Patent Document 1: WO2005/087268

Patent Document 2: Japanese Translated PCT Patent Application Laid-open No. 2010-537655

Patent Document 3: Japanese Translated PCT Patent Application Laid-open No. 2009-510002

Patent Document 4:WO2011/071059

Patent Document 5: Japanese Translated PCT Patent Application Laid-open No. 2011-512806

Patent Document 6: Japanese Translated PCT Patent Application Laid-open No. 2004-525875

NON-PATENT DOCUMENTS

[0007]

Non-Patent Document 1: Neuron 5, 735-743 (1990)

Non-Patent Document 2: J. Cell Biol. 173, 47-58 (2006)

Non-Patent Document 3: Cell Reports 10, 1-12 (2015)

SUMMARY

[0007a]

In a first aspect of the present disclosure, there is provided an isolated anti-RGMa antibody, or an antigen-binding fragment thereof, wherein the amino acid sequence of each of the light chain complementarity determining region 1 (LCDR1), the light chain complementarity determining region 2 (LCDR2), the light chain complementarity determining region 3 (LCDR3), the heavy chain complementarity

determining region 1 (HCDR1), the heavy chain complementarity determining region 2 (HCDR2) and the heavy chain complementarity determining region 3 (HCDR3) comprises the following:

LCDR1: RASQDISSYLN (SEQ ID NO: 30 in Sequence Listing),

LCDR2: YTSRLHS (SEQ ID NO: 31 in Sequence Listing),

LCDR3: QQLNTLP (SEQ ID NO: 32 in Sequence Listing),

HCDR1: DAWMD (SEQ ID NO: 33 in Sequence Listing),

HCDR2: EIRSKANNHATYYAESVKG (SEQ ID NO: 34 in Sequence Listing) and

HCDR3: RDGAY (SEQ ID NO: 35 in Sequence Listing);

or

LCDR1: RSSQSLVHSNGNTYLH (SEQ ID NO: 36 in Sequence Listing)

LCDR2: KVSNRFS (SEQ ID NO: 37 in Sequence Listing)

LCDR3:SQSTHVP (SEQ ID NO: 38 in Sequence Listing)

HCDR1: TSYYWN (SEQ ID NO: 39 in Sequence Listing)

HCDR2: YISYDGTNNYNPSLKN (SEQ ID NO: 40 in Sequence Listing) and

HCDR3: SFG, and

wherein in each of the CDR sequences one amino acid may be substituted and wherein the antibody inhibits RGMa activity.

[0007b]

In a second aspect of the present disclosure, there is provided a nucleic acid molecule coding for the protein portion of the anti-RGMa antibody or an antigen-binding

fragment thereof according to the first aspect.

[0007c]

In a third aspect of the present disclosure, there is provided a recombinant vector comprising the nucleic acid molecule according to the second aspect.

[0007d]

In a fourth aspect of the present disclosure, there is provided a host cell containing the recombinant vector according to the thrid aspect.

[0007e]

In a fifth aspect of the present disclosure, there is provided a method for producing the anti-RGMa antibody or an antigen-binding fragment thereof according to the first aspect, the method comprising a step of culturing the host cell according to the fourth aspect.

[0007f]

In a sixth aspect of the present disclosure, there is provided a pharmaceutical composition comprising the anti-RGMa antibody or an antigen-binding fragment thereof according to the first aspect.

[0007g]

In a seventh aspect of the present disclosure, there is provided the pharmaceutical composition according to the sixth aspect for use in preventing, treating, or preventing the relapse of neurological or immunological diseases.

