DESCRIPTION

Title of Invention: AGENT FOR TREATING AND/OR PREVENTING DISEASES ASSOCIATED WITH IMMUNE ABNORMALITIES BY COMBINING BIGUANIDE ANTIDIABETIC DRUG WITH IMMUNOSUPPRESSIVE FACTOR BLOCKING AGENT OR COSTIMULATORY RECEPTOR AGONIST

Technical Field

[0001]

The present invention relates to a method for enhancing functions of immune cells, immune cells with enhanced function, and an agent for treating and/or preventing diseases associated with immune abnormalities containing the immune cells with enhanced function as an active ingredient. The present invention further relates to a method for evaluating multifunctionality of immune cells.

Background Art

[0002]

T cells serve as immune cells and account for 70 to 80% of peripheral blood lymphocytes. T cells are distributed in the spleen or lymph nodes throughout the body and contribute to biological defense. T cells are classified into cytotoxic T cells ($CD8^+$T cells), which directly affect virally infected cells or cancer cells, and into helper T cells ($CD4^+$T cells), which assist the function of immunocompetent cells such as cytotoxic T cells. T cells have T cell receptors (TCR) expressed on their surfaces and recognize antigens by these TCR. A single T cell expresses TCR for recognizing one specific kind of antigen. This is called antigen specificity of T cells. T cells play an important role in various immune-related clinical conditions, including infections, tumors, organ transplants, and allergies.

[0003]

In recent years, the mechanism of immune exhaustion has been clarified, and there are reports that inhibition of the bonds of exhaustion molecules and ligands is important in cancer treatments. Some cancer patients have significantly inferior immune response (immune exhaustion). Immune exhaustion is caused

CLAIMS

1. An agent for treating and/or preventing diseases associated with immune abnormalities comprising, as an active ingredient, a biguanide antidiabetic drug selected from metformin, phenformin, and buformin, wherein the agent is to be administered in combination with at least one therapeutic agent selected from (i) an immunosuppressive factor blocking agent selected from anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody, PD-L1 fusion protein, PD-L2 fusion protein, anti-Tim-3 antibody, anti-LAG-3 antibody, anti-BTLA antibody, anti-VISTA antibody or any immunosuppressive factor blocking agent, preferably anti-PD-1 antibody and optionally to be administered in combination with (ii) a costimulatory receptor agonist selected from anti-CD137 antibody, anti-OX40 antibody, anti-HVEM antibody, anti-CD27 antibody, anti-GITR antibody, and anti-CD28 antibody or any costimulatory receptor agonist.

2. An agent for treating and/or preventing diseases associated with immune abnormalities, comprising, as an active ingredient, at least one therapeutic agent selected from (i) an immunosuppressive factor blocking agent selected from anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody, PD-L1 fusion protein, PD-L2 fusion protein, anti-Tim-3 antibody, anti-LAG-3 antibody, anti-BTLA antibody, anti-VISTA antibody or any immunosuppressive factor blocking agent, preferably anti-PD-1 antibody and optionally to be administered in combination with (ii) a costimulatory receptor agonist selected from anti-CD137 antibody, anti-OX40 antibody, anti-HVEM antibody, anti-CD27 antibody, anti-GITR antibody, and anti-CD28 antibody or any costimulatory receptor agonist, wherein the agent is to be administered in combination with a biguanide antidiabetic drug selected from metformin, phenformin, and buformin.

3. The agent for treating and/or preventing diseases associated with immune abnormalities according to claim 1 or 2, wherein the anti-CTLA-4 antibody is Ipilimumabor or Tremelimumab, the anti-PD-1 antibody is Nivolumab, Pembrolizumab, PDR-001, REGN-2810, BGB-A317, or AMP-514, and the anti-PD-L1 antibody is Atezolizumab, Avelumab, Durvalumab, or BMS-936559, and the PD-L2 fusion protein is AMP-224.

4. The agent for treating and/or preventing diseases associated with immune abnormalities according to any one of claims 1 to 3, wherein the diseases associated with immune abnormalities are selected from cancers, infections, and autoimmune diseases.

5. The agent for treating and/or preventing diseases associated with immune abnormalities according to claim 4, wherein the cancer is at least one cancer selected from head and neck cancers, esophagus cancer, gastric cancer, colorectal cancer, colon cancer, rectum cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, biliary tract cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, vaginal cancer, vulvar cancer, renal cancer, urothelial cancer, prostate cancer, testicular tumor, osteosarcoma, soft-tissue sarcoma, leukemia, myelodysplastic syndrome, malignant lymphoma, adult T-cell leukemia, multiple myeloma, skin cancer, brain tumor, pleural mesothelioma, and unknown primary cancer.

6. The agent for treating and/or preventing diseases associated with immune abnormalities according to claim 4 or 5, wherein the cancer treatment is suppression of cancer progression, and the cancer prevention is prevention of cancer recurrence.