2000 J. Immunol. 164 4105-4110., Harrop *et al.* 19998 J. Immunol. 161 1786). Furthermore, *in vivo* administration of LTβR-Ig or murine anti-LIGHT antibodies inhibits anti-host cytotoxic T lymphocyte (CTL) responses in a murine acute GVHD model (Tamada *et al.* 2000 Nat. Med. 6 283-289).

[0006] Although observations such as those discussed above indicate a role for LIGHT in inflammatory disorders, such as IBD or GVHD, to date no human anti-human LIGHT antibodies have been produced, nor have any human anti-hLIGHT antibodies or monoclonal anti-hLIGHT antibodies been shown to be antagonistic to hLIGHT biological activity. As such, a need continues to exist for identification of therapies, such as anti-LIGHT therapies, useful for treatment of inflammatory disorders in humans. Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

SUMMARY

[0007] Provided herein are antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided are isolated nucleic acids encoding antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Further provided are vectors and host cells comprising nucleic acids encoding antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided are methods of making antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided herein is a method of treating a hLIGHT-mediated disease comprising administering an antibody, such as a fully human antibody, that immunospecifically binds to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. In preferred embodiments, anti-hLIGHT antibodies provided herein are antagonist antibodies that ameliorate, neutralize or otherwise inhibit hLIGHT biological activity *in vivo* (*e.g.*, the hLIGHT-mediated production or secretion of CCL20, IL-8 or RANTES from cells expressing a hLIGHT ligand, such as a hLIGHT receptor, (*e.g.*, HVEM, LTβR and/or DcR3)). An antibody of the ~~invention~~disclosure can be a full-length antibody or an antigen-binding antibody fragment. The antibodies of the ~~invention~~disclosure are also useful for detecting hLIGHT, as well as for ameliorating, neutralizing or otherwise inhibiting hLIGHT activity, *e.g.*, in a human subject suffering from a disorder in which hLIGHT activity is detrimental.

[0008] [Thus, in one aspectembodiment, provided herein is an isolated antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT polypeptide fragment, or a hLIGHT epitope. In some embodiments, the antibody immunospecifically binds to (a) a trimeric (or native) hLIGHT epitope, (b) a monomeric (or denatured) hLIGHT epitope, (c) both a trimeric hLIGHT epitope and a monomeric hLIGHT epitope, (d) a trimeric hLIGHT epitope but not a monomeric hLIGHT epitope, or (e) a monomeric hLIGHT epitope but not a trimeric hLIGHT epitope. In preferred embodiments, the antibody immunospecifically binds a trimeric hLIGHT epitope but not a human monomeric hLIGHT epitope. In preferred embodiments, the antibody is an E1 antibody, E13 antibody, E63 antibody, F19 antibody, or F23 antibody.

[0008a] In one aspect, there is provided an isolated antibody that is fully human and specifically binds to a hLIGHT epitope,wherein the antibody comprises:

(a) a VH CDR1, VH CDR2 and VH CDR3 of an antibody produced by a hybridoma having ATCC Accession NO. PTA-7819 and

(b) a VL CDR1, VL CDR2 and VL CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819.

[0008b] In one aspect, there is provided an isolated antibody that is fully human and specifically binds to a hLIGHT epitope, wherein the antibody comprises:

(a) a heavy chain variable region comprising

a VH CDR1 of SEQ ID NO:20,

a VH CDR2 of SEQ ID NO:21, and

a VH CDR3 of SEQ ID NO:22

and

(b) a light chain variable region comprising:

(1) a VL CDR1 of SEQ ID NO: 93, a VL CDR2 of SEQ ID NO: 96 and a VL CDR3 of SEQ ID NO: 99,

(2) a VL CDR1 of SEQ ID NO: 35, a VL CDR2 of SEQ ID NO: 36 and a VL CDR3 of SEQ ID NO: 37,

(3) a VL CDR1 of SEQ ID NO: 94, a VL CDR2 of SEQ ID NO: 97 and a VL CDR3 of SEQ ID NO: 100, or

(4) a VL CDR1 of SEQ ID NO: 95, a VL CDR2 of SEQ ID NO: 98 and a VL CDR3 of SEQ ID NO: 101.

