many cases the fusion proteins of the invention are more potent than soluble TRAIL and its variants consisting of fragments of its sequence, as well as more potent than respective effector peptides. In many cases, novel fusion proteins also overcome resistance to TRAIL. Moreover, the incorporation of the effector peptide results in prolonged half-life and increased retention of protein in the tumor and its enhanced efficiency. Additionally, in certain variants novel fusion proteins may be able to link PEG, which has protective effect against non-specific proteases and additionally alters pharmacokinetic and pharmacodynamic properties, particularly with respect to prolongation of the biological half-life.

Summary

In one aspect, the present disclosure refers to a fusion protein comprising:

domain (a) which is a functional fragment of hTRAIL protein sequence of SEQ ID NO:16, which begins with an amino acid from the range hTRAIL95 to hTRAIL122, inclusive, and ends with the amino acid hTRAIL281, or a homolog of said functional fragment having at least 70% sequence identity;

wherein said functional fragment or homolog thereof has the ability of binding to cell surface death receptors and inducing apoptosis in mammalian cells; and

domain (b) which is a sequence of an immunostimulating effector peptide selected from the group consisting of the pseudodimer of interferon gamma of SEQ. No. 19 and the pseudodimer of interferon alpha 2b of SEQ. No. 46,

wherein the sequence of domain (b) is attached at the C-terminus or N-terminus of domain (a).

In another aspect, the present disclosure refers to a polynucleotide sequence, coding the fusion protein as disclosed herein.

In another aspect, the present disclosure refers to a pharmaceutical composition, comprising as an active ingredient the fusion protein as disclosed herein in combination with a pharmaceutically acceptable carrier.

In another aspect, the present disclosure refers to use of the fusion protein as disclosed herein in the manufacture of a medicament for the treatment of cancer diseases in mammals, including humans.

Claims

1. A fusion protein comprising:

domain (a) which is a functional fragment of hTRAIL protein sequence of SEQ ID NO:16, which begins with an amino acid from the range hTRAIL95 to hTRAIL122, inclusive, and ends with the amino acid hTRAIL281, or a homolog of said functional fragment having at least 70% sequence identity;

wherein said functional fragment or homolog thereof has the ability of binding to cell surface death receptors and inducing apoptosis in mammalian cells; and

domain (b) which is a sequence of an immunostimulating effector peptide selected from the group consisting of the pseudodimer of interferon gamma of SEQ. No. 19 and the pseudodimer of interferon alpha 2b of SEQ. No. 46,

wherein the sequence of domain (b) is attached at the C-terminus or N-terminus of domain (a).

2. The fusion protein according to claim 1 wherein domain (a) is selected from the group consisting of fragments of hTRAIL114-281, beginning with an amino acid in position 95, 116, 120, 121 or 122.

3. The fusion protein according to any one of claims 1 to 2, which between domain (a) and domain (b) contains at least one domain (c) comprising a protease cleavage site selected from the group consisting of a sequence recognized by metalloprotease MMP, sequence recognized by urokinase uPA, and combinations thereof.

4. The fusion protein according to claim 3, wherein the sequence recognized by metalloprotease MMP is SEQ. No. 20, and the sequence recognized by urokinase uPA is SEQ. No. 21.

5. The fusion protein according to claims 3 or 4, wherein domain (c) is a combination of the sequence recognized by metalloprotease MMP and the sequence recognized by urokinase uPA located next to each other.

6. The fusion protein according to any one of claims 3 to 5, which between two domains (c) contains a domain (d) of a linker for attachment of PEG molecule, selected from the group consisting of SEQ. No. 22, SEQ. No. 23, SEQ. No. 24 and SEQ. No. 25.

7. The fusion protein according to any one of claims 3 to 6 which additionally comprises a glycine-serine flexible steric linker between domains (a), (b), (c) and/or (d).

8. The fusion protein according to claim 7, wherein the glycine-serine linker is selected from the group consisting of SEQ. No. 26, SEQ. No. 27, SEQ. No. 28, and SEQ. No. 50.

9. The fusion protein according to claim 1 the amino acid sequence of which is selected from the group consisting of SEQ. No. 12; SEQ. No. 13; SEQ. No. 14; SEQ. No. 15; and SEQ. No. 44.

10. A polynucleotide sequence, coding the fusion protein defined as in any one of claims 1 to 9.

11. The polynucleotide sequence according to claim 10, selected from the group consisting of SEQ. No. 40; SEQ. No. 41; SEQ. No. 42; SEQ. No. 43; and SEQ. No. 48.

12. A pharmaceutical composition, comprising as an active ingredient the fusion protein as defined in any one of claims 1 to 9 in combination with a pharmaceutically acceptable carrier.

13. Use of the fusion protein as defined in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of cancer diseases in mammals, including humans.