Antibody Fc Variants

Field of the invention

The present invention concerns polypeptides comprising variants of an Fc region. More particularly, the present invention concerns Fc region-containing polypeptides that have altered effector function as a consequence of one or more amino acid substitutions in the Fc region of the polypeptide.

Summary

The present disclosure relates to the field of antibody variants and provides polypeptides comprising Fc variants with a decreased effector function, like decreased ADCC and/or C1q binding.

In particular the disclosure provides a polypeptide comprising an Fc variant of a wild-type human IgG Fc region, said Fc variant comprising an amino acid substitution at position Pro329 and at least one further amino acid substitution, wherein the residues are numbered according to the EU index of Kabat, and wherein said polypeptide exhibits a reduced affinity to the human FcγRIIIA and/or FcγRIIA and /or FcγRI compared to a polypeptide comprising the wildtype IgG Fc region, and wherein the ADCC induced by said polypeptide is reduced to at least 20% of the ADCC induced by the polypeptide comprising a wild-type human IgG Fc region.

In one aspect, the disclosure provides for a polypeptide comprising an Fc variant of a wild-type human IgG1 Fc region, said Fc variant comprising an amino acid substitution at position Pro329, wherein Pro329 of a wild-type human Fc region is substituted with glycine and at least one further amino acid substitution, wherein said at least one further amino acid substitution is L234A and L235A of the human IgG1 Fc region, wherein the residues are numbered according to the EU index of Kabat.

In a specific embodiment Pro329 of a wild-type human Fc region in the polypeptide described above is substituted with glycine or arginine or an amino acid residue large enough to destroy the proline sandwich within the Fc/Fcγ receptor interface, that is formed between the proline329 of the Fc and tryptophane residues Trp 87 and Trp 110 of FcgRIII (Sondermann et al.: Nature 406, 267-273 (20 July 2000)). In a further embodiment of the disclosure the at least one further amino acid substitution in the Fc variant is S228P, E233P, L234A, L235A, L235E, N297A, N297D, or P331S and still in another embodiment said at

least one further amino acid substitution is L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region.

In another embodiment of the disclosure the polypeptide provided exhibits a reduced affinity to at least one further receptor of the group comprising the human receptors FcγI, FcγIIA and C1q compared to the polypeptide comprising a wild-type human

IgG Fc region. In still another embodiment of the disclosure the polypeptide comprises a human IgG1 or IgG4 Fc region. In still another embodiment of the disclosure the polypeptide is an antibody or an Fc fusion protein.

In a further embodiment the thrombocyte aggregation induced by the polypeptide comprising the Fc variant is reduced compared to the thrombocyte aggregation induced by a polypeptide comprising a wild-type human IgG Fc region. In still a further embodiment, the polypeptide according to the disclosure exhibits a strongly reduced CDC compared to the CDC induced by a polypeptide comprising a wild-type human IgG Fc region.

In another aspect, the disclosure provides for the polypeptide as disclosed herein for use as a medicament. In another embodiment of the disclosure polypeptides comprising an Fc variant, as described above, are provided for use as a medicament. In a specific embodiment the polypeptide is an anti-CD9 antibody, which is characterized in that the polypeptide comprising the wildtype Fc region comprises as heavy chain variable region SEQ ID NO:9 and as variable light chain region SEQ ID NO:8.

There is also provided the polypeptides as described above for use in treating a disease wherein it is favorable that an effector function of the polypeptide comprising the Fc variant is strongly reduced compared to the effector function induced by a polypeptide comprising a wild-type human IgG Fc region. In another aspect, the disclosure provides for the polypeptide as disclosed herein for use in the treatment of a disease selected from the group consisting of cancer, inflammatory diseases, diabetes and neuronal diseases.

In another aspect, the disclosure provides for a pharmaceutical formulation comprising the polypeptide as disclosed herein and a pharmaceutically acceptable carrier.

In another embodiment the use of the polypeptides as described above is provided for the manufacture of a medicament for the treatment of a disease, wherein it is favorable that the effector function of the polypeptide comprising an Fc variant of a wild-type human IgG Fc region is strongly reduced compared to the effector function induced by a polypeptide comprising a wild-type human IgG Fc region. In another aspect, the disclosure provides for use of the polypeptide as disclosed herein in the manufacture of a medicament for the treatment of a disease selected

from the group consisting of cancer, inflammatory diseases, diabetes and neuronal diseases.

There is also provided a method of treating an individual having a disease, wherein it is favorable that the effector function of the polypeptide comprising an Fc variant of a wild-type human IgG Fc region is strongly reduced compared to the effector function induced by a polypeptide comprising a wildtype human Fc polypeptide, comprising administering to an individual an effective amount of the polypeptide described above.

