

mAbs) or soluble receptors (e.g., Fc-CTLA4). Soluble receptors suffer from a number of deficiencies. While useful for antagonizing interactions between proteins, soluble receptors often lack the ability to agonize such interactions. Antibodies have proven less limited in this regard and examples of both agonistic and antagonistic antibodies are known in the art. Nevertheless, both soluble receptors and antibodies lack important attributes that are critical to function in the IS. Mechanistically, cell surface proteins in the IS can involve the coordinated and often simultaneous interaction of multiple protein targets with a single protein to which they bind. IS interactions occur in close association with the junction of two cells, and a single protein in this structure can interact with both a protein on the same cell (cis) as well as a protein on the associated cell (trans), likely at the same time. Thus, there is a need for improved molecules for modulation of immune responses. Provided are embodiments that meet such needs.

Summary

[0004a] In one aspect, the present disclosure refers to an engineered immune cell that is a T cell comprising a transmembrane immunomodulatory protein (TIP), the transmembrane immunomodulatory protein comprising:

(i) an ectodomain comprising at least one CD80 affinity-modified immunoglobulin superfamily (IgSF) domain comprising one or more amino acid substitution(s) in a wild-type IgSF domain from CD80, wherein the at least one CD80 affinity-modified IgSF domain specifically binds to at least one cell surface cognate binding partner of the wild-type IgSF domain from CD80; and

(ii) a transmembrane domain.

[0004b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the engineered cell as disclosed herein and a pharmaceutically acceptable carrier.

[0004c] In yet another aspect, the present disclosure refers to use of the engineered immune cell as disclosed herein for the preparation of a medicament for modulating an immune response in a mammalian subject.

[0004d] In yet another aspect, the present disclosure refers to the pharmaceutical composition as disclosed herein for use in modulating an immune response in a mammalian subject.

[0004e] In yet another example, the present disclosure provides a transmembrane immunomodulatory protein (TIP) comprising:

(i) an ectodomain comprising at least one non-immunoglobulin affinity-modified immunoglobulin superfamily (IgSF) domain comprising one or more amino acid substitution(s) in a wild-type IgSF domain from a wild-type IgSF family member, wherein the at least one affinity-modified IgSF domain specifically binds to at least one cell surface cognate binding partner of the wild-type IgSF domain; and

(ii) a transmembrane domain.

[0004f] In yet another example, the present disclosure provides a pharmaceutical composition comprising the transmembrane immunomodulatory protein disclosed herein.

[0004g] In yet another example, the present disclosure provides a recombinant nucleic acid encoding the transmembrane immunomodulatory protein disclosed herein.

[0004h] In yet another example, the present disclosure provides a recombinant expression vector comprising the nucleic acid disclosed herein.

[0004i] In yet another example, the present disclosure provides a recombinant host cell comprising the nucleic acid disclosed herein or the expression vector disclosed herein.

[0004j] In yet another example, the present disclosure provides use of a transmembrane immunomodulatory protein disclosed herein for the preparation of a medicament for modulating an immune response in a mammalian subject.

[0005] [0004k] In yet another example, the present disclosure provides a pharmaceutical composition comprising the immunomodulatory protein disclosed herein for use in modulating an immune response in a mammalian subject. Provided herein are transmembrane immunomodulatory proteins (TIP) containing (1) an ectodomain comprising at least one non-immunoglobulin affinity-modified immunoglobulin superfamily (IgSF) domain containing one or more amino acid substitution(s) in a wild-type IgSF domain, wherein the at least one affinity-modified IgSF domain specifically binds at least one cell surface cognate binding partner of the wild-type IgSF domain and (2) a transmembrane domain.

[0006] In some of any such examples, the at least one cell surface cognate binding partner is expressed on a mammalian cell. In some of any such examples, the mammalian cell is an antigen presenting cell (APC), a tumor cell, or a lymphocyte. In some examples, the lymphocyte is a T-cell. In some of any such examples, the mammalian cell is a mouse, rat, cynomolgus monkey, or human cell.

