Peptide-6 were stable as compared to 2-44. In addition, the stability of Peptide-3 and Peptide-6 was found to be of the same level (FIG. 3).

INDUSTRIAL APPLICABILITY

[0083] The peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof of the present invention is used in the field of regenerative medicine.

CLAIMS

[Claim 1] A peptide selected from the group consisting of:

a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403,

a peptide consisting of an amino acid sequence having addition of one or more amino acids to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 and 403, and having an activity of stimulating migration of cells, and

a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 399 or at an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells,

a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 2] A peptide selected from the group consisting of:

a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283, 292 and 403,

a peptide consisting of an amino acid sequence having addition of one or more amino acids to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280,

282, 283, 292 and 403, and having an activity of stimulating migration of cells, and

a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 126, 128, 129, 138, 167, 248, 254, 280, 282, 283 and 292, or at an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 3] A peptide selected from the group consisting of:

a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 167 and 403,

a peptide consisting of an amino acid sequence having addition of one or more amino acids to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5, 167 and 403, and having an activity of stimulating migration of cells, and

a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 167 or at an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells,

a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 4] A peptide selected from the group consisting of:

a peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 403,

a peptide consisting of an amino acid sequence having addition of one or more amino acids to the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 and 403, and having an activity of stimulating migration of cells, and

a peptide comprising or consisting of an amino acid sequence having substitution, deletion, or insertion of one or more amino acids at an amino acid of position 1 to position 42 of the peptide having the amino acid sequence shown in any one of SEQ ID NOs: 1 to 5 or at an amino acid of position 1 to position 41 of the peptide having the amino acid sequence shown in SEQ ID NO: 403, and having an activity of stimulating migration of cells,

a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 5] A composition for use in stimulation of migration of PDGFRα-positive cells, comprising a peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof as defined in any one of the claims 1 to 4.

[Claim 6] A composition for use in recruitment of bone marrow mesenchymal stem cells from bone marrow to peripheral blood, comprising a peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate

thereof as defined in any one of the claims 1 to 4.

[Claim 7] A composition for use in regeneration of tissues, comprising a peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof as defined in any one of the claims 1 to 4.

[Claim 8] A composition for use in stimulation of migration of bone marrow-derived stromal cells, comprising a peptide, a derivative thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof as defined in any one of the claims 1 to 4.