DESCRIPTION

Title of the Invention: COMPOSITION FOR PROMOTING PROLIFERATION OF IMMUNE CELLS

TECHNICAL FIELD

[0001]

The invention relates to a composition for promoting the proliferation of immune cells.

BACKGROUND ART

[0002]

It is known that T cells, which play an important role in the immune system, are differentiated from an immature state to various effector T cells having various functions in response to extracellular stimuli, and contribute to the elimination of, e.g., pathogenic microorganisms, virus-infected cells, and cancer cells.

[0003]

One of the effector T cells, i.e., $CD4^+$ T cells (Th7R cells), having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$, can be used as a biomarker for predicting the response rate of an immune checkpoint inhibitor to cancer (Non Patent Document 1). Patent Document 1 discloses a method for determining the relative amount of a Th7R cell subpopulation in a $CD4^+$ T cell population in a sample derived from a subject, comprising the steps of selecting a $CXCR3^-$ cell subpopulation in the $CD4^+$ T cell population; setting a boundary between a $CCR4^-$ cell subpopulation and a $CCR4^+$ cell subpopulation in the $CXCR3^-$ cell subpopulation; and measuring the relative amount of the $CCR4^-CCR6^+$ cell subpopulation in the $CD4^+$ T cell population using the boundary. It is also known that Th7R cells contribute to suppressing cancer

recurrence after removal surgery (Non Patent Document 2).

[0004]

Also, MAIT cells and NKT cells, which are types of effector T cells, are cells characterized by contributing to acquired immunity and having rapid effector activation action, thereby contributing also to natural immunity. It is known that MAIT cells and NKT cells contribute to preventing cancer or suppressing cancer metastasis (Non Patent Documents 3 and 4).

[0005]

Meanwhile, it is known that a lactic acid bacterium, a fermentation product thereof, or an extracellular polysaccharide (EPS) derived from a lactic acid bacterium has several physiological activities. Examples of the physiological activities that have been known include preventing autoimmune diseases (Patent Document 2), NK cell activation (Patent Document 3), antiviral activity (Patent Document 4), preventing pneumococcal infection (Patent Document 5), suppressing acquired immune reduction (Patent Document 6), preventing and/or treating influenza (Patent Document 7), suppressing cytokine production (Patent Document 8), cellular immune activation (Patent Document 9), suppressing cancer cachexia (Patent Document 10), promotion of immune checkpoint inhibitor therapy (Patent Document 11), preventing secondary infection after viral infection or reduction of risk of developing the infection (Patent Document 12), anti-human coronavirus (Patent Document 13), suppressing viral proliferation (Patent Document 14), control of immune balance (Patent Document 15), promotion of interferon γ production (Patent Document 16), activation of T cells (Patent Document 17), increase of antibody titer (Patent Document 18), and retinoic acid production (Patent Document 19).

PRIOR ART REFERENCES

Patent Documents

[0006]

Patent Document 1: JP 7368678 B2

Patent Document 2: JP 2000-247895 A

Patent Document 3: JP 2005-194259 A

Patent Document 4: WO 2011/065300 A

Patent Document 5: WO 2015/133638 A

Patent Document 6: JP 2018-27904 A

Patent Document 7: JP 2018-74940 A

Patent Document 8: JP 2018-177740 A

Patent Document 9: JP 2018-203698 A

Patent Document 10: JP 2019-81733 A

Patent Document 11: WO 2019/240218 A

Patent Document 12: WO 2023/120547 A

Patent Document 13: WO 2023/204234 A

Patent Document 14: JP 2021-80187 A

Patent Document 15: JP 2021-101645 A

Patent Document 16: WO 2019/111904 A

Patent Document 17: WO 2020/067422 A

Patent Document 18: WO 2015/029967 A

Patent Document 19: WO 2015/137501 A

[0007]

Non Patent Documents

Non Patent Document 1: Hiroshi Kagamu et al, Single-Cell Analysis Reveals a CD4+ T-

cell Cluster That Correlates with PD-1 Blockade Efficacy. Cancer Res. 2022 Dec 16;82(24):4641-4653. doi: 10.1158/0008-5472.CAN-22-0112.

Non Patent Document 2: Akitoshi Yanagihara et al, A Th1-like CD4+ T-cell Cluster That Predicts Disease-free Survival in Early-stage Lung Cancer. Cancer Res Commun. 2023 Jul 19;3(7):1277-1285. doi: 10.1158/2767-9764.CRC-23-0167.

Non Patent Document 3: Benjamin Ruf et al, Activating Mucosal-Associated Invariant T Cells Induces a Broad Antitumor Response. Cancer Immunol Res. 2021 Sep;9(9):1024-1034. doi:10.1158/2326-6066.CIR-20-0925.

Non Patent Document 4: Chi Ma et al, Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science. 2018 May 25;360(6391):eaan5931. doi: 10.1126/science.aan5931.

SUMMARY OF THE INVENTION

Object to be Achieved by the Invention

[0008]

An object of the invention is a means for promoting the proliferation of types of effector T cells, that is, one or more of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$, MAIT cells, and NKT cells.

Means for Achieving the Object

[0009]

The following inventions are provided.

[1] A composition for promoting proliferation of either or both of (i) and (ii), comprising an extracellular polysaccharide of a lactic acid bacterium.

(i) $CD4^+$ T cells having a cell-surface marker expression pattern of

$CXCR3^{+}/CCR4^{low}/CCR6^{high}$.

(ii) MAIT cells and NKT cells.

[2] A composition for either or both of improving susceptibility to immune checkpoint inhibitor therapy and suppressing cancer recurrence after removal surgery, comprising an extracellular polysaccharide of a lactic acid bacterium.

[3] The composition according to [2], wherein improving susceptibility to immune checkpoint inhibitor therapy is that a subject changes from a poor responder to the immune checkpoint inhibitor therapy to a good responder, or that a subject who has become a poor responder to the immune checkpoint inhibitor therapy with time becomes a good responder again.

[4] A composition for treating a disease or condition that is ameliorated by promotion of proliferation of $CD4^{+}$ T cells having a cell-surface marker expression pattern of $CXCR3^{+}/CCR4^{low}/CCR6^{high}$, comprising an extracellular polysaccharide of a lactic acid bacterium.

[5] The composition according to [4], wherein treating the disease or condition that is ameliorated by promotion of proliferation of $CD4^{+}$ T cells having a cell-surface marker expression pattern of $CXCR3^{+}/CCR4^{low}/CCR6^{high}$ is improving susceptibility to immune checkpoint inhibitor therapy, and wherein the composition is for ingestion by a subject who is not receiving the immune checkpoint inhibitor therapy.

[6] A composition for treating a disease or condition that is ameliorated by promotion of proliferation of MAIT cells and NKT cells, comprising an extracellular polysaccharide of a lactic acid bacterium.

[7] The composition according to [6], wherein treating a disease or condition that is ameliorated by promotion of proliferation of MAIT cells and NKT cells is either or both of suppressing cancer metastasis and preventing cancer, and wherein the

composition is for ingestion by a subject who is not receiving cancer treatment.

[8] The composition according to any one of [1] to [7], wherein the lactic acid bacterium is a bacterium belonging to the genus Lactobacillus.

[9] The composition according to any one of [1] to [8], wherein the lactic acid bacterium is a bacterium belonging to Lactobacillus delbrueckii.

[10] The composition according to any one of [1] to [9], wherein the lactic acid bacterium is Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741.

[11] The composition according to any one of [1] to [10], wherein the extracellular polysaccharide of a lactic acid bacterium is contained as a fermentation product of the lactic acid bacterium.

[12] The composition according to any one of [1] to [11], which is a pharmaceutical composition.

[13] The composition according to any one of [1] to [11], which is a food composition.

[0010]

The following inventions are also provided.

[14] A method or a non-therapeutic method for promoting proliferation of either or both of (i) and (ii), including allowing a subject to ingest an extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium. An extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium for use in a method for promoting the proliferation of either or both of (i) and (ii). Use of an extracellular polysaccharide of a lactic acid bacterium or use of a composition comprising an extracellular polysaccharide of a lactic acid bacterium in producing a composition for promoting the proliferation of either or both of (i) and (ii).

Use or non-therapeutic use of an extracellular polysaccharide of a lactic acid bacterium or use or non-therapeutic use of a composition comprising an extracellular polysaccharide of a lactic acid bacterium for promoting the proliferation of either or both of (i) and (ii).

(i) $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$.

(ii) MAIT cells and NKT cells.

[15] A method or non-therapeutic method for improving susceptibility to immune checkpoint inhibitor therapy, or a method for suppressing the recurrence of cancer after removal surgery, including allowing a subject to ingest an extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium. An extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium, for use in a method for improving susceptibility to immune checkpoint inhibitor therapy or a method for suppressing the recurrence of cancer after removal surgery. Use of an extracellular polysaccharide of a lactic acid bacterium or use of a composition comprising an extracellular polysaccharide of a lactic acid bacterium in producing a composition for either or both of improving susceptibility to immune checkpoint inhibitor therapy and suppressing cancer recurrence after removal surgery. Use or non-therapeutic use of an extracellular polysaccharide of a lactic acid bacterium, or use or non-therapeutic use of a composition comprising an extracellular polysaccharide of a lactic acid bacterium, for improving susceptibility to immune checkpoint inhibitor therapy or suppressing the recurrence of cancer after removal surgery.