CLAIMS

WHAT IS CLAIMED:

1. An engineered immune cell that is a T cell comprising a transmembrane immunomodulatory protein (TIP), the transmembrane immunomodulatory protein comprising:
 - (i) an ectodomain comprising at least one CD80 affinity-modified immunoglobulin superfamily (IgSF) domain comprising one or more amino acid substitution(s) in a wild-type IgSF domain from CD80, wherein the at least one CD80 affinity-modified IgSF domain specifically binds to at least one cell surface cognate binding partner of the wild-type IgSF domain from CD80; and
 - (ii) a transmembrane domain.
2. The engineered immune cell of claim 1, wherein the at least one CD80 affinity modified IgSF domain has increased binding affinity to the at least one cell surface cognate binding partner compared to the binding affinity of the wild-type IgSF domain from CD80 to the at least one cell surface cognate binding partner.
3. The engineered immune cell of claim 1 or claim 2, wherein the at least one cell surface cognate binding partner comprises a CD28 stimulatory receptor expressed on a T cell and the at least one CD80 affinity-modified IgSF domain has increased binding affinity to the stimulatory receptor compared to the affinity of the wild-type CD80 IgSF domain to the CD28 stimulatory receptor.
4. The engineered immune cell of any one of claims 1-3, wherein the at least one cell surface cognate binding partner comprises a PD-L1 inhibitory ligand and the at least one CD80 affinity-modified IgSF domain has increased binding affinity to the PD-L1 inhibitory ligand compared to the affinity of the wild-type CD80 IgSF domain to the PD-L1 inhibitory ligand.
5. The engineered immune cell of claim 4, wherein the at least one CD80 affinity-modified IgSF domain binds non-competitively to both the PD-L1 inhibitory ligand and the CD28 costimulatory receptor.

6. The engineered immune cell of claim 4 or claim 5, wherein binding of the at least one CD80 affinity-modified IgSF domain to PD-L1 inhibits specific binding to the PD-1 inhibitory receptor expressed on a T cell.

7. The engineered immune cell of any one of claims 1-6, wherein the transmembrane immunomodulatory protein has at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 393.

8. The engineered immune cell of any one of claims 1-7, wherein the wild-type IgSF domain of CD80 is a human CD80 or has at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1.

9. The engineered immune cell of any of claims 1-8, wherein the at least one affinity-modified IgSF domain is a first affinity-modified IgSF domain and the ectodomain comprises a second affinity-modified IgSF domain, wherein the first and second affinity-modified IgSF domains are different.

10. The engineered immune cell of any of claims 1-9, wherein the transmembrane immunomodulatory protein further comprises an endodomain.

11. The engineered immune cell of claim 10, wherein:
the endodomain is the endodomain from the wild-type CD80 IgSF member or is a functionally active portion thereof; or
the transmembrane immunomodulatory protein is a chimeric receptor, wherein the endodomain is not the endodomain from the wild-type CD80 IgSF member.

12. The engineered immune cell of claim 10 or claim 11, wherein the endodomain comprises at least one ITAM (immunoreceptor tyrosine-based activation motif)-containing signaling domain, optionally wherein the endodomain comprises a CD3-zeta signaling domain.

13. The engineered immune cell of claim 12, wherein the endodomain further comprises at least one of: a CD28 costimulatory domain, an ICOS signaling domain, an OX40 signaling domain, and a 41BB signaling domain.

14. The engineered immune cell of any of claims 1-13, wherein:
the transmembrane domain is the wild-type CD80 transmembrane domain from the corresponding wild-type CD80 IgSF member; or the transmembrane domain is not the wild-type CD80 transmembrane domain from the corresponding wild-type CD80 IgSF member, optionally wherein the transmembrane domain is a transmembrane domain derived from CD8.

15. The engineered immune cell of any of claims 1-14, wherein the affinity-modified CD80 IgSF domain comprises no more than ten amino acid substitutions from the wild-type CD80 IgSF domain.

16. The engineered immune cell of any of claims 1-15, wherein the affinity-modified CD80 IgSF domain is or comprises an affinity-modified IgV domain or is a specific binding fragment thereof or affinity modified IgC domain or is a specific-binding fragment thereof, wherein the specific binding fragment thereof comprises the one or more amino acid substitution(s).

17. The engineered immune cell of any of claims 1-16, wherein the T cell is CD4+ or CD8+.

18. The engineered immune cell of any of claims 1-17, wherein the cell further comprises a chimeric antigen receptor (CAR) or an engineered T-cell receptor (TCR).

19. A pharmaceutical composition comprising the engineered cell of any of claims 1-18 and a pharmaceutically acceptable carrier.

20. Use of the engineered immune cell of any of claims 1-18 for the preparation of a medicament for modulating an immune response in a mammalian subject.

21. The pharmaceutical composition of claim 19 for use in modulating an immune response in a mammalian subject.

22. The use of claim 20 or the pharmaceutical composition of claim 21, wherein modulating the immune response treats a disease or disorder in the subject.

23. The use or pharmaceutical composition of any one of claims 20-22, wherein the modulated immune response is increased.

24. The use or pharmaceutical composition of claim 23, wherein the disease or disorder is a tumor or a cancer.

25. The use or pharmaceutical composition of any of claims 20-24, wherein the engineered immune cell is autologous to the subject.