comparison with a parent polypeptide. As a result, the present inventors discovered that a polypeptide comprising an antibody Fc region that comprises an alteration produced by substituting Pro at position 238 (EU numbering) with Asp or Leu at position 328 (EU numbering) with Glu enhances FcγRIIb-binding activity, and decreases Fc region-mediated binding activity towards both allotypes of FcγRIIa, types H and R. Furthermore, the present inventors discovered that a polypeptide comprising an antibody Fc region that comprises an alteration of substituting Pro at position 238 (EU numbering) with Asp and several other alterations that enhance FcγRIIb-binding activity, and maintains or decreases Fc region-mediated binding activities towards both allotypes of FcγRIIa, types H and R.

More specifically, the present invention relates to the following:

[1] a polypeptide variant comprising an ~~antibody~~ IgG Fc region with at least one amino acid alteration, which has maintained or decreased binding activities towards FcγRIIa (type R) and FcγRIIa (type H), and enhanced FcγRIIb-binding activity in comparison with a parent polypeptide, and wherein the value of [KD value of the polypeptide variant for FcγRIIa (type R)] / [KD value of the polypeptide variant for FcγRIIb] is 1.2 or more, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu, wherein the IgG Fc region is an IgG1 Fc region;

[2] the polypeptide of [1], wherein the value of [KD value of the polypeptide variant for FcγRIIa (type H)] / [KD value of the polypeptide variant for FcγRIIb] is 4.2 or more;

[3] the polypeptide of [1] or [2], wherein the value of [KD value of the parent polypeptide for FcγRIIb] / [KD value of the polypeptide variant for FcγRIIb] is 1.6 or more;

[4] the polypeptide of any one of [1] to [3], wherein the value of [KD value of the stronger of the binding activities of the polypeptide variant towards FcγRIIa (type R) and FcγRIIa (type H)] / [KD value of the stronger of the binding activities of the parent polypeptide towards FcγRIIa (type R) and FcγRIIa (type H)] is 0.7 or more;

[5] the polypeptide of any one of [1] to [4], which has maintained or decreased FcγRIIIa-binding activity compared with that of a parent polypeptide;

[6] the polypeptide of any one of [1] to [5], which has maintained or decreased FcγRIa-binding activity compared with that of a parent polypeptide;

~~[7] the polypeptide of any one of [1] to [6], wherein an amino acid alteration is substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu;~~

[~~8~~7] the polypeptide of any one of [1] to [~~7~~6], wherein ~~an~~ the at least one amino acid alteration ~~is~~ comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution selected from the group consisting of: substitution of Gly at position 237 (EU numbering) with Trp;

substitution of Gly at position 237 (EU numbering) with Phe;

substitution of Ser at position 267 (EU numbering) with Val;

substitution of Ser at position 267 (EU numbering) with Gln;
substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;
substitution of Lys at position 326 (EU numbering) with Leu;
substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr;
substitution of Ala at position 330 (EU numbering) with Lys;
substitution of Ala at position 330 (EU numbering) with Arg;
substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met;

[98] the polypeptide of any one of [1] to [87], wherein the polypeptide comprising the ~~antibody~~ IgG Fc region is an IgG antibody;

[109] the polypeptide of any one of [1] to [87], wherein the polypeptide comprising the IgG~~antibody~~ Fc region is an Fc fusion protein molecule;

[~~11~~10] a method for maintaining or decreasing binding activities towards FcγRIIa (type R) and FcγRIIa (type H) and enhancing FcγRIIb-binding activity of a polypeptide in comparison with a parent polypeptide, which comprises adding at least one amino acid alteration in the Fc region of the polypeptide comprising the IgG~~antibody~~ Fc region, wherein the at least one amino acid alteration ~~is~~ comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu, wherein the IgG Fc region is an IgG1 Fc region;

~~[12] a method for suppressing production of an antibody against a polypeptide comprising antibody Fc region in comparison with a parent polypeptide when administered *in vivo*, wherein the method comprises adding at least one amino acid alteration to the Fc region of the polypeptide, wherein the amino acid alteration is substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu;~~