[16] A method or a non-therapeutic method of treating a disease or condition

that is ameliorated by promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$, including allowing a subject to ingest an extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium. An extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium, for use in a method of treating a disease or condition that is ameliorated by promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$. Use of an extracellular polysaccharide of a lactic acid bacterium or use of a composition comprising an extracellular polysaccharide of a lactic acid bacterium in producing a composition for treating a disease or condition that is ameliorated by promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$. Use or non-therapeutic use of an extracellular polysaccharide of a lactic acid bacterium, or use or non-therapeutic use of a composition comprising an extracellular polysaccharide of a lactic acid bacterium, for treating a disease or condition that is ameliorated by promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$.

[17] The method or non-therapeutic method according to [16], wherein treating the disease or condition that is ameliorated by promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$ is improving susceptibility to immune checkpoint inhibitor therapy, and the subject is a subject who is not receiving the immune checkpoint inhibitor therapy. The extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium according to [16], wherein treating the disease or condition that is ameliorated by

promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$ is improving susceptibility to immune checkpoint inhibitor therapy, and wherein the extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium is for ingestion by a subject who is not receiving the immune checkpoint inhibitor therapy. The use or non-therapeutic use according to [16], wherein treating the disease or condition that is ameliorated by promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$ is improving susceptibility to immune checkpoint inhibitor therapy, and wherein the composition or extracellular polysaccharide of a lactic acid bacterium is for ingestion by a subject who is not receiving the immune checkpoint inhibitor therapy.

[18] A method or a non-therapeutic method of treating a disease or condition that is ameliorated by promotion of proliferation of either or both of MAIT cells and NKT cells, including allowing a subject to ingest an extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium. A composition comprising an extracellular polysaccharide of a lactic acid bacterium or an extracellular polysaccharide of a lactic acid bacterium for use in a method of treating a disease or condition that is ameliorated by promotion of proliferation of either or both of MAIT cells and NKT cells. Use of an extracellular polysaccharide of a lactic acid bacterium or use of a composition comprising an extracellular polysaccharide of a lactic acid bacterium in producing a composition for treating a disease or condition that is ameliorated by promotion of proliferation of either or both of MAIT cells and NKT cells. Use or non-therapeutic use of an extracellular polysaccharide of a lactic acid bacterium, or use or non-therapeutic use of a composition comprising an extracellular polysaccharide of a lactic acid bacterium, for treating a

disease or condition that is ameliorated by promotion of proliferation of either or both of MAIT cells and NKT cells.

[19] The method or non-therapeutic method according to [18], wherein treating a disease or condition that is ameliorated by promotion of proliferation of either or both of MAIT cells and NKT cells is either or both of suppressing cancer metastasis and preventing cancer, and the subject is a subject who is not receiving cancer treatment. The extracellular polysaccharide of a lactic acid bacterium or composition comprising an extracellular polysaccharide of a lactic acid bacterium according to [18], wherein treating a disease or condition that is ameliorated by promotion of proliferation of either or both of MAIT cells and NKT cells is either or both of suppressing cancer metastasis and preventing cancer, and wherein the extracellular polysaccharide of a lactic acid bacterium or composition comprising an extracellular polysaccharide of a lactic acid bacterium is for ingestion by a subject who is not receiving cancer treatment. The use or non-therapeutic use according to [18] for treating a disease or condition that is ameliorated by promotion of proliferation of either or both of MAIT cells and NKT cells in a subject who is not receiving cancer treatment, wherein treating the disease or condition that is ameliorated by promotion of proliferation of either or both of MAIT cells and NKT cells is either or both of suppressing cancer metastasis and preventing cancer.

[20] The method or non-therapeutic method, extracellular polysaccharide of a lactic acid bacterium or composition comprising an extracellular polysaccharide of a lactic acid bacterium, or use or non-therapeutic use according to any one of [14] to [19], wherein the lactic acid bacterium is a bacterium belonging to the genus Lactobacillus.

[21] The method or non-therapeutic method, extracellular polysaccharide of a lactic acid bacterium, or composition comprising an extracellular polysaccharide of a

lactic acid bacterium, or use or non-therapeutic use according to any one of [14] to [20], wherein the lactic acid bacterium is a bacterium belonging to Lactobacillus delbrueckii.

[22] The method or non-therapeutic method, extracellular polysaccharide of a lactic acid bacterium, or composition comprising an extracellular polysaccharide of a lactic acid bacterium, or use or non-therapeutic use according to any one of [14] to [21], wherein the lactic acid bacterium is Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741.

[23] The method or non-therapeutic method according to any one of [14] to [22], wherein the extracellular polysaccharide of a lactic acid bacterium is ingested as a fermentation product of a lactic acid bacterium. The composition, or use or non-therapeutic use according to any one of [14] to [22], wherein the extracellular polysaccharide of a lactic acid bacterium is contained in the composition as a fermentation product of the lactic acid bacterium.

[24] The method or a non-therapeutic method according to any one of [14] to [23], wherein a pharmaceutical composition comprising an extracellular polysaccharide of a lactic acid bacterium is ingested. The composition or use or non-therapeutic use according to any one of [14] to [23], wherein the composition is a pharmaceutical composition.

[25] The method or a non-therapeutic method according to any one of [14] to [23], wherein a food composition comprising an extracellular polysaccharide of a lactic acid bacterium is ingested. The composition or use or non-therapeutic use according to any one of [14] to [23], wherein the composition is a food composition.

Effects of the Invention

[0011]

According to the invention, proliferation of one or more of $CD4^+$ T cells (Th7R cells) having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$, MAIT cells, and NKT cells is promoted.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

Fig. 1 illustrates the amount of change in the component ratio of MAIT/NKT cells in PBMCs of a test subject before and after ingestion of a test product.

Fig. 2 illustrates the component ratio of each of clusters #44347, #44352, and #44360 in $CD4^+$ T cells in PBMCs after ingestion of a test product.

Fig. 3 illustrates the lineage of clusters in $CD4^+$ T cells in PBMCs after ingestion of a test product and the intensity of CCR6 expression of each of the clusters. The numerical value on the bar indicates high and low of the relative expression level, and the color of the bar corresponds to the color of each circle.

MODES FOR CARRYING OUT THE INVENTION

[0013]

The invention will be described below. Individual features of the invention described below can be arbitrarily combined.

[0014]

<Composition>

The invention relates to a composition comprising an extracellular polysaccharide (EPS) of a lactic acid bacterium.

[0015]

[Active Ingredient]

The active ingredient in the composition of the invention is an EPS of a lactic acid bacterium. The EPS used in the composition of the invention is not particularly limited as long as it has a desired effect. Examples of the EPS include those produced by lactic acid bacteria and those produced by microorganisms (for example, E. coli) into which an EPS-producing gene derived from a lactic acid bacterium is introduced. In an embodiment, an EPS of a lactic acid bacterium is an EPS produced by a lactic acid bacterium. The EPSs produced by lactic acid bacteria are structurally classified into homo-polysaccharides and hetero-polysaccharides (e.g., composed of galactose and glucose), and may be further modified with, e.g., phosphorylation and sulfation. The EPS is not particularly limited as long as it has a desired effect, and any EPS can be used as an active ingredient of the composition of the invention. The EPS may be a neutral polysaccharide or an acidic polysaccharide (for example, obtained by adding, e.g., a phosphate group to a neutral polysaccharide). Such EPS is known to be produced by, e.g., Lactobacillus delbrueckii subsp. bulgaricus, Lactococcus lactis subsp. lactis, or Lactococcus lactis subsp. cremoris. The EPS to be used in the present invention may be alone, or two or more of the EPSs may be used in combination. The EPS may be obtained from, e.g., a fermentation product of a lactic acid bacterium, by purification.

[0016]

Lactic acid bacteria collectively refer to microorganisms that assimilate glucose to produce lactic acid with a yield of 50% or more per glucose. The characteristic physiological properties of the bacteria are, e.g., gram-positive cocci or bacilli, no motility, no sporulation ability in most cases (a lactic acid bacterium, such as Bacillus coagulans, has sporulation ability), and catalase-negative. Lactic acid bacteria have been eaten from ancient times all over the world through, e.g., fermented milk, and

thus are deemed to be extremely safe microorganisms. Lactic acid bacteria are classified into a plurality of genera. In the invention, the lactic acid bacteria may be any bacteria as long as they produce EPS, and are preferably bacteria belonging to the genus Lactobacillus or bacteria belonging to the genus Lactococcus.

[0017]

Bacteria Belonging to the Genus Lactobacillus

Examples of the lactic acid bacteria belonging to the genus Lactobacillus include bulgaricus, casei, acidophilus, and plantarum.

