CLAIMS

1. A fusion protein for reversing the tumor microenvironment, wherein the fusion protein is a SIRPγ fusion protein, and the structure of the SIRPγ fusion protein comprises an extracellular domain, a transmembrane domain and an intracellular signaling domain.

2. The fusion protein according to claim 1, wherein the transmembrane domain is derived from human CD28 transmembrane domain or human CD8 transmembrane domain, preferably, the intracellular signaling domain is derived from CD28 or 4-1BB.

3. The fusion protein according to claim 2, wherein the amino acid sequence of the transmembrane domain is shown in SEQ ID NO:7 or SEQ ID NO:8; preferably, the intracellular signaling domain is derived from CD28, and the sequence of the intracellular signaling domain is shown in SEQ ID NO:9 or SEQ ID NO:38.

4. The fusion protein according to claim 1, wherein the structure of the SIRPγ fusion protein is SIRPγ-CD28TM-CD28 or SIRPγ-CD8TM-4-1BB.

5. The fusion protein according to claim 1, wherein the amino acid sequence of the extracellular domain of SIRPγ is shown in SEQ ID NO: 1 or is a functional variant thereof.

6. The fusion protein according to claim 4, wherein the amino acid sequence of the SIRPγ fusion protein SIRPγ-CD28TM-CD28 is shown in SEQ ID NO: 2 or is a functional variant thereof.

7. The fusion protein according to claim 4, wherein the amino acid sequence of the SIRPγ fusion protein SIRPγ-CD8TM-4-1BB is shown in SEQ ID NO: 3 or is a functional variant thereof.

8. The fusion protein according to claim 6, wherein the nucleotide sequence of the SIRPγ fusion protein SIRPγ-CD28TM-CD28 is shown in SEQ ID NO: 13.

9. The fusion protein according to claim 7, wherein the nucleotide sequence of the SIRPγ fusion protein SIRPγ-CD8TM-4-1BB is shown in SEQ ID NO: 14.

10. An expression vector comprising the fusion protein according to any one of claims 1-9.

11. The expression vector according to claim 10, wherein the expression vector is any one of a lentivirus expression vector, a retrovirus expression vector, an adenovirus expression vector, an adeno-associated virus expression vector, a DNA vector, an RNA vector, and a plasmid.

12. An immune cell comprising the expression vector according to any one of claims 10-11.

13. The immune cell according to claim 12, wherein the immune cell is a T cell, a T cell precursor or an NK cell.

14. The immune cell according to claim 13, wherein it comprises a structure with a chimeric antigen receptor that recognizes a tumor antigen, the chimeric antigen receptor comprises an extracellular domain recognizing a tumor antigen, a hinge region, a transmembrane domain and an intracellular signaling domain, the tumor antigen include but is not limited to PSCA, PSMA, CD19, BCMA, CD123, CD20, CD22, CEA, EGFR, EGFRVIII, GPC3, 5T4, CD33, Her2, GD2, CD70, CLL-1, Trop2, CD47, GPC3, CLND18.2, CD133, CS1, CD155, CD30, ROR1, MUC1, IL13RAα2 or mesothelin that can be used as an antigenic molecule for tumor targeting recognition.

15. A tumor immunosuppression-resistant CAR, wherein the CAR comprises the fusion protein according to any one of claims 1-9 and CAR1, and the CAR1 comprises an extracellular domain recognizing a tumor antigen, a hinge region, a transmembrane domain and an intracellular signaling domain.

16. The tumor immunosuppression-resistant CAR according to claim 15, wherein the fusion protein is linked to CAR1 through a polycistronic structure, and the polycistronic structure is a self-cleaving polypeptide or an internal ribosome entry site IRES, and the self-cleaving polypeptide is T2A, P2A, E2A or F2A.

17. The tumor immunosuppression-resistant CAR according to claim 15, wherein the CAR structure is an ScFv-hinge-TM-CD3ζ-self-cleaving peptide-SIRPγ fusion protein or an

ScFv-hinge-TM-4-1BB-CD3ζ-self-cleaving peptide-SIRPγ fusion protein.

18. The tumor immunosuppression-resistant CAR according to claim 15, wherein the CAR structure is an ScFv-hinge-TM-CD3ζ-self-cleaving peptide-SIRPγ-CD28TM-CD28 or an ScFv-hinge-TM-4-1BB-CD3ζ-self-cleaving peptide-SIRPγ-CD28TM-CD28.