TECHNICAL PROBLEM

[0008]

CLAIMS

1. An isolated anti-RGMa antibody, or an antigen-binding fragment thereof, wherein the amino acid sequence of each of the light chain complementarity determining region 1 (LCDR1), the light chain complementarity determining region 2 (LCDR2), the light chain complementarity determining region 3 (LCDR3), the heavy chain complementarity determining region 1 (HCDR1), the heavy chain complementarity determining region 2 (HCDR2) and the heavy chain complementarity determining region 3 (HCDR3) comprises the following:

LCDR1: RASQDISSYLN (SEQ ID NO: 30 in Sequence Listing),

LCDR2: YTSRLHS (SEQ ID NO: 31 in Sequence Listing),

LCDR3: QQLNTLP (SEQ ID NO: 32 in Sequence Listing),

HCDR1: DAWMD (SEQ ID NO: 33 in Sequence Listing),

HCDR2: EIRSKANNHATYYAESVKG (SEQ ID NO: 34 in Sequence Listing) and

HCDR3: RDGAY (SEQ ID NO: 35 in Sequence Listing);

or

LCDR1: RSSQSLVHSNGNTYLH (SEQ ID NO: 36 in Sequence Listing)

LCDR2: KVSNRFS (SEQ ID NO: 37 in Sequence Listing)

LCDR3:SQSTHVP (SEQ ID NO: 38 in Sequence Listing)

HCDR1: TSYYWN (SEQ ID NO: 39 in Sequence Listing)

HCDR2: YISYDGTNNYNPSLKN (SEQ ID NO: 40 in Sequence Listing) and

HCDR3: SFG, and

wherein in each of the CDR sequences one amino acid may be substituted and wherein the antibody inhibits RGMa activity.

2. The anti-RGMa antibody or an antigen-binding fragment thereof according to claim 1, wherein the amino acid substitution is conservative substitution.

3. The anti-RGMa antibody or an antigen-binding fragment thereof according to claim 1 or 2,

wherein the heavy chain variable region (VH) comprises the following:

VH:

EVQLVESGGGLVQPGRSLRLSCTASGFTFSDAWMDWVRQAPGKGLEWVAE IRSKANNHATYYAESVKGRFTISRDDSKSIVYLQMNSLRTEDTALYYCTRRD GAYWGKGTTVTVSS (SEQ ID NO: 41 in Sequence Listing) or an amino acid sequence having one or two amino acids may be substituted in said amino acid sequence by conservative substitution; and

wherein the light chainvariable region (VL) comprises the following:

VL:

DIQMTQSPSSVSASVGDRVTITCRASQDISSYLNWYQQKPGKAPKLLIYYTSR LHSGVPSRFSGSGSGTDFTLTISSLQPEDFASYFCQQLNTLPWTFGGGTKVEM E (SEQ ID NO: 42 in Sequence Listing) or an amino acid sequence having one or two amino acids may be substituted in said amino acid sequence by conservative substitution.

4. The anti-RGMa antibody or an antigen-binding fragment thereof according to any one of claims 1 to 3, wherein the anti-RGMa antibody is a humanized antibody.

5. The anti-RGMa antibody or an antigen-binding fragment thereof according to any one of claims 1 to 4, wherein the anti-RGMa antibody comprises constant regions of human IgG.

6. A nucleic acid molecule coding for the protein portion of the anti-RGMa antibody or an antigen-binding fragment thereof according to any one of claims 1 to 5.

7. The nucleic acid molecule according to claim 6, wherein the nucleotide sequences coding for the VH and VL amino acid sequences each is a nucleotide sequence comprising:

VH:

gaagtgcagctggtggaatctggcggcggactggtgcagcctggcagatccctgagactgtcctgtaccgcctccggct
tcaccttctccgacgcctggatggattgggtgcgacaggctcctggcaagggcctggaatgggtggccgagatccggtc
caaggccaacaaccacgccacctactacgccgagtctgtgaagggccggttcaccatctcccgggacgactccaagtcc
atcgtgtacctgcagatgaactccctgcggaccgaggacaccgccctgtactactgcaccagaagggacggcgcctact
ggggcaagggcaccacagtgacagtgtcctcc (SEQ ID NO: 43 in Sequence Listing), and

VL:

gacatccagatgacccagtccccctcctccgtgtctgcttccgtgggcgacagagtgaccatcacctgtcgggcctccca
ggacatctcctcctacctgaactggtatcagcagaagcccggcaaggcccccaagctgctgatctactacacctcccggc
tgcactccggcgtgccctctagattttccggctctggctccggcaccgactttaccctgaccatctccagcctgcagcccg
aggacttcgcctcctacttctgtcagcagctgaacaccctgccctggacctttggcggaggcaccaaggtggaaatggaa
(SEQ ID NO: 44 in Sequence Listing).