In the invention, the "bacteria belonging to the genus Lactobacillus" refer to bacteria belonging to any one of 25 genera newly set by the rearrangement of lactic acid bacteria published in the paper "A taxonomic note on the genus Lactobacillus: Description of 23 novel genera, emended description of the genus Lactobacillus Beijerinck 1901, and union of Lactobacillaceae and Leuconostocaceae" in INTERNATIONAL JOURNAL OF SYSTEMATIC AND EVOLUTIONARY MICROBIOLOGY, Volume 70, Issue 4 as of April 15, 2020, that is, the genera Lactobacillus, Paralactobacillus, Holzapfelia, Amylolactobacillus, Bombilactobacillus, Companilactobacillus, Lapidilactobacillus, Agrilactobacillus, Schleiferilactobacillus, Loigolactobacillus, Lacticaseibacillus, Latilactobacillus, Dellaglioa, Liquorilactobacillus, Ligilactobacillus, Lactiplantibacillus, Furfurilactobacillus, Paucilactobacillus, Limosilactobacillus, Fructilactobacillus, Acetilactobacillus, Apilactobacillus, Levilactobacillus, Secundilactobacillus, and Lentilactobacillus. In the invention, a lactic acid bacterium (also referred to as bulgaricus) classified into Lactobacillus delbrueckii subsp. bulgaricus is preferable. Furthermore, the bacterium belonging to the genus Lactobacillus is preferably a bacterium belonging to Lactobacillus delbrueckii, and more preferably a bacterium belonging to Lactobacillus

delbrueckii subsp. bulgaricus. That is, a particularly preferable EPS to be used in the composition of the invention is an EPS of a lactic acid bacterium classified in Lactobacillus delbrueckii subsp. bulgaricus.

[0018]

Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741

The bacterium belonging to the genus Lactobacillus is particularly preferably Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741 or a taxonomically equivalent strain to Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741. Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741 may also be referred to as Lactobacillus delbrueckii subsp. bulgaricus OLL1073R-1. Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741 has been internationally deposited at the National Institute of Technology and Evaluation, Patent Organism Depositary (IPOD, NITE) (Room No. 120, 2-5-8, Kazusakamatari, Kisarazu-shi, Chiba, Japan) under the Budapest Treaty (Depositor: Meiji Co., Ltd., Date of Deposit: November 29, 2006, Accession No.: FERM BP-10741).

[0019]

The base sequence (corresponding to the base sequence from positions 34 to 535 in the full-length sequence of the 16S rRNA gene) of the V1 to V3 regions of the 16S rRNA gene of Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741, is shown in SEQ ID NO: 1 of the Sequence Listing (16S rRNA gene. Lactobacillus delbrueckii subsp. bulgaricus OLL1073R-1 (SEQ ID NO:1)

GCTGGCGGCGTGCCTAATACATGCAAGTCGAGCGAGCTGAATTCAA
AGATYCCTTCGGGRTGATTTGTTGGACGCTAGCGGCGGATGGGTGAGTAACA
CGTGGGCAATCTGCCCTAAAGACTGGGATACCACTTGGAAACAGGTGCTAAT
ACCGGATAACAACATGAATCGCATGATTCAAGTTTGAAAGGCGGCGYAAGCT

GTCACTTTAGGATGAGCCCGCGGCGCATTAGCTAGTTGGTGGGGTAAAGGCC
TACCAAGGCAATGATGCGTAGCCGAGTTGAGAGACTGATCGGCCACATTGGG
ACTGAGACACGGCCCAAACTCCTACGGGAGGCAGCAGTAGGGAATCTTCCA
CAATGGACGCAAGTCTGATGGAGCAACGCCGCGTGAGTGAAGAAGGTTTTC
GGATCGTAAAGCTCTGTTGTTGGTGAAGAAGGATAGAGGCAGTAACTGGTCT
TTATTTGACGGTAATCAACCAGAAAGTCACGGCTAACTACGT

[0020]

A strain taxonomically equivalent to a certain strain (hereinafter, described as strain S) refers to, for example, any one of the following strains.

· A strain belonging to the same genus as that of strain S, preferably a strain belonging to the same species as that of strain S, in which all or a characteristic part (e.g., V1 region, V2 region, or all or part of V1 region and V2 region, or part including V1 region and V2 region) of the sequence of the 16S rRNA gene has a sequence identity of 90% or more, preferably 95% or more, more preferably 98% or more, still more preferably 98.5% or more, still more preferably more than 98.7%, still more preferably 99% or more, still more preferably 99.5% or more, and still more preferably 100% with the sequence of strain S;

· A strain belonging to the same genus as strain S, preferably belonging to the same species as strain S, more preferably belonging to the same subspecies as strain S, and having the same bacteriological properties as those of strain S.

[0021]

Note that regarding the determination criteria for determining whether species is the same or different based on the 16S rRNA gene sequence, those skilled in the art can refer to Stackebrandt E, Ebers J. Taxonomic parameters revisited: tarnished gold standards. Microbiology Today 2006;33:152-155.

[0022]

The bacteriological properties of Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741 are shown below.

(1) Morphological properties

Cell shape: rod

Motility: none

Presence or absence of spores: absence

Gram staining: positive

[0023]

(2) Growth State on Medium

If the strain is applied onto a BL agar medium (Eiken Chemical Co., Ltd.) on a flat plate and cultured at 37°C for 48 hours according to the steel wool method, the colonies exhibit an opaque and rough-form morphology.

[0024]

(3) Physiological Properties

Reduction of Nitrate: negative

Indole production: negative

Gelatin liquefaction: negative

Catalase: negative

Attitude towards oxygen: facultative anaerobic

D(-) lactic acid is produced by homolactic fermentation of glucose without generating gas, growth in a BL liquid medium at 10°C is negative, and growth at 45°C is positive.

Arginine degradability: negative

Gas production from malic acid: negative

Degradability of various carbohydrates (positive +, negative -):

Arabinose (-), xylose (-), rhamnose (-), ribose (-), glucose (+), mannose (+), fructose (+), galactose (-), sucrose (-), maltose (-), cellobiose (-), lactose (+), trehalose (-), melibiose (-), raffinose (-), melezitose (-), dextrin (-), starch (-), glycogen (-), inulin (-), mannitol (-), sorbitol (-), inositol (-), esculin (-), salicin (-)

[0025]

(4) EPS Productivity

The strain of the invention has an EPS productivity.

[0026]

As the bacteria belonging to the genus Lactobacillus having EPS productivity, for example, the following lactic acid bacteria are known.

Lactiplantibacillus plantarum C88 (Non Patent Document 5); Lactobacillus johnsonii strain 151 (Non Patent Document 6); Lactobacillus delbrueckii subsp. bulgaricus NCFB2074 (Non Patent Document 7); Lacticaseibacillus casei CG11 (Non Patent Document 8); Lacticaseibacillus rhamnosus E/N (Non Patent Document 9); Lactobacillus fermentum TDS030603 (Non Patent Document 10); and Lactobacillus gasseri FR4 (Non Patent Document 11).

[0027]

From this, it is considered that EPS produced from the above described bacteria belonging to, for example, the genus Lactobacillus, produces the effect of the invention.

[0028]

Bacteria Belonging to the Genus Lactococcus

Examples of the lactic acid bacteria belonging to the genus Lactococcus include lactis, plantarum, and raffinolactis. Among the lactic acid bacteria belonging

to the genus Lactococcus, a lactic acid bacterium classified into lactis is preferable in the invention. Furthermore, among the lactic acid bacteria belonging to the genus Lactococcus, a lactic acid bacterium classified into Lactococcus lactis subsp. lactis or Lactococcus lactis subsp. cremoris is more preferable. That is, a particularly preferable example of EPS to be used in the composition of the invention is an EPS of a lactic acid bacterium classified into Lactococcus lactis subsp. lactis or Lactococcus lactis subsp. cremoris.

[0029]

It is known that EPSs produced by lactic acid bacteria belonging to the genus Lactococcus contain galactose and glucose. For example, a repeating unit of an EPS produced by Lactococcus lactis NIZO B40 is composed of glucose, galactose, rhamnose, and phosphoric acid, and the ratio of them is 2:2:1:1 (Non Patent Document 12, Non Patent Document 13). Lactococcus lactis subsp. cremoris FC (which can be separated from "Fujicco Caspian Sea yogurt (registered trademark)") produces a phosphorylated polysaccharide comprising rhamnose, galactose, and glucose in a molar ratio of 1:1:3 (Non Patent Document 14). Lactococcus lactis subsp. lactis YZ1 produces a polysaccharide composed of, e.g., mannose, galactose, and glucose (Non Patent Document 15). From these, it is considered that an EPS produced by a lactic acid bacterium belonging to the genus Lactococcus also exerts the effect of the invention.

[0030]

Other than the above, a lactic acid bacterium having at least one DNA selected from the group consisting of DNA encoding any of the following proteins (a) to (d) (DNA for improving ropiness) can also be used.

