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~~invention~~ 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~~invention~~ 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, there is provided 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, wherein Pro329 of a wild-type human Fc region is substituted with glycine or arginine or an amino acid residue large enough to destroy the proline sandwich within the Fc/Fcγ receptor interface, 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 an at least 10-fold reduced affinity to the human FcγRIIIA and a reduced affinity to the human FcγRIIA, FcγRI and the human C1q receptor, 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 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 aspect of the invention 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 one embodiment,~~In another aspect of the invention~~ the polypeptide of the disclosure~~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 embodimentaspect of the disclosureinvention the polypeptide comprises a human IgG1 or IgG4 Fc region. In still another embodimentaspect of the disclosureinvention 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 disclosureinvention exhibits a strongly reduced CDC compared to the CDC induced by a polypeptide comprising a wild-type human IgG Fc region.

In another embodiment of the disclosureinvention 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.

In another aspect of the disclosure, the polypeptide as described above are provided for use as a medicament.

In another aspect of the disclosureinvention the polypeptides as described above are provided 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 of the disclosure,embodiment the use of the polypeptides as described above is provided infor 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 still another embodimentaspect of the disclosureinvention a method of treating an individual having a disease is provided, 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.

A further aspect of the disclosure~~invention~~ is 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, and at least one further amino acid substitution, 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 in the manufacture of a medicament 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.

Another embodimentaspect of the disclosureinvention is 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.

Another embodimentaspect of the disclosureinvention is 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.

In another embodimentaspect of the disclosureinvention 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 still another embodimentaspect of the disclosureinvention 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