[~~13~~11] the method of [~~11~~10] ~~or [12]~~, wherein the at least one amino acid alteration ~~is~~ comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution selected from the group consisting of:

substitution of Gly at position 237 (EU numbering) with Trp;
substitution of Gly at position 237 (EU numbering) with Phe;
substitution of Ser at position 267 (EU numbering) with Val;
substitution of Ser at position 267 (EU numbering) with Gln;
substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;
substitution of Lys at position 326 (EU numbering) with Leu;
substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr; substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg;

substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met;

[~~14~~12] the method of any one of [~~11~~10] to [~~13~~11], wherein the polypeptide comprising the IgG~~antibody~~ Fc region is an IgG antibody;

[~~15~~13] the method of any one of [~~11~~10] to [~~13~~11], wherein the polypeptide comprising the IgG~~antibody~~ Fc region is an Fc fusion protein molecule;

[~~16~~14] a method for producing a polypeptide having maintained or decreased binding activities towards FcγRIIa (type R) and FcγRIIa (type H) and having enhanced FcγRIIb-binding activity in comparison with a parent polypeptide, wherein the method comprises adding at least one amino acid alteration in the Fc region of a polypeptide comprising an IgG~~antibody~~ Fc region, wherein the at least one amino acid alteration ~~is~~ comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu, wherein the IgG Fc region is an IgG1 Fc region;

[~~17~~15] an in vitro method for producing a polypeptide with suppressed production of an antibody against the polypeptide in comparison with a parent polypeptide when administered *in vivo*, wherein the method comprises adding at least one amino acid alteration in the Fc region of a polypeptide comprising an IgG~~antibody~~ Fc region, wherein the at least one amino acid alteration ~~is~~ comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu, wherein the IgG Fc region is an IgG1 Fc region;

[~~18~~16] the method of [~~16~~14] or [~~17~~15], wherein the at least one amino acid alteration ~~is~~ comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution selected from the group consisting of:
substitution of Gly at position 237 (EU numbering) with Trp;
substitution of Gly at position 237 (EU numbering) with Phe; substitution of Ser at position 267 (EU numbering) with Val; substitution of Ser at position 267 (EU numbering) with Gln;

substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;
substitution of Lys at position 326 (EU numbering) with Leu;
substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr;
substitution of Ala at position 330 (EU numbering) with Lys;
substitution of Ala at position 330 (EU numbering) with Arg;
substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met;

[~~19~~17] the method of any one of [~~16~~14] to [~~18~~16], wherein the polypeptide comprising the IgG~~antibody~~ Fc region is an IgG antibody;

[~~20~~18] the method of any one of [~~16~~14] to [~~18~~16], wherein the polypeptide comprising the ~~antibody~~ IgG Fc region is an Fc fusion protein molecule;

~~[21] a polypeptide produced by the method of any one of [16] to [20];~~

[~~22~~19] a pharmaceutical composition comprising the polypeptide of any one of [1] to [~~109~~] ~~and [21]~~;

[~~23~~20] an agent for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprises the polypeptide of any one of [1] to [~~109~~] ~~and [21]~~;

[~~24~~21] an agent for treating or preventing an immunological inflammatory disease, which comprises the polypeptide of any one of [1] to [~~109~~] ~~and [21]~~;

[~~25~~22] the therapeutic agent or preventive agent of [~~24~~21], wherein the immunological inflammatory disease is an autoimmune disease and is a disease which may be caused by production of an antibody against an autoantigen;

[~~26~~23] an agent for treating a disease, which comprises the polypeptide of any one of [1] to [~~109~~] ~~and [21]~~, wherein the disease is a disease with deficiency of a biologically essential protein; and

[~~27~~24] an antiviral agent comprising the polypeptide of any one of [1] to [~~109~~] ~~and [21]~~.