(a) a protein comprising the amino acid sequence represented by SEQ ID NO:

2,

(b) a protein comprising an amino acid sequence in which one or more of the amino acids other than tyrosine at position 40 are substituted, deleted, inserted, and/or added in the amino acid sequence represented by SEQ ID NO: 2, and having an action of improving the ropiness of fermented milk;

(c) a protein comprising an amino acid sequence having an identity of 80% or more to the amino acid sequence represented by SEQ ID NO: 2, wherein the amino acid corresponding to position 40 of the amino acid sequence represented by SEQ ID NO: 2 is tyrosine, and having an action of improving the ropiness of fermented milk; and

(d) a protein comprising an amino acid sequence encoded by DNA hybridizing, under stringent conditions, with a complementary strand of DNA comprising the nucleotide sequence represented by SEQ ID NO: 3, wherein the amino acid corresponding to position 40 of the amino acid sequence represented by SEQ ID NO: 2 is tyrosine, and having an action of improving the ropiness of fermented milk.

[0031]

In the invention, “the ropiness of fermented milk” refers to a property of forming strings due to viscosity and/or elasticity of the fermented milk, whereas “the action of improving the ropiness of fermented milk” refers to an action of imparting the ropiness to fermented milk or improving the ropiness in fermented milk (in the specification, sometimes referred to as “ropiness-improving action”). The reason why the protein has the ropiness-improving action is not clear, but the present inventors estimate that the protein of the invention acts during the EPS biosynthesis process by a lactic acid bacterium, thereby generating an EPS having a structure exhibiting high ropiness.

[0032]

Whether or not a lactic acid bacterium has DNA for improving ropiness according to the invention can be determined by detecting the DNA. As a method for detecting DNA for improving ropiness, a known method or a similar method thereto can be appropriately employed.

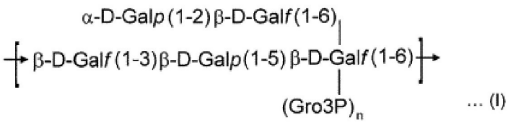
[0033]

(Constituent Sugars of EPS)

In one embodiment, an EPS of a lactic acid bacterium contained in the composition of the invention may comprise an acidic extracellular polysaccharide having a repeated structure in which the repeating unit represented by the following formula (I) appears in series.

[0034]

[Chem. 1]



... (I)

In formula (I),

n is 0 or 1;

α-D-Galp represents a pyranose-form α-D-galactose residue;

β-D-Galp represents a pyranose-form β-D-galactose residue;

β-D-Galf represents a furanose-type β-D-galactose residue;

Gro3P represents a glycerol 3-phosphate group, and

(1-2), (1-3), (1-5), and (1-6) represent a 1-2 linkage between residues (that is, C1-C2 linkage), a 1-3 linkage, a 1-5 linkage, and a 1-6 linkage, respectively.

[0035]

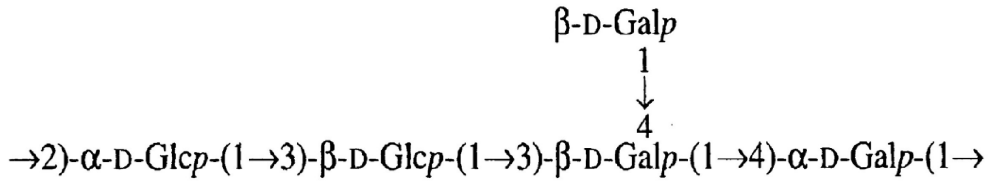
In one embodiment, in the acidic extracellular polysaccharide, it is preferable that, in a repeated structure in which the repeating unit represented by formula (I)

appears in series, a glycerol 3-phosphate group is added in a ratio of about 1 per repeating unit on average (e.g., 1 (n = 1) or 0 for each repeating unit, and about 1 per repeating unit on a weighted average in the entire acidic EPS), but the ratio is not limited thereto.

[0036]

In another embodiment, an EPS of a lactic acid bacterium contained in the composition of the invention may comprise a neutral polysaccharide having a repeated structure in which repeating units represented by the following formula (II) appear in series.

[Chem. 2]



Formula (II)

[0037]

Fermentation Product

EPS may be contained in the composition of the invention as a fermentation product of a lactic acid bacterium (preferably, a fermentation product of animal milk). The fermentation product of a lactic acid bacterium includes not only the fermentation product itself by a lactic acid bacterium, but also a processed material thereof. The fermentation product itself of a lactic acid bacterium includes, for example, fermented milk (specifically, e.g., yogurt). Examples of the processed material include a crudely purified product, a precipitate, which is obtained by removing bacteria from a fermentation product by filtering, centrifugation, or membrane separation, a

concentrated culture solution reduced in liquid content, a culture filtrate or culture supernatant, a concentrate obtained by concentrating a culture filtrate/supernatant, and a dried product of the concentrate. Alternatively, the processed material may be an agglomerated product of a granular material obtained by spraying a binder (binding agent) solution onto a culture solution, a concentrated culture solution, a culture filtrate, or a culture supernatant.

Note that the substrate for fermentation is not particularly limited, but may be a general medium for proliferating a lactic acid bacterium, preferably animal milk. Preferably, an extract of a legume plant is not contained. The composition of the invention may or may not contain bacterial cells.

[0038]

The method for preparing an EPS of a lactic acid bacterium may be, for example, a method following a conventional method disclosed in, e.g., Patent Document 4 mentioned above. Alternatively, EPS may be produced by chemical synthesis. In a case where an EPS of a lactic acid bacterium is prepared as a fermentation product of a lactic acid bacterium, a lactic acid bacterium producing an EPS is added to raw milk as a starter. The mixture is fermented to produce the EPS in a fermentation product. In this manner, the fermented milk comprising the EPS can be produced. The conditions for fermentation, for example, raw milk, fermentation temperature, and fermentation time, are not particularly limited as long as the lactic acid bacterium used can produce an EPS, and can be appropriately set by those skilled in the art.

[0039]

As the starter, for example, a bacterium belonging to the genus Lactobacillus, a bacterium belonging to Streptococcus thermophilus in addition to a bacterium

belonging to the genus Lactobacillus can be used. Accordingly, in an embodiment, the fermentation product of a lactic acid bacterium is a mixture of a fermentation product of a bacterium belonging to the genus Lactobacillus and a fermentation product of a bacterium belonging to Streptococcus thermophilus. The bacterium belonging to Streptococcus thermophilus is preferably Streptococcus thermophilus 1131. Streptococcus thermophilus 1131 can be isolated from Meiji Bulgaria Yoghurt LB81 (Meiji Co., Ltd.), and can be obtained from a commercially available product.

[0040]

[Application]

(Function)

Promotion of Proliferation of $CD4^+$ T Cells Having Cell-surface Marker Expression Pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$

The composition of the invention can be used for promoting the proliferation of cells (hereinafter, also referred to as Th7R cells or TH7R or $CXCR3^+/CCR4^{lo}/CCR6^{hi}$) having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$. The $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$ may be any cells as long as they have at least a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$, and, for example, cluster 44352 described in the Examples is known.

In the specification, the definitions of +, low (lo), high (hi), and -, which represent the expression levels of the chemokine receptors, are as follows.

The reference symbol "+" represents that expression of a chemokine receptor is positive, that is, the measured value in the expression analysis of a cell surface marker by, e.g., flow cytometry, is a measurement limit value or more.

The reference symbol "low" represents that the expression level of a

chemokine receptor is the median value or less of the expression intensity of a cell surface marker per cell in PBMCs of the population to be analyzed. Note that the term "or less" may include a case where the expression is negative.

The reference symbol "High" indicates that the expression level of a chemokine receptor is the median value or more of the expression intensity of a cell surface marker per cell in PBMCs of the population to be analyzed. Alternatively, the value may be arbitrarily set to be a higher value or more.

The reference symbol "-" represents that the expression of a chemokine receptor is negative, that is, the measured value in the analysis of a cell surface marker by, e.g., flow cytometry, is less than a measurement limit value. In other words, it cannot be said that the expression is positive.

Herein, the expression intensity can be measured by analyzing, for example, cells directly by flow cytometry using a fluorescently labeled antibody specific to a cell surface marker. As described in Examples, the expression intensity can be measured by analyzing cells directly by mass cytometry using a metal isotope element-labeled antibody specific to a cell surface marker and quantifying the metal isotope element. In a case where measurement by the above analysis is difficult, the expression intensity can be measured by the fluorescence intensity of the fluorescently labeled antibody. In a case where both methods are difficult, another method may be used as long as it is known to those skilled in the art.

[0041]

The promotion of proliferation of Th7R cells can be evaluated, for example, as shown in the Examples, by the fact that the component ratio of the population of Th7R cells, which are obtained by clustering of $CD4^+$ T cells and are present in $CD4^+$ T cells contained in PBMCs (peripheral blood mononuclear cells) collected from a subject

is confirmed to increase as compared to an appropriate control, after ingestion of the component to be evaluated. The promotion of proliferation of Th7R cells may include a case where Th7R cells themselves increase, a case where differentiation into Th7R cells is promoted, a case where death of Th7R cells is prevented to increase the component ratio of the population, and a case where inflow from another tissue is promoted to increase the component ratio of the population. In an embodiment, the promotion of proliferation of Th7R cells is the promotion of proliferation of Th7R cells in the blood. In the detection of Th7R cell populations, not only clustering but also other scientifically acceptable methods can be selected.