8. A recombinant vector comprising the nucleic acid molecule according to claim 6 or 7.

9. A host cell containing the recombinant vector according to claim 8.

10. A method for producing the anti-RGMa antibody or an antigen-binding fragment thereof according to any one of claims 1 to 5, the method comprising a step of culturing the host cell according to claim 9.

11. A pharmaceutical composition comprising the anti-RGMa antibody or an antigen-binding fragment thereof according to any one of claims 1 to 5.

12. The pharmaceutical composition according to claim 11 for use in preventing, treating, or preventing the relapse of neurological or immunological diseases.

13. The pharmaceutical composition according to claim 12, wherein the neurological diseases are selected from the group consisting of amyotrophic lateral sclerosis, brachial plexus injury, brain damage (including traumatic brain injury), cerebral palsy, Guillain-Barre syndrome, cerebral leukodystrophy, multiple sclerosis (including relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, secondary progressive multiple sclerosis), neuromyelitis optica, post-polio syndrome, spina bifida, spinal cord injury, spinal muscular atrophy, spinal neoplasm, transverse myelitis, dementia (including senile dementia, mild cognitive impairment, Alzheimer's disease, dementia associated with Alzheimer's disease), Huntington's disease, tardive dyskinesia, mania, Parkinson's disease, Steele-Richardson syndrome, Down's syndrome, myasthenia gravis, neurotrauma (including optic nerve trauma), vascular amyloidosis, cerebral hemorrhage associated with amyloidosis, brain infarction, cerebritis, acute confusional state, glaucoma, schizophrenia and retinal nerve fiber layer degeneration (including diabetic retinopathy, ischemic optic neuropathy, X-linked retinoschisis, drug-induced optic neuropathy, retinal dystrophy, age-related macular degeneration, eye diseases characterized by optic disc drusen, eye diseases characterized by genetic determinant for photoreceptor degeneration, autosomal recessive cone-rod dystrophy, mitochondrial disorder associated with optic neuropathy).

14. The pharmaceutical composition according to claim 12, wherein the immunological diseases are selected from the group consisting of multiple sclerosis (including relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, secondary progressive multiple sclerosis), neuromyelitis optica, psoriasis,

arthritis (including rheumatoid arthritis, osteoarthritis, psoriatic arthritis), Guillain-Barre syndrome, neuro-Behcet disease, pernicious anemia, type I (insulin-dependent)diabetes mellitus, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), Sjogren's syndrome, Goodpasture's syndrome, Graves' disease, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, asthma, pollinosis, atopic dermatitis, glomerulonephritis, myasthenia gravis, Hashimoto's disease, and sarcoidosis.

15. The pharmaceutical composition according to claim 12, wherein the neurological or immunological diseases are selected from the group consisting of spinal cord injury, neurotrauma (including optic nerve trauma), multiple sclerosis (including relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, secondary progressive multiple sclerosis).

RGMa BINDING PROTEIN AND USE THEREOF

ABSTRACT

The present invention addresses the problem of obtaining an anti-repulsive guidance molecule a (RGMa) antibody which has a high binding activity and few side effects and can be used as a medicine for preventing, treating, or preventing the relapse of neurological or immunological diseases. Said problem is solved by providing an isolated RGMa binding protein which does not inhibit binding between RGMa and neogenin, but neutralizes the neuritis growth inhibiting activity of RGMa, and preferably by providing an anti-RGMa antibody which has a complementarity determining region having an amino acid sequence of SEQ ID NOS: 30-35 or SEQ ID NOS: 36-40 in the sequence listing, and SFG.

[FIG. 5]