The present ~~invention~~ disclosure also relates to methods for treating or preventing immunological inflammatory diseases, which comprise the step of administering to a subject a polypeptide of the present ~~invention~~ disclosure or a polypeptide produced by the production methods of the present ~~invention~~disclosure. Furthermore, the present disclosure~~invention~~ relates to kits for use in the therapeutic methods or preventive methods of the present disclosure~~invention~~, which comprise a polypeptide of the present disclosure~~invention~~ or a polypeptide produced by the production methods of the present disclosure~~invention~~, or a pharmaceutical composition of the present disclosure~~invention~~. The present disclosure~~invention~~ also relates to use of a polypeptide of the present disclosure~~invention~~ or a polypeptide produced by the production methods of the present disclosure~~invention~~ in the production of therapeutic agents or preventive agents for immunological inflammatory diseases. In addition, the present disclosure~~invention~~ relates to a polypeptide of the present disclosure~~invention~~ or a polypeptide produced by the production methods of the present disclosure~~invention~~ for use in a therapeutic method or a preventive method of the present disclosure~~invention~~. The present disclosure~~invention~~ also relates to methods for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprise the step of administering to a subject a polypeptide of the present disclosure~~invention~~ or a polypeptide produced by the production methods of the present disclosure~~invention~~. The present disclosure~~invention~~ relates to kits for use in the inhibition method of the present disclosure~~invention~~, which comprises a polypeptide of the present disclosure~~invention~~ or a polypeptide produced by the production methods of the present disclosure~~invention~~, or a pharmaceutical composition of the present disclosure~~invention~~. The present disclosure~~invention~~ relates to use of a polypeptide of the present disclosure~~invention~~ or a polypeptide produced by the production methods of the present disclosure~~invention~~ in the production of agents that suppress activation of B cells, mast cells, dendritic cells, and/or basophils. The present disclosure~~invention~~ relates to polypeptides of the present disclosure~~invention~~ or polypeptides produced by the production methods of the present disclosure~~invention~~ for use in the inhibitory methods of the present disclosure~~invention~~. The present disclosure~~invention~~ relates to methods for treating diseases with deficiency of biologically essential proteins, which comprises the step of administering to a

subject a polypeptide of the present disclosureinvention or a polypeptide produced by the production methods of the present disclosureinvention. The present disclosureinvention relates to kits for use in the therapeutic method of the present disclosureinvention, which comprises a polypeptide of the present disclosureinvention or a polypeptide produced by the production methods of the present disclosureinvention, or a pharmaceutical composition of the present disclosureinvention. The present disclosureinvention relates to use of a polypeptide of the present disclosureinvention or a polypeptide produced by the production methods of the present disclosureinvention in the production of therapeutic agents for diseases with deficiency of biologically essential proteins. The present disclosureinvention also relates to a polypeptide of the present disclosureinvention or a polypeptide produced by the production methods of the present disclosureinvention for use in a therapeutic method of the present disclosureinvention. The present disclosureinvention relates to methods for inhibiting viruses, which comprises the step of administering to a subject a polypeptide of the present disclosureinvention or a polypeptide produced by the production methods of the present disclosureinvention. The present disclosureinvention relates to kits for use in the inhibition method of the present disclosureinvention, which comprises a polypeptide of the present disclosureinvention or a polypeptide produced by the production methods of the present disclosureinvention, or a pharmaceutical composition of the present disclosureinvention. Furthermore, the present disclosureinvention relates to use of a polypeptide of the present disclosureinvention or a polypeptide produced by the production methods of the present disclosureinvention in the production of an antiviral agent. Furthermore, the present disclosureinvention relates to a polypeptide of the present disclosureinvention or a polypeptide produced by the production methods of the present disclosureinvention for use in the inhibition method of the present disclosureinvention.

[Effects of the Invention]

Polypeptides comprising an Fc region having maintained or decreased binding activities towards both allotypes of FcγRIIa, types R and H, and having enhanced FcγRIIb-binding activity in comparison with a parent polypeptide are provided by the present invention. By using the polypeptides with enhanced binding selectivity for FcγRIIb than for both allotypes of FcγRIIa (types H and R), it is possible to transmit inhibitory signals of inflammatory immune response mediated by phosphorylation of ITIM of FcγRIIb in patients carrying either of the allotypes, type R and type H. Furthermore, by conferring an antibody Fc with the property of selective FcγRIIb binding, it may be possible to suppress anti-antibody production through the FcγRIIb-mediated immunosuppressive action.

Brief Description of the Drawings

Fig. 1 shows comparison of FcγRIa binding and FcγRIIb binding. Binding of the antibody with substitution of Pro at position 238 (EU numbering) with Asp, and binding of the antibody with substitution of Leu at position 328 (EU numbering) with Glu have been labeled.

