IMMUNO-MODULATORY PROGENITOR (IMP) CELL

Field of the Invention

The invention relates to immuno-modulatory progenitor (IMP) cells and their use in therapy.

Background to the Invention

Mesodermal cells are derived from a number of tissues and act as the supportive structure for other cell types. Bone marrow for instance is made of both haematopoietic and mesenchymal derived cells. Two principle mesenchymal cell types have been previously described and characterized, namely (i) mesenchymal stem cells (MSCs) and their precursors and (ii) mesenchymal precursor cells (MPCs) found in the bone marrow. Mesenchymal stem cells (MSCs) are multipotent, adult stem cells. MSCs differentiate to form the different specialised cells found in the skeletal tissues. For example, they can differentiate into cartilage cells (chondrocytes), bone cells (osteoblasts) and fat cells (adipocytes).

MSCs are used in a variety of therapies, such as the treatment of Age-related Macular Degeneration (AMD) and myocardial infarct. Once administered to the patient, the MSCs typically migrate (or home) to the damaged tissue and exert their therapeutic effects through paracrine signaling and by promoting survival, repair and regeneration of the neighbouring cells in the damaged tissue.

Current therapies typically involve the infusion of a mixture of MSC subtypes some of which do not migrate efficiently to the tissue of interest. This necessitates the use of a high cell-dose which can lead to off-target side effects and volume-related side effects. MSCs are typically obtained from bone marrow and so it is difficult to obtain large amounts.

Summary

This present disclosure relates to a novel cell type that has not been previously identified or isolated, the immuno-modulatory progenitor cell. This IMP cell is quite distinct and different to both MSCs and MPCs in its composition, function and characteristics which impart an enhanced immuno-modulatory capacity.

The inventors have surprisingly identified a new immuno-modulatory progenitor (IMP) cell having a specific marker expression pattern. In particular, the IMP cell expresses MIC A/B, CD304 (Neuropilin 1), CD178 (FAS ligand), CD289 (Toll-like receptor 9), CD363 (Sphingosine-1-phosphate receptor 1), CD99, CD181 (C-X-C chemokine receptor type 1; CXCR1), epidermal growth factor receptor (EGF-R), CXCR2 and CD126, The IMP cell expresses significantly greater amounts of these markers than a mesencymal stem cell (MSC). The IMP cells of the present disclosure can be isolated from

mononuclear cells (MCs), such as peripheral blood MCs. The IMP cells are capable of efficiently migrating to and repairing damaged tissues. In particular, they are capable of homing, adherence, transmigration, proliferation, angiogenic effects and paracrine signalling.

Accordingly, the present disclosure provides an immuno-modulatory progenitor (IMP) cell, wherein the cell expresses detectable levels of MIC A/B, CD304 (Neuropilin 1), CD178 (FAS ligand), CD289 (Toll-like receptor 9), CD363 (Sphingosine-1-phosphate receptor 1), CD99, CD181 (C-X-C chemokine receptor type 1; CXCR1), epidermal growth factor receptor (EGF-R), CXCR2 and CD126.

The present disclosure also provides:

- a population of two or more IMP cells of the present disclosure;
- a population of immuno-modulatory progenitor (IMP) cells, wherein
  (i) at least 90% of the cells in the population express detectable levels of MIC A/B,
  (ii) at least 60% of the cells in the population express detectable levels of CD304 (Neuropilin 1),
  (iii) at least 45% of the cells in the population express detectable levels of CD178 (FAS ligand),
  (iv) at least 10% of the cells in the population express detectable levels of CD289 (Toll-like receptor 9),
  (v) at least 15% of the population express detectable levels of CD363 (Sphingosine-1-phosphate receptor 1),
  (vi) at least 20% of the cells in the population express detectable levels of CD99,
  (vii) at least 80% of the cells in the population express detectable levels of CD181 (C-X-C chemokine receptor type 1; CXCR1),
  (viii) at least 30% of the cells in the population express detectable levels of epidermal growth factor receptor (EGF-R),
  (xi) at least 60% of the cells in the population express detectable levels of CXCR2 and
  (x) at least 5% of the cells in the population express detectable levels of CD126;
- a pharmaceutical composition comprising (a) an IMP cell of the present disclosure or a population of the present disclosure and (b) a pharmaceutically acceptable carrier or diluent, one or more liposomes and/or one or more microbubbles;
- a method of producing a population of IMP cells of the present disclosure, comprising (a) culturing mononuclear cells (MCs) under conditions which induce the MCs to differentiate into IMP cells and (b) harvesting and culturing those IMP cells which have an expression pattern as defined above and thereby producing a population of the present disclosure;

- a method of repairing a damaged tissue in a patient, comprising administering to the patient a population of the present disclosure or a pharmaceutical composition of the present disclosure, wherein the population or composition comprises a therapeutically effective number of cells, and thereby treating the damaged tissue in the patient;
- a population of the present disclosure or a pharmaceutical composition of the present disclosure for use in a method of repairing a damaged tissue in a patient; and
- a population of the present disclosure or a pharmaceutical composition of the present disclosure for use in a method of treating a cardiac, bone, cartilage, tendon, ligament, liver, kidney or lung injury or disease in a patient.