[0042]

The composition of the invention can be used for treating diseases or conditions that are ameliorated by promoting Th7R cell proliferation. In the present invention, "treating" includes preventing, ameliorating, and suppressing the progression of a disease or condition.

[0043]

Th7R cells can be used as a biomarker for predicting the response rate of an immune checkpoint inhibitor for cancer (Non Patent Document 1). Thus, the composition of the invention that can promote the proliferation of Th7R cells can be used for improving susceptibility to immune checkpoint inhibitor therapy. In addition, the composition of the invention can be used for improving susceptibility to immune checkpoint inhibitor therapy by promoting the proliferation of Th7R cells. The improvement in susceptibility to immune checkpoint inhibitor therapy means that a subject changes from a poor responder to the immune checkpoint inhibitor therapy to a good responder (providing), and that a subject who has become a poor responder to the immune checkpoint inhibitor therapy with time, becomes a good responder again

(recovery). The effect of the immune checkpoint inhibitor therapy includes, for example, an effect of extending the survival period of a tumor-bearing patient, an effect of killing cancer cells to shrink cancer (to reduce the tumor volume), an effect of retarding the growth of cancer (to suppress the increase in the tumor volume), an effect of curing cancer, an effect of preventing metastasis/the recurrence of cancer, and an effect of killing cancer cells that may have metastasized.

[0044]

The immune checkpoint inhibitor therapy is not particularly limited as long as it is a therapy of inhibiting an immune checkpoint. Examples thereof may include PD-1 inhibitor therapy, PD-L1 inhibitor therapy, CTLA-4 inhibitor therapy, LAG-3 inhibitor therapy, TIGIT inhibitor therapy, CSF-1/CSF-1R inhibitor therapy, and TIM-3 inhibitor therapy. These may be used in combination, or an immune checkpoint inhibitor therapy may be used in combination with an anticancer therapy such as chemotherapy, radiation therapy, or surgical therapy. Preferably, PD-1 inhibitor therapy is used. The PD-1 inhibitor therapy, the PD-L1 inhibition therapy, the CTLA-4 inhibition therapy, and the LAG-3 inhibition therapy refer to therapies using a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, and a LAG-3 inhibitor, respectively. Examples of the PD-1 inhibitor include pembrolizumab and nivolumab. Examples of the PD-L1 inhibitor include atezolizumab, avelumab, and durvalumab. Examples of the CTLA-4 inhibitor include ipilimumab and tremelimumab. LAG-3 inhibitors include relatlimab. In addition, examples of the immune checkpoint inhibitors used in combination include a mixture of two agents: an anti-PD-1 antibody, nivolumab, and an anti-LAG-3 antibody, relatlimab (for example, Opdualag).

[0045]

Th7R cells are known to contribute to suppressing cancer recurrence after

removal surgery (Non Patent Document 2). Thus, the composition of the invention that can promote the proliferation of Th7R cells can be used for suppressing the recurrence of cancer (particularly lung cancer) after removal surgery. Furthermore, the composition of the invention can be used for suppressing the recurrence of cancer (particularly lung cancer) after removal surgery by promoting the proliferation of Th7R cells.

[0046]

Promotion of Proliferation of MAIT and NKT Cells (hereinafter, also referred to as MAIT/NKT cells)

The composition of the invention can be used for promoting the proliferation of Mucosal-Associated Invariant T Cells (MAIT) cells and Natural Killer T Cells (NKT) cells. MAIT cells and NKT cells, which are types of effector T cells, are characterized by contributing to acquired immunity and having rapid effector activation action, thereby contributing also to natural immunity. MAIT cells and NKT cells can be detected and measured by, for example, a method described in Examples, as cells having an expression pattern of cell surface markers of $CD3^+$, $CD4^-$, $CD28^+$, and $CD161^+$, for example, in PBMCs.

[0047]

The promotion of the proliferation of MAIT cells and NKT cells can be evaluated by mass cytometry, which comprehensively analyzes markers expressed in cells in PBMCs collected from a subject, for example, as shown in Examples, based on the fact that the amount of a change in the component ratio of MAIT/NKT cells (the sum of MAIT cells and NKT cells) in PBMCs before and after ingestion of a component to be evaluated increases compared to an appropriate control. The promotion of proliferation of MAIT cells and NKT cells may include an increase in the number of

MAIT cells and NKT cells themselves, promotion of the differentiation into MAIT cells and NKT cells, preventing the killing of MAIT cells and NKT cells to increase the component ratio of cell populations, and promotion of the inflow from another tissue to increase the component ratio of cell populations. In an embodiment, the promotion of proliferation of MAIT cells and NKT cells is the promotion of MAIT cells and NKT cells in the blood.

[0048]

The composition of the invention can be used for treating a disease or condition that is ameliorated by the promotion of MAIT and NKT cells.

[0049]

MAIT cells contribute to suppressing cancer metastasis (Non Patent Document 3), and NKT cells are known to contribute to preventing cancer (particularly, liver cancer) (Non Patent Document 4). Therefore, the composition of the invention capable of promoting the proliferation of MAIT cells and NKT cells can be used for either or both of suppressing cancer metastasis and preventing cancer. Furthermore, the composition of the invention can be used for suppressing cancer metastasis by promoting the proliferation of MAIT cells, or can be used for preventing cancer (particularly liver cancer) by promoting the proliferation of NKT cells.

[0050]

(Subject)

The subject by whom the composition of the invention is to be ingested may be, for example, a mammal, preferably a human. The age and gender of the subject are not particularly limited. In the case of humans, examples of the subjects include babies, infants, children, adults, and elderly persons.

[0051]

It is known that if the proportion of Th7R cell cluster in the peripheral blood is a predetermined value or more, the susceptibility to immune checkpoint inhibitor therapy improves (Non Patent Document 1). Thus, in order to improve the susceptibility to immune checkpoint inhibitor therapy, it is considered preferable that the proliferation of Th7R cells is promoted. Thus, if the composition of the invention is used for improving susceptibility to immune checkpoint inhibitor therapy, a suitable subject by whom the composition of the invention is to be ingested may be a subject for whom promotion of Th7R cell proliferation is required or desired. The subject for whom promotion of proliferation of Th7R cells is required or desired may be, for example, a subject whose component ratio of Th7R cells in $CD4^+$ T cells contained in PBMCs is 6.0% or less, preferably 5.0% or less, and more preferably 4.0% or less.

[0052]

MAIT cells contribute to suppressing cancer metastasis (Non Patent Document 3), and NKT cells are known to contribute to preventing cancer (particularly, liver cancer) (Non Patent Document 4). Thus, in a case where the composition of the invention is used for either or both of suppressing cancer metastasis and preventing cancer, it can be said that the composition of the invention is preferably ingested, particularly by a subject for whom the proliferation of MAIT cells and NKT cell is required or desired. In Examples herein, it is disclosed that the component ratio of MAIT cells and NKT cells in PBMCs increases by about 0.14% from about 2.56% by ingestion of the composition of the invention. The subject for whom the proliferation of MAIT cells and NKT cell is required or desired may be, for example, a subject whose component ratio of MAIT cells and NKT cells in PBMCs is 4.0% or less, preferably 3.5% or less, more preferably 3.0% or less, and still more preferably 2.5% or less.

[0053]

Alternatively, further examples of subjects to which the composition of the invention is suitably administered include the following subjects:

Healthy subjects for whom the promotion of proliferation of any one or more of Th7R cells, MAIT cells, and NKT cells is required or desired; healthy subjects in whom any one or more of Th7R cells, MAIT cells, and NKT cells in the blood or PBMCs have been confirmed to be low; healthy subjects in whom Th7R cells in $CD4^+$ T cells contained in the blood or PBMCs have been confirmed to be low; healthy subjects who are not receiving cancer therapy; healthy subjects who are not receiving immune checkpoint inhibitor therapy; healthy subjects who have not received cancer removal surgery; healthy subjects (e.g., subjects after cancer therapy) for whom suppressing cancer metastasis or recurrence is required or desired; healthy subjects who have a high risk of developing cancer (particularly, liver cancer) (e.g., persons taking alcohol, smokers, persons having a basic disease, such as hepatitis B, hepatitis C, obesity, fatty liver, or diabetes, and elderly persons); and healthy subjects whoare not receiving cancer therapy (e.g., surgical therapy, radiotherapy, chemotherapy).

Note that regarding the invention, administration is used to mean not only a case where a pharmaceutical product is administered to a subject, but also a case where food products other than a pharmaceutical product are ingested by a subject (a subject ingests).

The healthy subject refers to a human who is not received the diagnosis of any disease (pre-disease state) or a companion animal described later. That is, in a case where the composition of the invention is used for these healthy subjects, the composition of the invention is not provided for therapeutic purposes.

[0054]

The composition of the invention can also be used for non-therapeutic

purposes on healthy subjects. In one embodiment, the composition of the invention can be used in the form of, e.g., a food product (for example, as a food composition). In the above embodiment, the composition of the invention is provided not as a medicine but in the form of, e.g., a food product described later. The use of non-therapeutic purposes means uses for maintenance of conditions, temporary relief, support (aid), and use in consideration of conditions.