CLAIMS

1. A polypeptide variant comprising an IgG Fc region with at least one amino acid alteration, which has maintained or decreased binding activities towards FcγRIIa (type R) and FcγRIIa (type H), and enhanced FcγRIIb-binding activity in comparison with a parent polypeptide, and wherein the value of [KD value of the polypeptide variant for FcγRIIa (type R)] / [KD value of the polypeptide variant for FcγRIIb] is 1.2 or more, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu,
wherein the IgG Fc region is an IgG1 Fc region.

2. The polypeptide of claim 1, wherein the value of [KD value of the polypeptide variant for FcγRIIa (type H)] / [KD value of the polypeptide variant for FcγRIIb] is 4.2 or more.

3. The polypeptide of claim 1 or 2, wherein the value of [KD value of the parent polypeptide for FcγRIIb] / [KD value of the polypeptide variant for FcγRIIb] is 1.6 or more.

4. The polypeptide of any one of claims 1 to 3, wherein the value of [KD value of the stronger of the binding activities of the polypeptide variant towards FcγRIIa (type R) and FcγRIIa (type H)] / [KD value of the stronger of the binding activities of the parent polypeptide towards FcγRIIa (type R) and FcγRIIa (type H)] is 0.7 or more.

5. The polypeptide of any one of claims 1 to 4, which has maintained or decreased FcγRIIIa-binding activity compared with that of a parent polypeptide.

6. The polypeptide of any one of claims 1 to 5, which has maintained or decreased FcγRIa-binding activity compared with that of a parent polypeptide.

7. The polypeptide of any one of claims 1 to 6, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution selected from the group consisting of:
substitution of Gly at position 237 (EU numbering) with Trp;
substitution of Gly at position 237 (EU numbering) with Phe;
substitution of Ser at position 267 (EU numbering) with Val;
substitution of Ser at position 267 (EU numbering) with Gln;
substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;

substitution of Lys at position 326 (EU numbering) with Leu;
substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr;
substitution of Ala at position 330 (EU numbering) with Lys;
substitution of Ala at position 330 (EU numbering) with Arg;
substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met.

8. The polypeptide of any one of claims 1 to 7, wherein the polypeptide comprising the IgG Fc region is an IgG antibody.

9. The polypeptide of any one of claims 1 to 7, wherein the polypeptide comprising the IgG Fc region is an Fc fusion protein molecule.

10. A method for maintaining or decreasing binding activities towards FcγRIIa (type R) and

FcγRIIa (type H) and enhancing FcγRIIb-binding activity of a polypeptide in comparison with a parent polypeptide, which comprises adding at least one amino acid alteration in the Fc region of the polypeptide comprising the IgG Fc region, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu,
wherein the IgG Fc region is an IgG1 Fc region.

11. The method of claim 10, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution selected from the group consisting of:
substitution of Gly at position 237 (EU numbering) with Trp;
substitution of Gly at position 237 (EU numbering) with Phe;
substitution of Ser at position 267 (EU numbering) with Val;
substitution of Ser at position 267 (EU numbering) with Gln;
substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;
substitution of Lys at position 326 (EU numbering) with Leu;
substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr;
substitution of Ala at position 330 (EU numbering) with Lys;
substitution of Ala at position 330 (EU numbering) with Arg;
substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;

substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met.

12. The method of claim 10 or 11, wherein the polypeptide comprising the IgG Fc region is an IgG antibody.

13. The method of claim 10 or 11, wherein the polypeptide comprising the IgG Fc region is an Fc fusion protein molecule.

14. A method for producing a polypeptide having maintained or decreased binding activities towards FcγRIIa (type R) and FcγRIIa (type H) and having enhanced FcγRIIb-binding activity in comparison with a parent polypeptide, wherein the method comprises adding at least one amino acid alteration in the Fc region of a polypeptide comprising an IgG Fc region, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu,
wherein the IgG Fc region is an IgG1 Fc region.

15. An in vitro method for producing a polypeptide with suppressed production of an antibody against the polypeptide in comparison with a parent polypeptide when administered *in vivo*, wherein the method comprises adding at least one amino acid alteration in the Fc region of a polypeptide comprising an IgG Fc region, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu,
wherein the IgG Fc region is an IgG1 Fc region.

