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[Summary]

[Technical Problem]

[0008]

The present invention has been made in light of these circumstances. An object of the present invention is to provide a ligand binding molecule that activates a ligand such as a cytokine or a chemokine selectively in a target tissue, a pharmaceutical composition comprising the ligand binding molecule, and methods for producing the pharmaceutical composition and the active ingredient.

[Solution to Problem]

[0009]

The present inventors have conducted diligent studies to attain the object and consequently developed a ligand binding molecule whose ligand binding activity is attenuated by the cleavage of a cleavage site. The present inventors have also found that the ligand binding molecule or a pharmaceutical composition comprising the ligand binding molecule is useful in the treatment of a disease using the ligand and also found that: the ligand binding molecule or the

pharmaceutical composition is useful in the treatment of a disease which involves administering the ligand binding molecule; and the ligand binding molecule is useful in the production of a drug for the treatment of a disease. The present inventors have also developed a method for producing the ligand binding molecule, completing the present disclosure.

[0009a]

In one aspect, the present invention refers to a ligand binding molecule which is a molecule capable of binding to a ligand, wherein the molecule is a polypeptide having at least one cleavage site, and the ligand binding of the molecule cleaved at the at least one cleavage site is attenuated. In another aspect, the present invention refers to a fusion protein of a ligand binding molecule as described herein fused with a ligand. In another aspect, the present invention refers to the polynucleotide encoding a ligand binding molecule according to any of claims 1 to 11 or a fusion protein as described herein. In yet another aspect, the present invention refers to a host cell comprising a polynucleotide of the present invention, or a vector comprising the polynucleotide of the present invention. In yet another aspect, the present invention refers to a pharmaceutical composition comprising a ligand binding molecule of the present invention. In yet another aspect, the present invention refers to a pharmaceutical composition comprising a ligand binding molecule of the present invention and a ligand. In yet another aspect, the present invention refers to a pharmaceutical composition comprising a fusion protein of the present invention. In yet another aspect, the present invention refers to a method for producing a ligand binding molecule of the present invention, or a fusion protein of the present invention.

[0010]

The present disclosure is based on these findings and specifically encompasses exemplary examples described below.

- (1) A ligand binding molecule which is a molecule capable of binding to a ligand, wherein the molecule is a polypeptide having at least one cleavage site, and the ligand binding of the molecule cleaved at the at least one cleavage site is attenuated.
- (2) The ligand binding molecule according to (1), wherein the ligand is released from the ligand binding molecule cleaved at the cleavage site.
- (3) The ligand binding molecule according to (1) or (2), wherein the cleavage site comprises a protease cleavage sequence.
- (4) The ligand binding molecule according to (3), wherein the protease is a target tissue specific protease.
- (5) The ligand binding molecule according to (4), wherein the target tissue is a cancer tissue, and the target tissue specific protease is a cancer tissue specific protease.

- (6) The ligand binding molecule according to (4), wherein the target tissue is an inflammatory tissue, and the target tissue specific protease is an inflammatory tissue specific protease.
- (7) The ligand binding molecule according to any of (3) to (6), wherein the protease is at least one protease selected from matriptase, urokinase (uPA), and metalloproteinase.
- (8) The ligand binding molecule according to (3), wherein the protease cleavage sequence is a sequence comprising a sequence selected from the sequences represented by SEQ ID NOs: 3, 34, 66, 70, 71, 72, 73, 35, 75, 76, and 345.
- (9) The ligand binding molecule according to any of (3) to (8), wherein a first flexible linker is further attached to one end of the protease cleavage sequence.
- (10) The ligand binding molecule according to (9), wherein a second flexible linker is further attached to the other end of the protease cleavage sequence.
- (11) The ligand binding molecule according to (9), wherein the first flexible linker is a flexible linker consisting of a glycine-serine polymer.
- (12) The ligand binding molecule according to (10), wherein the second flexible linker is a flexible linker consisting of a glycine-serine polymer.
- (13) The ligand binding molecule according to any of (1) to (12), wherein the ligand binding molecule comprises antibody VH, antibody VL, and an antibody constant region.

10. The ligand binding molecule according to any of claims 1 to 9, wherein the ligand binding molecule is bound with the ligand.
11. The ligand binding molecule according to any of claims 1 to 9, wherein the ligand binding molecule is fused with the ligand.
12. A fusion protein of a ligand binding molecule according to any of claims 1 to 9 fused with a ligand.
13. The fusion protein according to claim 12, wherein the ligand binding molecule fused with the ligand does not further bind to another ligand.
14. The fusion protein according to claim 12 or 13, wherein the ligand binding molecule is fused with the ligand via a linker.
15. A polynucleotide encoding a ligand binding molecule according to any of claims 1 to 11 or a fusion protein according to any of claims 12 to 14.
16. A host cell comprising a polynucleotide according to claim 15, or a vector comprising the polynucleotide aforementioned.
17. A pharmaceutical composition comprising a ligand binding molecule according to any of claims 1 to 11.
18. A pharmaceutical composition comprising a ligand binding molecule according to any of claims 1 to 10 and a ligand.
19. A pharmaceutical composition comprising a fusion protein according to any of claims 12 to 14.
20. A method for producing a ligand binding molecule according to any of claims 1 to 11, or a fusion protein according to any of claims 12 to 14.