[0055]

Additional examples of the suitable subject by whom the composition of the invention is ingested are as follows:

Subjects having a disease for whom the promotion of proliferation of any one or more of Th7R cells, MAIT cells, and NKT cells is required or desired; subjects having a disease in whom any one or more of Th7R cells, MAIT cells, and NKT cells in the blood or PBMCs have been confirmed to be low; subjects having a disease in whom Th7R cells in $CD4^+$ T cells contained in the blood or PBMCs have been confirmed to be low; subjects having a disease who are notreceiving cancer therapy; subjects having a disease who are receiving or who would benefit from receiving immune checkpoint inhibitor therapy; subjects having a disease who are not receiving immune checkpoint inhibitor therapy; subjects having a disease who are scheduled to receive immune checkpoint inhibitor therapy; subjects having a disease in whom the effect of immune checkpoint inhibitor therapy has not been sufficiently obtained (for example, subjects in whom cancer is observed to progress despite immune checkpoint inhibitor therapy; subjects having a disease in whom the effect of immune checkpoint inhibitor therapy has been determined to be PD (progressive disease)); subjects having a disease who have received or who would benefit from receiving cancer removal surgery; subjects having a disease who have not received cancer removal surgery; subjects having a

disease who are scheduled to receive cancer removal surgery; subjects having a disease for whom suppressing cancer metastasis is required or desired (e.g., subjects diagnosed with cancer; subjects during or after cancer therapy); subjects having a disease who have a high risk of developing cancer (particularly, liver cancer (e.g., persons taking alcohol, smokers, persons having a basic disease, such as hepatitis B, hepatitis C, obesity, fatty liver, or diabetes, and elderly persons)); subjects having a disease who are not receiving cancer therapy (e.g., surgical therapy, radiotherapy, chemotherapy); and subjects having a disease who are scheduled to receive cancer therapy.

The subject having a disease refers to a human or a companion animal described later who has been diagnosed with the disease. In a case where the composition of the invention is used for a subject having these diseases, the composition of the invention is not provided for a therapeutic purpose, but is provided for a non-therapeutic purpose, such as a treatment aid.

[0056]

The composition of the invention can be used for a non-therapeutic purpose in a subject having a disease. In one embodiment, the composition of the invention can be used as a composition for treatment aid in the form of, e.g., food (for example, as a food composition). Here, the treatment aid refers to a treatment for a disease or a disorder, which is a non-therapeutic use. Examples of the treatment aid include an embodiment in which the composition is used for a subject under treatment for a disease or a disorder for the purpose of increasing the therapeutic effect thereof and providing nutritional support during treatment; an embodiment in which the composition is used for a subject who received treatment for a disease or a disorder, for the purpose of improving the prognosis thereof and maintaining good prognosis and providing nutritional support after treatment; and an embodiment in which the composition is used

for a subject who is scheduled to receive treatment for a disease or a disorder for the purpose of increasing the effect of treatment to be applied later and providing nutritional support before the treatment. In these embodiments, the composition of the invention is provided not as a medicine but in the form of, e.g., a food product described later. Examples of treatment for a disease or a disorder for a non-therapeutic purpose include uses for nutritional management of subjects for whom special consideration is required, uses as hospital meals, and uses in the consideration of conditions such as maintenance, temporary relief, and support (aid) of conditions.

[0057]

When the composition of the invention is used for non-therapeutic purpose, whether or not the composition is desirable or necessary is determined based on the judgements as non-therapeutic act, such as advice, other than diagnoses by medical practitioners such as a doctor, a nurse, a pharmacist, a midwife, and a clinical laboratory technician; judgements by persons engaged in non-therapeutic acts, such as a dietitian (including an administrative dietitian and a sports dietitian), a public health nurse, a sports instructor, a pharmaceutical manufacturer, a pharmaceutical distributor, a food manufacturer, and a food distributor; and judgments by the subjects themselves or by family members. Examples of the judgments mentioned above include judgments based on lifestyle, eating habits, nutritional state, questionnaires about self-reported symptoms, and output results of, e.g., health examination data regarding the immune system, and judgments based on self-reported symptoms (e.g., concern about obesity and lifestyle-related diseases).

[0058]

The subject may be a human or a non-human animal. Examples of non-human animal include mammals, birds, reptiles, amphibians, and fish. The non-human

animal may be a commercial animal, a research animal, or a companion animal. The term “companion animal” refers to a farm animal or a domestic animal that can readily satisfy physical, emotional, behavioral, and social needs as an in-home companion or through daily close contact with a single or a plurality of humans. In one embodiment, species included in the definition of the companion animal include dogs, canines, cats, felines, cows, horses, goats, sheep, pigs, primates (e.g., monkeys), rabbits, ferrets, rodents (e.g., guinea pigs, hamsters, mice, rats), and other small mammals. In another embodiment, species included in the definition of the companion animal are dogs, cats, horses, rabbits, ferrets, guinea pigs, and other small mammals, birds, small reptiles, fish, and livestock animals.

[0059]

The age of the subject is not particularly limited. If the subject is a human, the subject may be, for example, a newborn baby (within 28 days after birth); a baby (less than one year after birth); an infant (1 to 6 years after birth); a child (7 years old or more and less than 15 years old); a grown person (15 years old or more); a person of 40 years or more, a person of 50 years or more, a person of 60 years or more; and a person of 65 years or more.

[0060]

An embodiment of the invention relates to a method of promoting the proliferation of Th7R cells in a subject; a method of improving susceptibility to immune checkpoint inhibitor therapy in a subject; or a method for suppressing the recurrence of cancer after removal surgery in a subject. These methods may include the following steps:

(a) obtaining information on Th7R cells in the blood or PBMCs of a subject.

(b) determining whether or not ingestion of an extracellular polysaccharide of

a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium is required based on the information.

[0061]

An embodiment of the invention relates to a method of promoting the proliferation of MAIT cells and NKT cells in a subject; a method of suppressing cancer metastasis in a subject; or a method of preventing cancer in a subject. These methods may include the following steps:

(a) obtaining information on MAIT cells and NKT cells in the blood or PBMCs of a subject.

(b) determining whether or not ingestion of an extracellular polysaccharide of a lactic acid bacterium or a composition comprising an extracellular polysaccharide of a lactic acid bacterium is required based on the information.

[0062]

In the methods described above, examples of the information on the Th7R cells in the blood or PBMCs or the information on the MAIT cells and the NKT cells may include the number of cells, component ratio and concentration of Th7R cells or the MAIT cells and the NKT cells in the blood or PBMCs. The acquisition of information on these may be performed by any method. For example, if the information of cells is a component ratio in the blood or PBMCs, the information can be obtained using an immunological technique based on cell surface markers, as shown in Examples.

[0063]

(Others)

The following uses may be excluded from the use of the composition of the invention:

Treating rheumatoid arthritis; NK cell activation; promotion of YAC-1 cell-killing activity of NK cells; antiviral activity; promotion of YAC-1 cell-killing activity of NK cells stimulated with IFN-α; preventing pneumococcal infection; suppressing reduction of acquired immune function by anti-influenza drug; preventing and/or treating influenza; increase of influenza virus-cross-reactive IgA in the saliva; control of cytokine (IL-1β, TNF-α, CXCL1) production; cellular immune activation; cellular immune activation against melanoma antigen, influenza antigen, or HBV antigen; suppressing cancerous cachexia; promotion of immune checkpoint inhibitor therapy; preventing a secondary infection after influenza infection or reduction of the risk of developing the secondary infection; suppressing an increase in expression of cell adhesion molecules (particularly tight junction molecules such as CEACAM-1) after influenza virus infection; suppressing proliferation of human coronavirus (especially HCoV-229E); suppressing proliferation of norovirus; enhancement of the function of Th1, Th2, and Treg; maintenance of function of Th17; promotion of IFN-γ production by T cells; activation of T cells; increase in expression rate of CD69 of T cells; promotion of maturation from CD8+TEM to CD8+TEMRA; increase in antibody titer; use as adjuvant; and retinoic acid production.

[0064]

[Form of Composition]

The composition of the invention can be used as a food composition or a pharmaceutical composition. The food product and pharmaceutical product include not only those for humans but also those for animals other than humans, unless otherwise specified. The food includes, unless otherwise specified, a general food, a functional food, a nutritional composition, and a therapeutic diet (which achieves therapeutic purpose, or a meal cooked based on the menu prepared by e.g., a dietitian in

accordance with a dietary recipe provided by a doctor), a dietary meal, an ingredient-adjusted meal, a nursing care food, a food for treatment aid, and precision nutrition (personalized nutrition, an appropriate meal (nutrition) proposed according to individual's physical constitution). The food includes not only solid products but also liquid products such as a beverage, a health drink, a liquid meal, and a soup, unless otherwise specified. The functional food refers to a food that can impart a predetermined functionality to a living body. Examples thereof include general health foods such as a food for specified health use (including conditional Tokuho [food for specified health use]), a food with functional claims, a food with health claims including a food with nutrient function claims, a food for special dietary use, nutritional supplement food, health supplement food, dietary supplement, food supplement, medical food (according to the definition by the Food and Drug Administration (FDA)), supplement (e.g., those having various dosage forms such as tablet, coated tablet, sugar-coated tablet, capsule, and solution), and beauty diets (e.g., diet food). In the invention, the term "functional food" includes health foods to which a health claim based on the food standard of Codex (the Codex Alimentarius Commission established jointly by FAO and WHO) is applied. The food supplement is a supplement for regular meals, obtained by concentrating supplemental nutrients or other substances having a nutritional or physiological effect, alone or in combination, and labeled as Food Supplement. The dietary supplement is a product (excluding tobacco) to be used for the purpose of supplementing a meal, contains one or more target ingredients, and is labeled as Dietary supplement.