[0009] Hybridomas that produce each of the E1, E13, E63, F19 and F23 antibodies were deposited under provisions of the Budapest Treaty with the American Type Culture Collection (ATCC, 10801 University Blvd., Manassas, VA 20110-2209) on July 12, 2006 (ATCC Accession Nos. PTA-7729 (hybridoma 124 E1) and PTA-7728 (hybridoma 124 F23), respectively), August 17, 2006 (ATCC Accession Nos. PTA-7818 (hybridoma 124 E63) and PTA-7819 (hybridoma 124 F19) and August 23, 2006 (ATCC Accession No. PTA-7842 (hybridoma 124 E13), and are herein incorporated by reference. Antibodies produced by each of hybridomas 124 E1, 124 E13, 124 E63, 124 F19 and 124 F23 may also be referred to herein as E1, E13, E63, F19, F23, respectively, and/or by the ATCC Accession Numbers. PTA-7729, PTA-7842, PTA-7818, PTA-7819, and PTA-7728, respectively.

[0010] These antibodies, hybridomas, methods of making these antibodies, and methods of using these antibodies are all included in the ~~invention~~disclosure.

[0011] In specific embodiments, an antibody of the ~~invention~~disclosure is one that is competitively blocked (*e.g.*, in a dose-dependent manner) by an E1 antibody, an E13 antibody, and/or an E63 antibody for binding to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT fragment, or a hLIGHT epitope. In other embodiments, the antibody is competitively blocked (*e.g.*, in a dose-dependent manner) by an F19 antibody and/or an F23 antibody for binding to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT fragment, or a hLIGHT epitope. In specific embodiments, the antibody is competitively blocked (*e.g.*, in a dose-dependent manner) by an E1 antibody, an E13 antibody and/or an E63 antibody, but is not competitively blocked (*e.g.*, in a dose-dependent manner) by an F19

antibody and/or an F23 antibody, for binding to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT fragment, or a hLIGHT epitope. In other embodiments, the antibody is competitively blocked (*e.g.*, in a dose-dependent manner) by an F19 antibody and/or an F23 antibody, but is not competitively blocked (*e.g.*, in a dose-dependent manner) by an E1 antibody, an E13 antibody and/or an E63 antibody, for binding to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT fragment, or a hLIGHT epitope. Exemplary competitive blocking tests are provided in the Examples herein.

[0012] PAlso provided herein are antibodies, or antigen binding antibody fragments thereof that immunospecifically bind to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT polypeptide fragment, or a hLIGHT epitope. In certain embodiments, the antibody or antigen-binding fragment comprises a VH chain, VL chain, VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of E1, E13, E63, F19 or F23.

[0013] In certain embodiments, the antibody or antigen binding fragment thereof comprises less than six CDRs. In some embodiments, the antibody or antigen binding fragment thereof comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3. In specific embodiments, the antibody or antigen binding fragment thereof comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of E1, E13, E63, F19 or F23.

[0013a] In one aspect, there is provided a composition comprising the antibody as defined above.

[0014] Also provided herein are pharmaceutical compositions comprising an anti-hLIGHT antibody of the ~~invention~~disclosure, such as E1, E13, E63, F19 or F23.

[0015] In specific embodiments, an antibody of the ~~invention~~disclosure is a fully human antibody, a monoclonal antibody, a recombinant antibody, an antagonist antibody, or any combination thereof. In particular embodiments, the antibody is a fully human antibody, such as a fully human monoclonal antibody, or antigen binding fragment thereof, that immunospecifically binds to hLIGHT. In preferred embodiments, the antibody is an antagonist antibody.

[0016] In certain embodiments, the antibody competes (*e.g.*, in a dose dependent manner) with HVEM, LTβR, DcR3, or fusion proteins thereof (*e.g.*, Fc:HVEM, Fc:LTβR or Fc:DcR3), for binding to a hLIGHT polypeptide, such as a cell surface-expressed hLIGHT polypeptide or soluble hLIGHT polypeptide, a hLIGHT polypeptide

fragment, or a hLIGHT epitope. Exemplary competitive blocking tests are provided in the Examples herein.

[0017] In ~~a second aspect~~one embodiment, provided herein are isolated nucleic acids encoding antibodies that immunospecifically bind to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT polypeptide fragment, or a hLIGHT epitope. In certain embodiments, the nucleic acid encodes a VH chain, VL chain, VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of E1, E13, E63, F19 or F23.