In one aspect of the present disclosure, there is provided an immuno-modulatory progenitor (IMP) cell, wherein the cell expresses on its surface detectable levels of MIC A/B, CD304 (Neuropilin 1), CD178 (FAS ligand), CD289 (Toll-like receptor 9), CD363 (Sphingosine-1-phosphate receptor 1), CD99, CD181 (C-X-C chemokine receptor type 1; CXCR1), epidermal growth factor receptor (EGF-R), CXCR2 and CD126.

In another aspect of the present disclosure, there is provided a population of two or more IMP cells as defined herein.

In yet another aspect of the present disclosure, there is provided a population of immuno-modulatory progenitor (IMP) cells, wherein

(i) at least 90% of the cells in the population express on their surfaces detectable levels of MIC A/B,

(ii) at least 60% of the cells in the population express on their surfaces detectable levels of CD304 (Neuropilin 1),

(iii) at least 45% of the cells in the population express on their surfaces detectable levels of CD178 (FAS ligand),

(iv) at least 10% of the cells in the population express on their surfaces detectable levels of CD289 (Toll-like receptor 9),

(v) at least 15% of the population express on their surfaces detectable levels of CD363 (Sphingosine-1-phosphate receptor 1),

(vi) at least 20% of the cells in the population express on their surfaces detectable levels of CD99,

(vii) at least 80% of the cells in the population express on their surfaces detectable levels of CD181 (C-X-C chemokine receptor type 1; CXCR1),

(viii) at least 30% of the cells in the population express on their surfaces detectable levels of epidermal growth factor receptor (EGF-R),

(xi) at least 60% of the cells in the population express on their surfaces detectable levels of CXCR2 and

(x) at least 5% of the cells in the population express on their surfaces detectable levels of CD126.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising (a) an IMP cell as defined herein or a population as defined herein and (b) a pharmaceutically acceptable carrier or diluent, one or more liposomes and/or one or more microbubbles.

In another aspect of the present disclosure, there is provided a method of producing a population of IMP cells as defined herein, comprising (i) culturing mononuclear cells (MCs) for from 15 to 25 days in a medium comprising platelet lysate, at less than 20% oxygen (O_2) and under conditions which allow the IMP cells to adhere to induce the MCs to differentiate into IMP cells and (ii) harvesting and culturing those IMP cells which have an expression pattern as defined herein and thereby producing a population as defined herein.

In yet another aspect of the present disclosure, there is provided a population as defined herein or a pharmaceutical composition as defined herein for use in a method of repairing a damaged tissue in a patient or treating a cardiac, bone, cartilage, tendon, ligament, liver, kidney or lung injury or disease in a patient.

Detailed Description of the Invention

It is to be understood that different applications of the disclosed products and methods may be tailored to the specific needs in the art. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

In addition, as used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a cell" includes "cells", reference to "a tissue" includes two or more such tissues, reference to "a patient" includes two or more such patients, and the like.

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

IMP cell of the invention

The present invention provides an immuno-modulatory progenitor (IMP) cell. The IMP cell expresses detectable levels of MIC A/B, CD304 (Neuropilin 1), CD178 (FAS ligand), CD289 (Toll-like receptor 9), CD363 (Sphingosine-1-phosphate receptor 1), CD99, CD181 (C-X-C chemokine receptor type 1; CXCR1), epidermal growth factor receptor (EGF-R), CXCR2 and CD126.

MIC allows adaptation of cells and their immuno-behaviour in an inflammatory context by decreasing their susceptibility to NK killing.

CD304 (alternate name Neuropilin 1) is a co-receptor for vascular endothelial growth factor (VEGF) and has roles in angiogenesis, cell survival, migration and invasion.