[0065]

[Ingestion Route]

The composition of the invention may be ingested orally, non-orally, for

example, via a tube (gastric fistula or intestinal fistula), or nasally, but oral ingestion is preferred.

[0066]

[Content and Dosage of Active Ingredient]

The content of an EPS of a lactic acid bacterium in the composition of the invention may be satisfactory as long as a desired effect is exhibited. The ingestion dose of the composition can be appropriately set in consideration of various factors such as the age, body weight, symptom, metabolism/excretion function, and concomitant drug of the subject, but the amount of EPS of a lactic acid bacterium per day can be, for example, 0.1 mg or more, and is preferably 0.6 mg or more, more preferably 3 mg or more, and still more preferably 3.3 mg or more or 6 mg or more. The upper limit value of the amount of EPS per day can be 4800 mg or less, regardless of the lower limit value, and is preferably set to 3600 mg or less, more preferably 1800 mg or less, and particularly preferably 900 mg or less.

In the invention, each component in the composition is used at an ingestion dose ensuring safety or less, or an acceptable daily intake (ADI) or less by giving priority to the food safety laws of individual countries.

[0067]

The amount of EPS of a lactic acid bacterium per ingestion or meal, that is, per dose, can be set to, for example, 0.03 mg or more, and preferably 0.2 mg or more, and more preferably 1 mg or more. The upper limit value of the amount of EPS per dose can be set to 1600 mg or less, regardless of the lower limit value, and preferably 1200 mg or less, more preferably 600 mg or less, and particularly preferably 300 mg or less.

[0068]

In a case where the composition of the invention comprises EPS as a fermentation product (fermented milk) of a lactic acid bacterium, the daily dose of fermented milk can be, for example, 10 g or more, preferably 30 g or more, more preferably 60 g or more, still more preferably 100 g or more, and particularly preferably 112 g or more. The upper limit value of the daily dose of the fermented milk can be, for example, 1500 g or less, regardless of the lower limit value, preferably 1200 g or less, and more preferably 600 g or less.

[0069]

The amount of fermented milk per ingestion or meal, that is, per dose, can be set to, for example, 3 g or more, preferably 10 g or more, and more preferably 20 g or more. The upper limit value of the amount of fermented milk per dose can be, for example, 800 g or less, and is preferably 400 g or less, and more preferably 200 g or less, regardless of the lower limit value.

[0070]

The composition may be ingested once a day, or a plurality of times a day, for example, with every meal, that is, three times a day. The composition comprises an EPS of a lactic acid bacterium, which has long been used and experienced as food, as an active ingredient. Therefore, the composition of the invention may be ingested repeatedly or over a long period of time, and for example, can be ingested continuously for one week or more, preferably 2 weeks or more, more preferably 3 weeks or more, and still more preferably 4 weeks or more.

[0071]

Examples of the method for preparing fermented milk according to an embodiment of the invention include “a method including sterilizing raw milk followed by cooling, adding a lactic acid bacterium starter comprising the above-described lactic

acid bacterium to the raw milk, and fermenting the raw milk comprising the lactic acid bacterium starter at a fermentation temperature and a fermentation time such that a predetermined lactic-acid acidity is obtained". The extracellular polysaccharide is produced by a lactic acid bacterium belonging to the genus Lactobacillus during fermentation. In the method, the lactic-acid acidity is, for example, 0.6 to 1.2. The lactic-acid acidity is preferably 0.6 to 0.8. The fermentation temperature is, for example, 40 to 45°C. The fermentation time is, for example, 2 to 12 hours. The fermentation time is preferably 3 to 8 hours.

[0072]

[Other Components and Additives]

The composition of the invention may comprise other active ingredients and nutritional components acceptable as a food or a pharmaceutical product. Examples of such ingredients/components include amino acids (e.g., lysine, arginine, glycine, alanine, glutamic acid, leucine, isoleucine, and valine), carbohydrates (glucose, sucrose, fructose, maltose, trehalose, erythritol, maltitol, palatinose, xylitol, and dextrin), electrolytes (e.g., sodium, potassium, calcium, and magnesium), vitamins (e.g., vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, vitamin K, biotin, folic acid, pantothenic acid, and nicotinic acids), minerals (e.g., copper, zinc, iron, cobalt, and manganese), antibiotics, dietary fibers, proteins, and lipids.

[0073]

In addition, the composition of the invention may further comprise an additive acceptable as a food or a medicine. Examples of the additive include an inert carrier (solid or liquid carrier), an excipient, a surfactant, a binder, a disintegrant, a lubricant, a solubilizing agent, a suspending agent, a coating, a colorant, a preservative, a buffering

agent, a pH adjusting agent, an emulsifier, a stabilizer, a sweetener, an antioxidant, a flavor, an acidulant, and a natural product. More specific examples thereof include water, other aqueous solvents, pharmaceutically acceptable organic solvents, collagen, polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymer, sodium alginate, water-soluble dextran, water-soluble dextrin, sodium carboxymethyl starch, pectin, xanthan gum, gum Arabic, casein, gelatin, agar, glycerin, propylene glycol, polyethylene glycol, petrolatum, paraffin, stearyl alcohol, stearic acid, human serum albumin, mannitol, sodium chloride, propylene glycol, glycerin, benzalkonium chloride, methyl paraoxybenzoate, milk sugar, starch, maltose, sorbitol, lactose, sucralose, stevia, aspartame, acesulfame potassium, citric acid, lactic acid, malic acid, tartaric acid, phosphoric acid, acetic acid, fruit juice, and vegetable juice.

[0074]

[Dosage Form/Form]

The pharmaceutical composition of the invention can also be formed into any dosage form as long as it is suitable for oral ingestion. Examples of the dosage form include solid preparations such as tablets, granules, powders, pills, and capsules; liquid preparations such as solutions, suspensions, and syrups; gels; and aerosols.

[0075]

The food composition of the invention may be prepared in any form such as a solid, a liquid, a mixture, a suspension, a powder, a granule, a paste, a jelly, a gel, or a capsule. The food composition according to the invention can be formed into any form such as a milk product, a supplement, a confection, a beverage, a health drink, a seasoning, a processed food, a daily dish, or a soup. More specifically, the composition of the invention may take forms such as a dairy beverage, a soft drink, a fermented milk, a yogurt, an ice cream, a tablet, a cheese, bread, biscuit, cracker, pizza

crust, a modified milk powder, liquid meal, a food for the sick, a nutritional food, a frozen food, and a processed food, and may take forms such as a granule, a powder, a paste, and a concentrated liquid for mixing it with a beverage or a food to ingest it.

[0076]

[Others]

In producing the composition of the invention, the stage at which an EPS of a lactic acid bacterium is blended can be appropriately selected. The blending stage is not particularly limited as long as the properties of an EPS of a lactic acid bacterium are not significantly impaired. For example, EPS can be blended by mixing it with raw materials at an early stage of production. In a case where the composition of the invention comprises EPS as the fermentation product of a lactic acid bacterium, the lactic acid bacterium producing EPS is added to raw milk as a starter, and the mixture is fermented to produce EPS. In this manner, fermented milk comprising EPS can be produced.

Alternatively, the composition of the invention comprising EPS can be produced by culturing a lactic acid bacterium in, e.g., a medium suitable for culturing a lactic acid bacterium, a medium suitable for producing a large amount of EPS, milk (including animal milk or soy milk, and preferably animal milk); concentrating the culture solution itself by a method known in the food field, such as centrifugation, removal of denatured proteins, or filtration; and using the resulting concentrated culture solution, a dried product of the culture solution, or a granulated product of the culture solution or the concentrated culture solution (such as spray dried product using a binder) directly as the composition of the invention comprising EPS, or by blending it with various dosage forms of compositions.

Alternatively, a lactic acid bacterium is cultured in a medium suitable for culturing lactic acid bacteria, a medium suitable for increasing or producing EPS, or milk (including animal milk and soy milk, with animal milk being preferred), and bacteria are removed from the resulting culture by filtration, centrifugation, or membrane separation to obtain a culture filtrate, a culture supernatant, or culture isolate, or a concentrate or dried concentrate thereof. By using such a crude product, purified product, lyophilized product, or dried concentrate of EPS as a functional material or incorporating it into various compositions, a composition comprising EPS can be produced.Note that the purification described herein is satisfactory as long as the EPS concentration in the purified product increases from that before purification. The purity is not necessary to be 99 to 100%. Bacterial body, bacterial components, and medium components may be contained in the range of error (e.g., carry-over from a cultured product).

