

Antibody targeting CD47 and application thereof

Technical Field

The present disclosure belongs to the technical field of biological medicines. Specifically, it relates to an antibody targeting CD47 and an application thereof, and more specifically, relates to an anti-CD47 antibody or an antigen-binding fragment thereof, a nucleic acid, a vector, a cell, a composition, an application and a kit.

Background

Cancer immunotherapy is a major event in the field of biological sciences in recent years. Immune checkpoint inhibitor therapies of T-cell-based CTLA4 antibody, PD-1 antibody, PD-L1 antibody and the like and cell therapies of CAR-T, TCR-T and the like are all hot immunotherapies in recent years. These revolve around how to restore T cell functions without exception, and in other words, how to improve the acquired immune system capacity. However, a road of using an immune checkpoint as a target point, and activating the T cell function, to improve the capacity of an acquired immune system so as to conquer a cancer is still full of twists and turns. However, the action of an innate immune system in tumor immunotherapy is not exerted for a long time. In fact, in the entire tumor-infiltrating area, macrophages account for about 50% of tumor tissues. More importantly, the number of the macrophages is inversely related to the prognosis of tumors, which further indicates that the macrophages have very important effect in the tumors. The phagocytosis exerted by the macrophages requires two signals to act simultaneously: one is the activation of an "eat me" signal on the surface of a target cell, and the other is the inactivation of a "don't eat me" signal on the surface of the same target. The absence of any one signal is not sufficient to trigger the phagocytosis. It is indicated from more and more evidences that CD47 is a type of the "don't eat me" signal, and it inhibits the phagocytosis of the macrophages by mutually combining with a signal regulatory protein α (SIRP α) on the surface of the macrophages. Tumor cells may also escape the macrophage phagocytosis through the expression of CD47 (for example, referring to EP2242512 and related documents cited therein).

What is claimed is:

1. An anti-CD47 antibody or an antigen-binding fragment thereof, wherein the antibody comprises the following complementarity determining regions (CDRs):

LCDR1 as shown in SEQ ID NO:1 or an amino acid sequence having at least 95% of sequence identity with SEQ ID NO:1, LCDR2 as shown in SEQ ID NO:2 or an amino acid sequence having at least 95% of sequence identity with SEQ ID NO:2, and LCDR3 as shown in SEQ ID NO:3 or an amino acid sequence having at least 95% of sequence identity with SEQ ID NO:3; and

HCDR1 as shown in SEQ ID NO:10 or an amino acid sequence having at least 95% of sequence identity with SEQ ID NO:10, HCDR2 as shown in SEQ ID NO:11 or an amino acid sequence having at least 95% of sequence identity with SEQ ID NO:11, and HCDR3 as shown in SEQ ID NO:12 or an amino acid sequence having at least 95% of sequence identity with SEQ ID NO:12

optionally, the anti-CD47 antibody or the antigen-binding fragment thereof, comprising:

the HCDR1, HCDR2, and HCDR3 are identical to complementarity determining regions of SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17 or SEQ ID NO:18; and the LCDR1, LCDR2, and LCDR3 are identical to complementarity determining regions of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9;

optionally, the anti-CD47 antibody or the antigen-binding fragment thereof, comprising:

A) the HCDR1, HCDR2, and HCDR3 are identical to complementarity determining regions of SEQ ID NO:14 and the LCDR1, LCDR2, and LCDR3 are identical to complementarity determining regions of SEQ ID NO:8, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are defined by Kabat numbering;

B) the HCDR1, HCDR2, and HCDR3 are identical to complementarity determining regions of SEQ ID NO:14 and the LCDR1, LCDR2, and LCDR3 are identical to complementarity determining regions of SEQ ID NO:6, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are defined by Kabat numbering; or

C) the HCDR1, HCDR2, and HCDR3 are identical to complementarity determining regions of SEQ ID NO:17 and the LCDR1, LCDR2, and LCDR3 are identical to complementarity determining regions of SEQ ID NO:6, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are defined by Kabat numbering;

optionally, the anti-CD47 antibody or the antigen-binding fragment thereof, comprising:

- a) LCDR1 with an amino acid sequence: KSSQSLLNTRTRKNYLA, LCDR2 as shown in SEQ ID NO:2 , and LCDR3 as shown in SEQ ID NO:3, and HCDR1 as shown in SEQ ID NO:10, HCDR2 as shown in SEQ ID NO:11, and HCDR3 as shown in SEQ ID NO:12;
 - b) LCDR1 as shown in SEQ ID NO:1, LCDR2 as shown in SEQ ID NO:2 , and LCDR3 as shown in SEQ ID NO:3, and HCDR1 as shown in SEQ ID NO:10, HCDR2 as shown in SEQ ID NO:11, and HCDR3 as shown in SEQ ID NO:12; or
 - c) LCDR1 as shown in SEQ ID NO:1, LCDR2 as shown in SEQ ID NO:2 , and LCDR3 as shown in SEQ ID NO:3, and HCDR1 as shown in SEQ ID NO:10, HCDR2 with an amino acid sequence: MIHPDSETRLNQKFQG, and HCDR3 as shown in SEQ ID NO:12.
2. The anti-CD47 antibody or the antigen-binding fragment thereof according to claim 1, wherein the antibody comprises at least one of a heavy chain variable region sequence and a light chain variable region sequence, at least a part of at least one of the heavy chain variable region sequence and the light chain variable region sequence is from at least one of a mouse-derived antibody, a humanized antibody, a primate-derived antibody or a mutant thereof.
 3. The anti-CD47 antibody or the antigen-binding fragment thereof according to claim 2, wherein the amino acid sequence of the light chain variable region is as shown in any one of SEQ ID NOs:5~9 or a sequence having at least 95% sequence identity with any one of SEQ ID NOs:5~9.
 4. The anti-CD47 antibody or the antigen-binding fragment thereof according to claim 2, wherein the amino acid sequence of the heavy chain variable region is as shown in any one of SEQ ID NOs:14~18 or a sequence having at least 95% sequence identity with any one of SEQ ID NOs:14~18.
 5. The anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 2-4, wherein the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:5, the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:14; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:6, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:14; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:6, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:15; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:6, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:16; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:6, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:17; or the

amino acid sequence of the light chain variable region is as shown in SEQ ID NO:6, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:18; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:8, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:14; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:9, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:14; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:7, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:16; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:8, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:16; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:9, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:16; or the amino acid sequence of the light chain variable region is as shown in SEQ ID NO:9, and the amino acid sequence of the heavy chain variable region is as shown in SEQ ID NO:18;

optionally, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:8, and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:14.

6. The anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1-5, wherein the antibody has a constant region, and the heavy chain constant region is selected from any one of IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE or IgD; and the light chain constant region is a κ or λ chain.
7. The anti-CD47 antibody or the antigen-binding fragment thereof according to claim 6, wherein the species source of the constant region is selected from mouse, rabbit, sheep, monkey, or human

optionally, the light chain constant region is a human κ chain and the heavy chain constant region is a human IgG4 having S228P mutant;

optionally, the light chain constant region is a human κ chain, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:8; and the heavy chain constant region is a human IgG4 having S228P mutation, and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:14.

8. The anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims

- 1-7, wherein the antibody is any one or more of a CDR-transplanted antibody, a multimeric antibody or a bispecific antibody.
9. The anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1-8, wherein the antigen-binding fragment is any one or more of F (ab')₂, Fab, scFv, Fv, and a single-domain antibody.
 10. The anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1-9, wherein the CD47 is a human CD47, a mouse CD47 or a monkey CD47.
 11. A nucleic acid, wherein the nucleic acid encodes the anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1~10.
 12. A vector, wherein the vector comprises the nucleic acid according to claim 11.
 13. A cell, wherein the cell comprises the nucleic acid according to claim 11 or the vector according to claim 12.
 14. A pharmaceutical composition, wherein the pharmaceutical composition comprises the anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1~10, the nucleic acid according to claim 11, the vector according to claim 12 or the cell according to claim 13 ; optionally, wherein the composition further comprises a pharmaceutically acceptable carrier.
 15. Use of the anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1~10, the nucleic acid according to claim 11, the vector according to claim 12, the cell according to claim 13 or the composition according to claim 14 in preparation of a drug for treating and/or preventing a CD47-positive tumor; optionally, wherein the drug can reduce hemagglutination of red blood cells or wherein the drug can reduce its binding activity to the red blood cells.
 16. Use of the anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1~10, the nucleic acid according to claim 11, the vector according to claim 12, or the cell according to claim 13 in preparation of a kit for detecting CD47 or diagnosing a CD47-related disease.
 17. A kit for detecting CD47, wherein the kit comprises the anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1~10.

18. A kit for diagnosing a CD47-related disease, wherein the kit comprises the anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1~10.
19. The anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1~10, the nucleic acid according to claim 11, the vector according to claim 12, the cell according to claim 13 or the composition according to claim 14 for use as a medicament.
20. The anti-CD47 antibody or the antigen-binding fragment thereof according to any one of claims 1~10, the nucleic acid according to claim 11, the vector according to claim 12, the cell according to claim 13 or the composition according to claim 14 for use in a method for treating and/or preventing a CD47-positive tumor.