

antigen-binding fragment, and a pharmaceutically acceptable carrier. Further embodiments provide for a method of treating inflammatory bowel disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody or an antigen-binding fragment. In some embodiments, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof. In some embodiments, prior to administering the antibody or antigen-binding fragment to the subject, the subject over-expresses TL1A. In some embodiments, the subject comprises a risk variant associated with the inflammatory bowel disease.

[0004a] In another aspect, provided herein is a polynucleotide encoding the antibody or antigen-binding fragment as described herein.

[0005] In another aspect, provided herein is a polypeptide comprising: one or more complementarity determining regions selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 30, SEQ ID NO: 31, and SEQ ID NO: 32.

[0005a] In another aspect, provided herein is an antibody or antigen binding fragment that binds to the same region of human TL1A as a reference antibody, wherein the reference antibody is the antibody or antigen-binding fragment as described herein.

[0006] In another aspect, provided herein is an antibody or antigen binding fragment that binds to the same region of human TL1A as a reference antibody comprising the heavy chain complementarity determining regions (CDRs) of SEQ ID NOs: 6 - 8 and the light chain complementarity determining regions (CDRs) of SEQ ID NOs: 14 - 16. In some embodiments, the reference antibody comprises a heavy chain variable domain of SEQ ID NO: 5 and a light chain variable domain of SEQ ID NO: 13. In some embodiments, the antibody or antigen-binding fragment is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. Further embodiments provide for a pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment, and a pharmaceutically acceptable carrier. Further embodiments provide for a method of treating inflammatory bowel disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody or an antigen-binding fragment. In some embodiments, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof. In some embodiments, prior to administering the antibody or antigen-binding fragment to the subject, the subject over-expresses

TL1A. In some embodiments, the subject comprises a risk variant associated with the inflammatory bowel disease.

[0007] In another aspect, provided herein is an antibody or antigen binding fragment that binds to the same region of human TL1A as a reference antibody comprising the heavy chain complementarity determining regions (CDRs) of SEQ ID NOs: 22 - 24 and the light chain

F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. In some embodiments, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof.

[0013a] In another aspect, provided herein is a pharmaceutical composition comprising: a therapeutically effective amount of the antibody or antigen-binding fragment as described herein, and a pharmaceutically acceptable carrier.

[0013b] In another aspect, provided herein is the antibody or an antigen-binding fragment as described herein for use in therapy.

[0013c] In another aspect, provided herein is the use of the antibody or an antigen-binding fragment as described herein in the manufacture of a medicament for treating an inflammatory bowel disease in a subject in need thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0014] Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[0015] FIG. 1 depicts agarose gel electrophoresis of total RNA from the hybridoma 684842-3 (5C3D11). DNA marker, Marker III, is shown in Lane M and Total RNA of 684842-3 is shown in Lane R.

[0016] FIG. 2 depicts agarose gel electrophoresis of PCR products of 684842-3. DNA marker, Marker III, is shown in Lane M, the variable heavy chain (VH) of 684842-3 is shown in Lane 1, and the variable light chain (VL) of 684842-3 is shown in Lane 2.

[0017] FIG. 3 depicts an agarose gel electrophoresis of total RNA from hybridoma 684842-6 (9E12E5). DNA marker, Marker III, is shown in Lane M and Total RNA of 684842-6 is shown in Lane R.

[0018] FIG. 4 depicts an agarose gel electrophoresis of PCR products of 684842-6. DNA marker, Marker III, is shown in Lane M, the VH of 684842-6 is shown in Lane 1, and the VL of 684842-6 is shown in Lane 2.

[0019] FIG. 5 demonstrates the inhibition of human TL1A induced IFN- γ production by 9E12E5 (panel A) and 5C3D11 (panel B).

[0020] FIG. 6 demonstrates the recognition capability of 5C3D11 (panel A) and 9E12E5 (panel B), to murine TL1A.

[0021] FIG. 7 depicts histogram graphs showing the fluorescent staining of 5C3D11 (panel A) and 9E12E5 (panel B) anti-TL1A antibodies on the TL1A expressing HEK293 cell line compared to the untransfected HEK293 cell line.

DESCRIPTION OF THE INVENTION

[0022] Tumor necrosis factor-like protein 1A (TL1A) has been associated with the development and severity of severe colitis and Crohn's Disease. In addition, preclinical and human genetic association data suggests that TL1A is a potential therapeutic target in Crohn's disease. The present disclosure describes neutralizing antibodies against TL1A and offers a novel therapeutic for the treatment of IBD.