16. The method of claim 14 or 15, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution selected from the group consisting of:
substitution of Gly at position 237 (EU numbering) with Trp;
substitution of Gly at position 237 (EU numbering) with Phe;

substitution of Ser at position 267 (EU numbering) with Val;
substitution of Ser at position 267 (EU numbering) with Gln;
substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;
substitution of Lys at position 326 (EU numbering) with Leu;
substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr;
substitution of Ala at position 330 (EU numbering) with Lys;
substitution of Ala at position 330 (EU numbering) with Arg;
substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met.

17. The method of any one of claims 14 to 16, wherein the polypeptide comprising the IgG Fc region is an IgG antibody.

18. The method of any one of claims 14 to 16, wherein the polypeptide comprising the IgG Fc region is an Fc fusion protein molecule.

19. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 9.

20. An agent for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprises the polypeptide of any one of claims 1 to 9.

21. An agent for treating or preventing an immunological inflammatory disease, which comprises the polypeptide of any one of claims 1 to 9.

22. The therapeutic agent or preventive agent of claim 21, wherein the immunological inflammatory disease is an autoimmune disease and is a disease which may be caused by production of an antibody against an autoantigen.

23. An agent for treating a disease, which comprises the polypeptide of any one of claims 1 to 9, wherein the disease is a disease with deficiency of a biologically essential protein.

24. An antiviral agent comprising the polypeptide of any one of claims 1 to 9.

CLAIMS

1. A polypeptide variant comprising an IgG Fc region with at least one amino acid alteration, which has maintained or decreased binding activities towards FcγRIIa (type R) and FcγRIIa (type H), and enhanced FcγRIIb-binding activity in comparison with a parent polypeptide, and wherein the value of [KD value of the polypeptide variant for FcγRIIa (type R)] / [KD value of the polypeptide variant for FcγRIIb] is 1.2 or more, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu.

2. The polypeptide of claim 1, wherein the value of [KD value of the polypeptide variant for FcγRIIa (type H)] / [KD value of the polypeptide variant for FcγRIIb] is 4.2 or more.

3. The polypeptide of claim 1 or 2, wherein the value of [KD value of the parent polypeptide for FcγRIIb] / [KD value of the polypeptide variant for FcγRIIb] is 1.6 or more.

4. The polypeptide of any one of claims 1 to 3, wherein the value of [KD value of the stronger of the binding activities of the polypeptide variant towards FcγRIIa (type R) and FcγRIIa (type H)] / [KD value of the stronger of the binding activities of the parent polypeptide towards FcγRIIa (type R) and FcγRIIa (type H)] is 0.7 or more.

5. The polypeptide of any one of claims 1 to 4, which has maintained or decreased FcγRIIIa-binding activity compared with that of a parent polypeptide.

6. The polypeptide of any one of claims 1 to 5, which has maintained or decreased FcγRIa-binding activity compared with that of a parent polypeptide.

7. The polypeptide of any one of claims 1 to 6, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution selected from the group consisting of:
substitution of Gly at position 237 (EU numbering) with Trp;
substitution of Gly at position 237 (EU numbering) with Phe;
substitution of Ser at position 267 (EU numbering) with Val;
substitution of Ser at position 267 (EU numbering) with Gln;
substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;
substitution of Lys at position 326 (EU numbering) with Leu;

substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr;
substitution of Ala at position 330 (EU numbering) with Lys;
substitution of Ala at position 330 (EU numbering) with Arg;
substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met.

8. The polypeptide of any one of claims 1 to 7, wherein the polypeptide comprising the IgG Fc region is an IgG antibody.

9. The polypeptide of any one of claims 1 to 7, wherein the polypeptide comprising the IgG Fc region is an Fc fusion protein molecule.

10. A method for maintaining or decreasing binding activities towards FcγRIIa (type R) and FcγRIIa (type H) and enhancing FcγRIIb-binding activity of a polypeptide in comparison

with a parent polypeptide, which comprises adding at least one amino acid alteration in the Fc region of the polypeptide comprising the IgG Fc region, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu.

11. An in vitro method for suppressing production of an antibody against a polypeptide comprising IgG Fc region in comparison with a parent polypeptide when administered *in vivo*, wherein the method comprises adding at least one amino acid alteration to the Fc region of the polypeptide, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu.

