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 amino acid substitutions P329G, L234A and L235A within 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

Patent Claims

1. A polypeptide comprising an Fc variant of a wild-type human IgG1 Fc region, said Fc variant comprising amino acid substitutions P329G, L234A and L235A within 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 antibody-dependent cell-mediated cytotoxicity (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 comprising an Fc variant 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 complement-dependent cytotoxicity (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 IgG1 Fc region.

11. The polypeptide for use 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.