[0102] Particular conservative substitutions include, for example; Ala into Gly or into Ser; Arg into Lys; Asn into Gln or into His; Asp into Glu; Cys into Ser; Gln into Asn; Glu into Asp; Gly into Ala or into Pro; His into Asn or into Gln; Ile into Leu or into Val; Leu into Ile or into Val; Lys into Arg, into Gln or into Glu; Met into Leu, into Tyr or into Ile; Phe into Met, into Leu or into Tyr; Ser into Thr; Thr into Ser; Trp into Tyr; Tyr into Trp; and/or Phe into Val, into Ile or into Leu.

[0103] In some embodiments, the antibody and/or antigen-binding fragment thereof described herein can be a variant of a sequence described herein, e.g., a conservative substitution variant of an antibody polypeptide. In some embodiments, the variant is a conservatively modified variant. A "variant," as referred to herein with respect to a polypeptide, is a polypeptide substantially homologous to a native or reference polypeptide, but which has an amino acid sequence different from that of the native or reference polypeptide because of one or a plurality of deletions, insertions or substitutions. Variant polypeptide-encoding DNA sequences encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to a native or reference DNA sequence, but that encode a variant protein or fragment thereof that retains activity, e.g., antigen-specific binding activity for the relevant target polypeptide.

[0104] Alterations of the native amino acid sequence can be accomplished by any of a number of techniques known to one of skill in the art. Mutations can be introduced at particular loci or by oligonucleotide-directed site-specific mutagenesis procedures. Techniques for making such alterations are very well established and include, for example, those disclosed by Walder et al. (Gene 42: 133, 1986); Bauer et al. (Gene 37:73, 1985); Craik (BioTechniques, January 1985, 12-19); Smith et al. (Genetic Engineering: Principles and Methods, Plenum Press, 1981); and U.S. Pat. Nos. 4,518,584 and 4,737,462.

[0105] In certain embodiments, provided are polynucleotides that encode a polypeptide that specifically binds TL1A or a fragment thereof. For example, provided is a polynucleotide comprising a nucleic acid sequence that encodes an antibody to TL1A or encodes a fragment of such an antibody. The polynucleotides can be in the form of RNA or in the form of DNA. DNA includes cDNA, genomic DNA, and synthetic DNA; and can be double-stranded or single-stranded, and if single stranded can be the coding strand or non-coding (anti-sense) strand. In certain embodiments, the polynucleotides are isolated. In certain embodiments, the polynucleotides are substantially pure.

[0106] Further provided is a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1, 9, 17, 25 and a combination thereof. Also provided are variants of the herein described polynucleotides encoding, for example, fragments, analogs, and derivatives.

CLAIMS

WHAT IS CLAIMED IS:

1. An antibody or antigen-binding fragment that specifically binds to a TL1A polypeptide, comprising: a heavy chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 6 - 8 and a light chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 14 – 16.
2. The antibody or antigen-binding fragment of claim 0, wherein the antibody or antigen-binding fragment is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof.
3. The antibody or antigen-binding fragment of claim 1, wherein the heavy chain comprises a heavy chain variable region comprising an amino acid sequence set forth in any one of SEQ ID NOs: 5, 35, 36, 37, 38, or 39; and the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 13, 40, 41, 42, 43, or 44.
4. A pharmaceutical composition comprising: a therapeutically effective amount of the antibody or antigen-binding fragment of any one of claims 1 to 3, and a pharmaceutically acceptable carrier.
5. The antibody or an antigen-binding fragment of any one of claims 1 to 3 for use in therapy.
6. Use of the antibody or an antigen-binding fragment of any one of claims 1 to 3 in the manufacture of a medicament for treating an inflammatory bowel disease in a subject in need thereof.
7. The use of claim 6, wherein the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractory-ulcerative colitis, or a combination thereof.
8. The use of claim 7, wherein the subject over-expresses TL1A.
9. The use of claim 7, wherein the subject comprises a risk variant associated with the inflammatory bowel disease.
10. A polynucleotide encoding the antibody or antigen-binding fragment of any one of claims 1 to 3.

11. An antibody or antigen binding fragment that binds to the same region of human TL1A as a reference antibody, wherein the reference antibody is the antibody or antigen-binding fragment of any one of claims 1 to 3.
 12. The antibody or antigen-binding fragment of claim 11 wherein that the antibody or antigen-binding fragment is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof.
 13. The antibody or antigen-binding fragment of claim 11 or 12 for use in therapy.
 14. Use of the antibody or antigen-binding fragment of claim 11 or 12 in the manufacture of a medicament for treating an inflammatory bowel disease in a subject in need thereof.
 15. The use of claim 14, wherein the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractory-ulcerative colitis, or a combination thereof.
 16. The use of claim 15, wherein the subject over-expresses TL1A.
 17. The use of claim 15, wherein the subject comprises a risk variant associated with the inflammatory bowel disease.
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