[0077]

The composition of the invention may have an indication of the purpose of use (application). Also, a message that ingestion is recommended for a specific subject can be displayed. The purpose of use and the subject can be selected as described in the sections of [Application] and [Subject], respectively. The indication can be directly or indirectly made. Examples of the direct indication include indications on tangible objects such as a product itself, a package, a container, a label, and a tag. Examples of the indirect indication include advertisement or publicity by means of sites or measures, such as package insert, pharmaceutical product interview form (IF), website, storefront, pamphlet, exhibition, seminar such as media seminar, book, newspaper, magazine, television, radio, mail, e-mail, sales talk, video streaming sites, SNS, influencer marketing, or voice.

[0078]

The following materials may be excluded from the composition of the invention:

A composition which is produced by culturing Lactobacillus and yeast, or Lactobacillus, yeast and Lactococcus in a medium comprising an aqueous soybean extract, filtering to remove solid matter, and concentrating the liquid solution prepared by sterilization; and a fermentation product which is obtained by fermenting a mixture comprising a lactic acid bacterium and yeast in a medium comprising an aqueous soybean extract under conditions that enable fermentation of the soybean extract by microorganisms.

EXAMPLES

[0079]

Hereinafter, the invention will be described with reference to Examples. Note that the examples are merely illustrative descriptions of the invention, and do not limit the invention.

[0080]

An analytical study was performed using PBMC (peripheral blood mononuclear cell) specimens, which were separated from blood samples collected before and after the test period and obtained in a randomized, placebo-controlled, double-blind, parallel group comparative test for healthy Japanese men and women of 35 years old or more and less than 60 years old (specifically, subjects excluding the following persons: persons with, under treatment for, or having a history of diseases including a severe disease such as diabetes, kidney/liver disease, or heart disease, persons suffering from thyroid disease, adrenal disease, or other metabolic diseases;

persons who have a chronic disease and receive regular medication; and persons who have a history of a digestive disease affecting digestion and absorption, and a history of a digestive-system surgery). In this test, fermented milk (yogurt described in Production Example 1, 112 g, EPS content: 3.3 mg or more) using Lactobacillus delbrueckii subsp. bulgaricus OLL1073R-1 strain as a test product, and an acid milk (112 g, comprising no EPS) as a placebo were ingested by test subjects every day for 4 weeks.

[0081]

In order to comprehensively measure markers expressed in PBMC specimens and to perform immunological deep profiling, mass cytometric analysis was performed according to Maxpar Direct Immune Profiling Assay (Standard BioTools Inc.) staining all 30 markers. Note that 7 types of T-cell related markers, CD11a, Tim-3, CD69, PD-1, ICOS, CXCR4, and TIGIT, were added. A total of 174 specimens (fermented milk group n = 44, placebo group n = 43) that passed through the QC were separately analyzed by the following 2 types of methods.

[0082]

<Analysis 1: Manual Gating Analysis>

Gating of PBMCs was performed according to the technical note of Standard BioTools Inc., "Approach to Bivariate Analysis of Data Acquired Using the Maxpar Direct Immune Profiling Assay". The amount of change in the resulting component ratio of each immune cell population before and after the ingestion of the test product was compared with that of the placebo. As a result, the amount of change of MAIT/NKT cells before and after ingestion was significantly large (Fig. 1: a fermented milk group: the average component ratio of MAIT/NKT cells in PBMCs changed from 2.56% (before ingestion of test product) to 2.7% (after ingestion) (0.14% increase),

whereas a placebo group: the average component ratio of MAIT/NKT cells in PBMCs changed from 2.71% (before ingestion of test product) to 2.33% (after ingestion) (0.38% decrease)). Note that MAIT/NKT cells were detected as the cells having expression patterns of cell surface markers of $CD3^+$, $CD4^-$, $CD28^+$, and $CD161^+$ in PBMCs, according to the above technical notes.

[0083]

<Analysis 2: Machine Learning Analysis>

Using cytometric analysis software enabling various machine learning analyses, clustering of PBMCs, and comparison between specimen populations were performed. CITRUS (cluster identification, characterization, and regression: statistical comparison between groups using correlation or prediction algorithms) was performed on $CD4^+$ T cells in specimens of the fermented milk group and the placebo group after the test period (after ingestion). As a result, 3 clusters (#44347, #44352, #44360) having significantly different component ratios (FDR < 0.01 and $p < 0.05$) were confirmed. Among them, Cluster #44352 was a cluster where the component ratio after ingestion of the test product was higher (Fig. 2) and strongly expressed CCR6, and found to be completely different in lineage from other strongly expressed CCR6 clusters (Fig. 3). Furthermore, considering the expression patterns of the chemokine receptors CXCR3 and CCR4 ($CXCR3^+$, $CCR4^{low}$) and the differentiation markers CD45RA and IL-7Ra ($CD45RA^-$, $IL\text{-}7Ra^+$), and the fact that they are not Treg cells defined as $CD25^+CD127^-$, it was found that it is very similar to Th7R (e.g., Non Patent Document 1) recently discovered as a new lineage-specific $CCR6^+CD4^+$ T cell population. Thus, it was presumed that the composition of the invention may have a proliferation-promoting action on a cell population classified as Cluster #44352 (the cell-surface marker expression pattern is $CXCR3^+/CCR4^{low}/CCR6^{high}$).

[0084]

[Production Examples]

Production Example 1. EPS-comprising Yogurt

Lactobacillus delbrueckii subsp. bulgaricus OLL1073R-1 and Streptococcus thermophilus were added to a skimmed milk powder medium, as a lactic acid bacterium starter, and the skimmed milk powder medium was fermented under a temperature environment of 43°C for 2.5 hours to obtain a yogurt.

[0085]

Production Example 2. Preparation of EPS

Trichloroacetic acid was added to the culture obtained by culturing Lactobacillus delbrueckii subsp. bulgaricus OLL1073R-1 in a 10 mass% skimmed milk powder medium at 37°C for 18 hours so as to have a final concentration of 10 mass% to remove denatured proteins. Cold ethanol was added, and the mixture was allowed to stand at 4°C for 2 hours to obtain a precipitate comprising an EPS. This was dialyzed against MilliQ water using a dialysis membrane (molecular weight cutoff: 6 to 8 kDa). After nucleic acids and proteins were enzymatically decomposed, ethanol precipitation was performed again to obtain a precipitate. This was dissolved in MilliQ water and dialyzed again, and then purified by lyophilization to obtain an EPS.

[0086]

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CLAIMS

[Claim 1] A composition for promoting proliferation of either or both of (i) and (ii), comprising an extracellular polysaccharide of a lactic acid bacterium.

(i) $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$

(ii) MAIT cells and NKT cells.

[Claim 2] A composition for either or both of improving susceptibility to immune checkpoint inhibitor therapy and suppressing cancer recurrence after removal surgery, comprising an extracellular polysaccharide of a lactic acid bacterium.

[Claim 3] The composition according to claim 2, wherein improving susceptibility to immune checkpoint inhibitor therapy is that a subject changes from a poor responder to the immune checkpoint inhibitor therapy to a good responder, or that a subject who has become a poor responder to the immune checkpoint inhibitor therapy with time becomes a good responder again.

[Claim 4] A composition for treating a disease or condition that is ameliorated by promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$, comprising an extracellular polysaccharide of a lactic acid bacterium.

[Claim 5] The composition according to claim 4, wherein treating the disease or condition that is ameliorated by promotion of proliferation of $CD4^+$ T cells having a cell-surface marker expression pattern of $CXCR3^+/CCR4^{low}/CCR6^{high}$ is improving susceptibility to immune checkpoint inhibitor therapy, and the composition is for ingestion by a subject who is not receiving the immune checkpoint inhibitor therapy.

[Claim 6] A composition for treating a disease or condition that is ameliorated by promotion of proliferation of MAIT cells and NKT cells, comprising an extracellular

polysaccharide of a lactic acid bacterium.

[Claim 7] The composition according to claim 6, wherein treating a disease or condition that is ameliorated by promotion of proliferation of MAIT cells and NKT cells is either or both of suppressing cancer metastasis and preventing cancer, and the composition is for ingestion by a subject who is not receiving cancer treatment.

[Claim 8] The composition according to any one of claims 1 to 7, wherein the lactic acid bacterium is a bacterium belonging to the genus Lactobacillus.

[Claim 9] The composition according to any one of claims 1 to 7, wherein the lactic acid bacterium is a bacterium belonging to Lactobacillus delbrueckii.

[Claim 10] The composition according to any one of claims 1 to 7, wherein the lactic acid bacterium is Lactobacillus delbrueckii subsp. bulgaricus FERM BP-10741.

[Claim 11] The composition according to any one of claims 1 to 7, wherein the extracellular polysaccharide of a lactic acid bacterium is contained as a fermentation product of the lactic acid bacterium.

[Claim 12] The composition according to any one of claims 1 to 7, wherein the composition is a pharmaceutical composition.

[Claim 13] The composition according to any one of claims 1 to 7, wherein the composition is a food composition.