12. The method of claim 10 or 11, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution selected from the group consisting of:
substitution of Gly at position 237 (EU numbering) with Trp;
substitution of Gly at position 237 (EU numbering) with Phe;
substitution of Ser at position 267 (EU numbering) with Val;
substitution of Ser at position 267 (EU numbering) with Gln;
substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;
substitution of Lys at position 326 (EU numbering) with Leu;
substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr;
substitution of Ala at position 330 (EU numbering) with Lys;
substitution of Ala at position 330 (EU numbering) with Arg;

substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met.

13. The method of any one of claims 10 to 12, wherein the polypeptide comprising the IgG Fc region is an IgG antibody.

14. The method of any one of claims 10 to 12, wherein the polypeptide comprising the IgG Fc region is an Fc fusion protein molecule.

15. A method for producing a polypeptide having maintained or decreased binding activities towards FcγRIIa (type R) and FcγRIIa (type H) and having enhanced FcγRIIb-binding activity in comparison with a parent polypeptide, wherein the method comprises adding at least one amino acid alteration in the Fc region of a polypeptide comprising an IgG Fc region, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu.

16. An in vitro method for producing a polypeptide with suppressed production of an antibody against the polypeptide in comparison with a parent polypeptide when administered *in vivo*, wherein the method comprises adding at least one amino acid alteration in the Fc region of a polypeptide comprising an IgG Fc region, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu.

17. The method of claim 15 or 16, wherein the at least one amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp, and at least one substitution

selected from the group consisting of:
substitution of Gly at position 237 (EU numbering) with Trp;
substitution of Gly at position 237 (EU numbering) with Phe;
substitution of Ser at position 267 (EU numbering) with Val;
substitution of Ser at position 267 (EU numbering) with Gln;
substitution of His at position 268 (EU numbering) with Asn;
substitution of Pro at position 271 (EU numbering) with Gly;
substitution of Lys at position 326 (EU numbering) with Leu;
substitution of Lys at position 326 (EU numbering) with Gln;
substitution of Lys at position 326 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Met;
substitution of Ser at position 239 (EU numbering) with Asp;
substitution of Ser at position 267 (EU numbering) with Ala;
substitution of Leu at position 234 (EU numbering) with Trp;
substitution of Leu at position 234 (EU numbering) with Tyr;
substitution of Gly at position 237 (EU numbering) with Ala;
substitution of Gly at position 237 (EU numbering) with Asp;
substitution of Gly at position 237 (EU numbering) with Glu;
substitution of Gly at position 237 (EU numbering) with Leu;
substitution of Gly at position 237 (EU numbering) with Met;
substitution of Gly at position 237 (EU numbering) with Tyr;
substitution of Ala at position 330 (EU numbering) with Lys;
substitution of Ala at position 330 (EU numbering) with Arg;
substitution of Glu at position 233 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Asp;
substitution of His at position 268 (EU numbering) with Glu;
substitution of Lys at position 326 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ser;
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;
substitution of Val at position 323 (EU numbering) with Met;
substitution of Tyr at position 296 (EU numbering) with Asp;
substitution of Lys at position 326 (EU numbering) with Ala;
substitution of Lys at position 326 (EU numbering) with Asn; and
substitution of Ala at position 330 (EU numbering) with Met.

18. The method of any one of claims 15 to 17, wherein the polypeptide comprising the IgG Fc region is an IgG antibody.

19. The method of any one of claims 15 to 17, wherein the polypeptide comprising the IgG Fc region is an Fc fusion protein molecule.

20. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 9.

21. An agent for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprises the polypeptide of any one of claims 1 to 9.

22. An agent for treating or preventing an immunological inflammatory disease, which comprises the polypeptide of any one of claims 1 to 9.

23. The therapeutic agent or preventive agent of claim 22, wherein the immunological inflammatory disease is an autoimmune disease and is a disease which may be caused by production of an antibody against an autoantigen.

24. An agent for treating a disease, which comprises the polypeptide of any one of claims 1 to 9, wherein the disease is a disease with deficiency of a biologically essential protein.

25. An antiviral agent comprising the polypeptide of any one of claims 1 to 9.