CD178 (alternate name FAS ligand) maintains cell phenotype and controls differentiation. It is also capable of inducing proliferation of cells. Although FAS ligand is known primarily in apoptotic

CLAIMS

1. An immuno-modulatory progenitor (IMP) cell, wherein the cell expresses on its surface detectable levels of MIC A/B, CD304 (Neuropilin 1), CD178 (FAS ligand), CD289 (Toll-like receptor 9), CD363 (Sphingosine-1-phosphate receptor 1), CD99, CD181 (C-X-C chemokine receptor type 1; CXCR1), epidermal growth factor receptor (EGF-R), CXCR2 and CD126.

2. An IMP cell according to claim 1, wherein:

(a) the IMP cell is capable of migrating to, adhering to, proliferating in, having anti-inflammatory effects in, and/or promoting angiogenesis in a specific, damaged tissue in a patient;

(b) the IMP cell is capable of transmigrating through the vascular endothelium to a specific, damaged tissue in a patient;

(c) the IMP cell is capable of migrating to, adhering to, proliferating in, having anti-inflammatory effects in and/or promoting angiogenesis in damaged cardiac, bone, cartilage, tendon, ligament, liver, kidney or lung tissue in a patient; or

(d) the IMP cell is capable of transmigrating through the vascular endothelium to damaged cardiac, bone, cartilage, tendon, ligament, liver, kidney or lung tissue in a patient.

3. An IMP cell according to claim 1 or 2, wherein:

(a) the IMP cell is capable of differentiating into a mesodermal cell *in vitro*;

(b) the IMP cell is autologous or allogeneic; and/or

(c) the IMP cell is loaded or transfected in vitro or ex vivo with a therapeutic and/or diagnostic agent.

4. A population of two or more IMP cells according to any one of the preceding claims.

5. A population of immuno-modulatory progenitor (IMP) cells, wherein
(i) at least 90% of the cells in the population express on their surfaces detectable levels of MIC A/B,
(ii) at least 60% of the cells in the population express on their surfaces detectable levels of CD304 (Neuropilin 1),
(iii) at least 45% of the cells in the population express on their surfaces detectable levels of CD178 (FAS ligand),
(iv) at least 10% of the cells in the population express on their surfaces detectable levels of CD289 (Toll-like receptor 9),
(v) at least 15% of the population express on their surfaces detectable levels of CD363 (Sphingosine-1-phosphate receptor 1),
(vi) at least 20% of the cells in the population express on their surfaces detectable levels of CD99,
(vii) at least 80% of the cells in the population express on their surfaces detectable levels of CD181 (C-X-C chemokine receptor type 1; CXCR1),
(viii) at least 30% of the cells in the population express on their surfaces detectable levels of epidermal growth factor receptor (EGF-R),
(xi) at least 60% of the cells in the population express on their surfaces detectable levels of CXCR2 and
(x) at least 5% of the cells in the population express on their surfaces detectable levels of CD126.

6. A population according to claim 5, wherein
(a)
(i) at least 97% of the cells in the population express on their surfaces detectable levels of MIC A/B,
(ii) at least 65% of the cells in the population express on their surfaces detectable levels of CD304 (Neuropilin 1),
(iii) at least 51% of the cells in the population express on their surfaces detectable levels of CD178 (FAS ligand),
(iv) at least 11% of the cells in the population express on their surfaces detectable levels of CD289 (Toll-like receptor 9),
(v) at least 18% of the population express on their surfaces detectable levels of CD363 (Sphingosine-1-phosphate receptor 1),
(vi) at least 24% of the cells in the population express on their surfaces detectable levels of CD99,
(vii) at least 85% of the cells in the population express detectable levels of CD181 (CXCR1),
(viii) at least 33% of the cells in the population express detectable levels of epidermal growth factor receptor (EGF-R),
(ix) at least 68% of the cells in the population express detectable levels of CXCR2 and
(x) at least 7% of the cells in the population express detectable levels of CD126;

(b) at least 90% of the cells in the population express on their surfaces detectable levels of one or more of CD10, CD111, CD267, CD47, CD273, CD51/CD61, CD49f, CD49d, CD146, CD55, CD340, CD91, Notch2, CD175s, CD82, CD49b, CD95, CD63, CD245, CD58, CD108, B2-microglobulin, CD155, CD298, CD44, CD49c, CD105, CD166, CD230, HLA-ABC, CD13, CD29, CD49e, CD59, CD73, CD81, CD90, CD98, CD147, CD151 and CD276;

(c) at least 80% of the cells in the population express on their surfaces detectable levels of one or more of, or all of, CD156b, CD61, CD202b, CD130, CD148, CD288, CD337, SSEA-4, CD349 and CD140b;

(d) at least 70% of the cells in the population express on their surfaces detectable levels of one or more of, or all of, CD318, CD351, CD286, CD46, CD119 and CD132;