There is also provided a use of a polypeptide comprising an Fc variant of a wild-type human IgG Fc region, said polypeptide having Pro329 of the human IgG Fc region substituted with glycine, wherein the residues are numbered according to the EU index of Kabat, wherein said polypeptide exhibits a reduced

affinity to the human FcγRIIIA and FcγRIIA for down-modulation of ADCC to at least 20% of the ADCC induced by the polypeptide comprising the wildtype human IgG Fc region, and/or for down-modulation of ADCP.

There is also provided use of a polypeptide comprising an Fc variant of a wild-type human IgG Fc region, said polypeptide having Pro329 of the human IgG Fc region substituted with glycine and wherein the Fc variant comprises at least two further amino acid substitutions at L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region, wherein the residues are numbered according to the EU index of Kabat, wherein said polypeptide exhibits a reduced affinity to the human FcγRIIIA and FcγRIIA, for down-modulation of ADCC to at least 20% of the ADCC induced by the polypeptide comprising the wildtype human IgG Fc region, and/or for down-modulation of ADCP.

There is also provided use of the polypeptide described above, wherein the thrombocyte aggregation induced by the polypeptide described above is reduced compared to the thrombocyte aggregation induced by a polypeptide comprising a wildtype human Fc region, wherein the polypeptide is a platelet activating antibody.

There is also provided a method of treating an individual having a disease is provided, wherein said individual is treated with a polypeptide, said polypeptide having Pro329 of the human IgG Fc region substituted with glycine, wherein the residues are numbered according to the EU index of Kabat, wherein said polypeptide is characterized by a strongly reduced binding FcγRIIIA and/or FcγRIIA compared to a polypeptide comprising a wildtype human IgG Fc region, comprising administering to the individual an effective amount of said polypeptide.

In an embodiment of the disclosure the polypeptide used in said method comprises at least two further amino acid substitutions at L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region.

Background

Monoclonal antibodies have great therapeutic potential and play an important role in today's medical portfolio. During the last decade, a significant trend in the pharmaceutical industry has been the development of monoclonal antibodies (mAbs) as therapeutic agents for the treatment of a number of diseases, such as

Patent Claims

1. A polypeptide comprising an Fc variant of a wild-type human IgG1 Fc region, said Fc variant comprising an amino acid substitution at position Pro329, wherein Pro329 of a wild-type human Fc region is substituted with glycine and at least one further amino acid substitution, wherein said at least one further amino acid substitution is L234A and L235A of the human IgG1 Fc region, wherein the residues are numbered according to the EU index of Kabat.

2. The polypeptide according to claim 1, wherein the wild-type human IgG1 polypeptide induces an ADCC and wherein the ADCC induced by the IgG1 Fc variant polypeptide is reduced to 0-20% of the ADCC induced by the polypeptide comprising the wild-type human IgG1 Fc region.

3. The polypeptide according to claims 1 or 2, wherein the polypeptide comprising the Fc variant, exhibits a reduced or ablated affinity for an Fc receptor responsible for an effector function compared to a polypeptide comprising the wild-type human IgG1 Fc region.

4. The polypeptide according to any one of claims 1-3, wherein the polypeptide is an antibody or an Fc fusion protein.

5. The polypeptide according to any one of claims 1-4, wherein the wild-type human IgG1 polypeptide induces thrombocyte aggregation and wherein the thrombocyte aggregation induced by the IgG1 Fc variant polypeptide is reduced compared to the thrombocyte aggregation induced by a polypeptide comprising a wild-type human IgG1 Fc region.

6. The polypeptide according to any one of claims 1-5, wherein the wild-type human IgG1 polypeptide induces CDC and wherein the CDC induced by the IgG1 Fc variant polypeptide is strongly reduced compared to the CDC induced by a polypeptide comprising a wild-type human IgG Fc region.

7. The polypeptide according to any one of claims 1-6 for use as a medicament.

8. The polypeptide according to any of claims 1-7 for use in the treatment of a disease selected from the group consisting of cancer, inflammatory diseases, diabetes and neuronal diseases.

9. The polypeptide according to claim 7 for use in the treatment of a disease, wherein it is favourable to down-regulate the FcγRIIIA, FcγRIIA and FcγRI receptors.

10. The polypeptide according to claim 7 for use in the treatment of a disease wherein it is favorable that an effector function of the polypeptide is strongly reduced compared to the effector function induced by a polypeptide comprising a wild-type human IgG Fc region.

11. The polypeptide according to claim 10, wherein the effector function is ADCC.

12. A pharmaceutical formulation comprising the polypeptide according to claims 1-11 and a pharmaceutically acceptable carrier.

13. Use of the polypeptide according to any one of claims 1-11 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of cancer, inflammatory diseases, diabetes and neuronal diseases.

14. The use of claim 13, wherein the medicament is for down-regulating the FcγRIIIA, FcγRIIA and FcγRI receptors.