19. The tumor immunosuppression-resistant CAR according to claim 15, wherein in the CAR1 structure: the amino acid sequence of the hinge is shown in SEQ ID NO: 24 or is a functional variant thereof, and the amino acid sequence of the TM is shown in SEQ ID NO: 7 or SEQ ID NO: 8, the amino acid sequence of CD3ζ is shown in SEQ ID NO: 11 or is a functional variant thereof; and in the structure of the fusion protein: the amino acid sequence of the extracellular domain of SIRPγ is shown in SEQ ID NO: 1 or is a functional variant thereof; the amino acid sequence of the transmembrane domain derived from human CD28 is shown in SEQ ID NO:7; the amino acid sequence of the intracellular signaling domain derived from human CD28 is shown in SEQ ID NO:9.

20. The tumor immunosuppression-resistant CAR according to any one of claims 17-19, wherein the ScFv recognizes any one or more of CD19, CD123, MOv-γ, PSMA, IL13Rα2, EGFRvIII, EGFR, EPCAM, GD2, MUC1, HER2, GPC3, CEA, Meso, CD133, NKG2D, CD138, LeY, k-Light, CD33, ROR1, BCMA, CD30, CD20, CD22, PSCA, CLL-1, CD70, and CD47.

21. The tumor immunosuppression-resistant CAR according to claim 20, wherein the amino acid sequence of the ScFv is shown in SEQ ID NO: 25 or is a functional variant thereof.

22. The tumor immunosuppression-resistant CAR according to claim 15 or 16, wherein the CAR1 comprises one of the following:

a) the CAR1 comprising a CEA single chain antibody, a CD8 hinge region, a CD8 transmembrane domain, a CD137-CD3ξ dual-stimulus signal; preferably, the amino acid sequence of the CAR structure is shown in SEQ ID NO: 26 or is a functional variant thereof ;

or b) the CAR1 comprising a CD19 single chain antibody, a CD8 hinge region, a CD8 transmembrane domain, a CD137-CD3ξ dual-stimulus signal; preferably, the amino acid sequence of the CAR structure is shown in SEQ ID NO: 27 or is a functional variant thereof;

or c) the CAR1 comprising a PSCA single-chain antibody, a hinge region, a CD28

transmembrane domain, a CD28-CD137-CD3ξ tristimulus signal; the hinge region is G4H or 7H; preferably, the amino acid sequence of the CAR structure is shown in SEQ ID NO: 28 or is a functional variant thereof; or is shown in SEQ ID NO: 29 or is a functional variant thereof.

23. The tumor immunosuppression-resistant CAR according to claim 22, wherein the CAR1 structures in a) and b) further comprise a hypoxia inducible promoter, and the nucleic acid sequence of the hypoxia inducible promoter comprises the sequence shown in SEQ ID NO:30.

24. A nucleic acid sequence, wherein it encodes the tumor immunosuppression-resistant CAR according to claim 21 or 22, the nucleic acid sequence comprises the sequence shown in SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34 or SEQ ID NO: 35.

25. An expression vector comprising the tumor immunosuppression-resistant CAR according to any one of claims 15-23, wherein the expression vector is any one of a lentivirus expression vector, a retrovirus expression vector, an adenovirus expression vector, an adeno-associated virus expression vector, DNA vector, RNA vector and plasmid.

26. An immune cell comprising the expression vector according to claim 25.

27. The immune cell according to claim 26, wherein the immune cell is a T cell, a T cell precursor or an NK cell.

28. A method for preparing the immune cell according to claim 14, wherein the CAR structure not comprising the SIRPγ fusion protein and the SIRPγ fusion protein are co-expressed in a vector when transfecting immune cells; or the CAR structure not comprising the SIRPγ fusion protein and the SIRPγ fusion protein are expressed separately in two vectors when transfecting immune cells.

29. A pharmaceutical composition, wherein the pharmaceutical composition comprises the fusion protein according to any one of claims 1-9 or the tumor immunosuppression-resistant CAR according to any one of claims 15-23 or the immune cell according to any one of claims 12-14 or the immune cell according to any one of claims 26-27 or the expression vector according to any one of claims 10-11 or the expression vector according to claim 25 or the nucleic acid sequence according

to claim 24.

30. The pharmaceutical composition according to claim 19, wherein the pharmaceutical composition further comprises an active agent that can enhance the expression activity of the CAR and/or a therapeutic agent.

31. The use of the pharmaceutical composition of claim 29 or 30 in the preparation of medicaments of tumors.

32. The use according to claim 31, wherein the tumors are malignant tumors, including acute lymphoid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, prostate cancer, colorectal cancer, breast cancer, ovarian cancer, cervical cancer, pancreatic cancer, lung cancer, kidney cancer, liver cancer, brain cancer and skin cancer, the tumors highly express any one or more of CD19, CD123, MOv-γ, PSMA, IL13Rα2, EGFRvIII, EGFR, EPCAM, GD2, MUC1, HER2, GPC3, CEA, Meso, CD133, NKG2D, CD138, LeY, k-Light, CD33, ROR1, BCMA, CD30, CD20, CD22, PSCA, CLL-1, CD70, and CD47.