(e) 1% or fewer of the cells in the population express on their surfaces detectable levels of one or more of, or all of, CD72, CD133, CD192, CD207, CD144, CD41b, FMC7, CD75, CD3e, CD37, CD158a, CD172b, CD282, CD100, CD94, CD39, CD66b, CD158b, CD40, CD35, CD15, PAC-1, CLIP, CD48, CD278, CD5, CD103, CD209, CD3, CD197, HLA-DM, CD20, CD74, CD87, CD129, CDw329, CD57, CD163, TPBG, CD206, CD243 (BD), CD19, CD8, CD52, CD184, CD107b, CD138, CD7, CD50, HLA-DR, CD158e2, CD64, DCIR, CD45, CLA, CD38, CD45RB, CD34, CD101, CD2, CD41a, CD69, CD136, CD62P, TCR alpha beta, CD16b, CD1a, ITGB7, CD154, CD70, CDw218a, CD137, CD43, CD27, CD62L, CD30, CD36, CD150, CD66, CD212, CD177, CD142, CD167, CD352, CD42a, CD336, CD244, CD23, CD45RO, CD229, CD200,

CD22, CDH6, CD28, CD18, CD21, CD335, CD131, CD32, CD157, CD165, CD107a, CD1b, CD332, CD180, CD65 and CD24;

(f) the population have the properties defined in claim 2 or 3; and/or

(g) the population comprises at least 5000 cells, at least 50,000 cells or at least 250,000 cells.

7. A pharmaceutical composition comprising (a) an IMP cell according to any one of claims 1 to 3 or a population according to any one of claims 4 to 6 and (b) a pharmaceutically acceptable carrier or diluent, one or more liposomes and/or one or more microbubbles.

8. A method of producing a population of IMP cells according to any one of claims 4 to 6, comprising (i) culturing mononuclear cells (MCs) for from 15 to 25 days in a medium comprising platelet lysate, at less than 20% oxygen (O_2) and under conditions which allow the IMP cells to adhere to induce the MCs to differentiate into IMP cells and (ii) harvesting and culturing those IMP cells which have an expression pattern as defined in claim 1 and thereby producing a population according to any one of claims 4 to 6.

9. A method according to claim 8, wherein:

(a) the MCs are peripheral blood mononuclear cells (PBMCs); and/or

(b) the MCs are obtained from a patient or an allogeneic donor.

10. A population according to any one of claims 4 to 6 or a pharmaceutical composition according to claim 7 for use in a method of repairing a damaged tissue in a patient or treating a cardiac, bone, cartilage, tendon, ligament, liver, kidney or lung injury or disease in a patient.

11. A population of claim 10 for use according to claim 10, wherein:

(i) the damaged tissue is derived from the mesoderm;

(ii) the damaged tissue is cardiac, bone, cartilage, tendon, ligament, liver, kidney or lung tissue; and/or

(iii) the damaged tissue is damaged by injury or disease; or

(i) the cardiac injury or disease is selected from myocardial infarct, left ventricular hypertrophy, right ventricular hypertrophy, emboli, heart failure, congenital heart deficit, heart valve disease, arrhythmia and myocarditis, and/or the population is produced using MCs obtained from the patient or an allogeneic donor; or

(ii) the bone injury or disease is selected from fracture, Salter-Harris fracture, greenstick fracture, bone spur, craniosynostosis, Coffin-Lowry syndrome, fibrodysplasia ossificans progressive, fibrous dysplasia, Fong Disease (or Nail-patella syndrome), hypophosphatasia, Klippel-Feil syndrome, Metabolic Bone Disease, Nail-patella syndrome, osteoarthritis, osteitis deformans (or Paget's disease of bone), osteitis fibrosa cystica (or Osteitis fibrosa or Von Recklinghausen's disease of bone), osteitis pubis, condensing osteitis (or osteitis condensans), osteitis condensans ilii, osteochondritis dissecans, osteogenesis imperfecta, osteomalacia, osteomyelitis, osteopenia, osteopetrosis, osteoporosis, osteonecrosis, porotic hyperostosis, primary hyperparathyroidism, renal osteodystrophy, bone cancer, a bone lesion associated with metastatic cancer, Gorham Stout disease, primary hyperparathyroidism, periodontal disease, and aseptic loosening of joint replacements, and/or

the population is produced using MCs obtained from the patient or an allogeneic donor.

12. A population of claim 10 for use according to claim 10 or 11, wherein the population is produced using MCs obtained from the patient or an allogeneic donor.