[0017a] In one aspect, there is provided an isolated nucleic acid molecule

(i) comprising or consisting of a nucleic acid sequence that encodes (a) a VH amino acid sequence of an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819; and/or (b) a VL amino acid sequence of an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819, or

(ii) comprising a nucleic acid sequence that encodes (a) a VH CDR1, VH CDR2 and/or VH CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819, and/or (b) a VL CDR1, VL CDR2 and/or VL CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819, or a combination thereof, or

(iii) comprising or consisting of a nucleic acid sequence that encodes an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819,

(iv) comprising (a) a sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence as depicted in SEQ ID NO: 44; and/or (b) a sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence as depicted in any one of the SEQ ID NOS:49, 104, 105 or 106.

[0018] In ~~a third aspect~~one embodiment, provided herein are vectors and host cells comprising nucleic acids encoding antibodies that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope.

[0018a] In one aspect, there is provided a vector comprising the nuclei acid molecule as defined above.

[0018b] In one aspect, there is provided a host cell comprising the vector as defined above.

[0018c] In one aspect, there is provided a method of producing the antibody as defined above, the method comprising culturing the host cell as defined above under conditions that promote production of the antibody.

[0019] In ~~a fourth aspect~~one embodiment, provided herein are methods of making antibodies that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. In certain embodiments, the antibody immunospecifically binds to a single nucleotide polymorphism (SNP) variant of a hLIGHT polypeptide, such as 214E-32S, 214K-32S, 214E-32L and/or 214K-32L. Also provided herein are hybridomas that produce antibodies that immunospecifically bind to a hLIGHT polypeptide, or SNP variant thereof. In preferred embodiments, the hybridoma is the hybridoma that produces E1, E13, E63, F19 or F23.

[0019a] In one aspect, there is provided a hybridoma that produces an antibody as defined above, the hybridoma optionally having ATCC Accession No. PTA-7819.

[0019b] In one aspect, there is provided the composition as defined above

(i) for use in a method for alleviating one or more symptoms of inflammatory bowel disease (IBD) in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(ii) for use in a method for alleviating one or more symptoms of graft-versus-host disease (GVHD) in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(iii) for use in a method for decreasing or inhibiting binding of hLIGHT to HVEMLTβR, DcR3, or any combination thereof, in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(iv) for use in a method for decreasing or inhibiting the secretion of CCL20, IL-8, RANTES, or any combination thereof, in a human in need thereof, the method comprising administering to the human an effective amount of the composition.

[0020] In ~~a fifth aspect~~one embodiment, provided herein are methods of treating or otherwise alleviating one or more symptoms of a hLIGHT-mediated disease in a subject (*e.g.*, a human subject), comprising administering to the subject an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), wherein hLIGHT activity is inhibited by the antibody. In certain embodiments, the hLIGHT-mediated disease is an IBD, such as Crohn's disease or ulcerative colitis. In other embodiments, the hLIGHT mediated disease is GVHD.

[0021] In ~~a sixth aspect~~one embodiment, provided herein are methods for decreasing or inhibiting binding of hLIGHT to HVEM, LTβR and/or DcR3 in a subject (*e.g.*, a human subject), comprising administering to the subject an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT).

[0022] In ~~a seventh aspect~~one embodiment, provided herein are methods for decreasing or inhibiting a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, in a

subject (*e.g.*, a human subject), comprising administering to the subject an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed hLIGHT), wherein hLIGHT biological activity is decreased or inhibited by the antibody.

[0023] In ~~an eighth aspect~~one embodiment, provided herein are methods for decreasing or inhibiting binding of hLIGHT to HVEM, LTβR and/or DcR3 in a cell having cell surface-expressed hLIGHT, contacting the cell with an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), such as a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope.

[0024] In ~~a ninth aspect~~one embodiment, provided herein are methods for decreasing or inhibiting a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, in a cell having a cell surface-expressed hLIGHT receptor (such as, HVEM, LTβR and/or Dc3R), contacting the cell with an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT, or SNP variant thereof), wherein hLIGHT biological activity is decreased or inhibited by the antibody.

[0025] In ~~a tenth aspect~~one embodiment, provided herein is an antibody that immunospecifically binds to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope, wherein said antibody further comprises a detectable tag. In certain embodiments, anti-hLIGHT antibodies that comprise a detectable tag are used in a method for the detection of hLIGHT in a sample, said method comprising contacting the sample with the anti-hLIGHT antibody. In specific embodiments, the sample comprises a cell expressing hLIGHT on the surface of the cell.

[0026] In ~~an eleventh aspect~~one embodiment, provided herein are kits comprising an antibody that immunospecifically binds to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope.

[0026a] In one aspect, there is provided a kit comprising the antibody as defined above, or the composition as defined above.

TERMINOLOGY

[0027] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.