

ANTI-JAGGED1 ANTIGEN BINDING PROTEINS

FIELD OF THE INVENTION

[0001] The present disclosure relates to the treatment or amelioration of lung disease using an antigen binding protein specific for Jagged1.

BACKGROUND OF THE INVENTION

[0002] The Notch signaling pathway regulates a diverse array of cell functions (Kopan et al., *Cell* 137, 216-233 (2009)). Four Notch receptors have been identified in mammals, i.e., Notch 1-4, that share basic structural elements that include an extracellular domain, a transmembrane domain, and an intracellular domain. Similarly, the canonical ligands of Notch share certain structural similarities but a number of non-canonical ligands of Notch have also been identified (Kopan et al., *Cell* 137, 216-233 (2009)). The five canonical ligands in mammals are Delta-like 1, Delta-like 3, Delta-like 4, Jagged1 and Jagged2. Binding of a Notch ligand to the extracellular domain of a Notch receptor sets a signaling cascade in motion that begins with proteolytic cleavage at the extracellular S2 site by an alpha secretase of the ADAM (a disintegrin and metalloprotease) family. Cleavage at S2 is followed by proteolytic cleavage by a gamma secretase at the intracellular S3 site, which results in release of the intracellular domain and downstream events that ultimately activate Notch-dependent transcription factors such as Hes1 and Hey.

[0003] Aberrant Notch expression and signaling has been implicated in a number of diseases, including cancer (Koch et al., *Cell. Mol. Life Sci.* 64, 2746-2762 (2007)). It is clear that there continues to be a need for agents that have clinical attributes that are optimal for development as therapeutic agents. The invention described herein meets this need and provides other benefits.

SUMMARY

[0004] In one aspect the present disclosure is directed to the use of an antigen binding protein as described herein that specifically binds to Jagged1 in the manufacture of a medicament for treating a subject with a condition related to lung disease, comprising that a therapeutically effective amount of the antigen binding protein is to be administered to the subject. In another aspect, the present disclosure provides an isolated antigen binding protein that specifically binds to a Jagged1 polypeptide, wherein the antigen binding protein is an antibody or a fragment thereof, and wherein the antibody comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein each CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, respectively, comprises a sequence selected from SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 230, SEQ ID NO: 231, and SEQ ID NO: 232. Also described herein is a method of treating a subject with a condition

related to lung disease, the method comprising administering to the subject a therapeutically effective amount of an antigen binding protein that specifically binds to a protein having an amino acid sequence having at least 90% amino acid sequence identity to an amino acid sequence of a Jagged1. In certain examples the subject is human. In certain examples the antigen binding protein is administered intravenously, by nebulization, or by subcutaneous injection.

[0005] Also described in the present disclosure is an antigen binding protein that specifically binds to a protein having an amino acid sequence having at least 90% amino acid sequence identity to an amino acid sequence of a Jagged1.

[0005] In certain examples the antigen binding protein is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof. In certain examples the antigen binding protein is a Fab fragment, a Fab' fragment, or a F(ab')₂ fragment. In certain examples the antigen binding protein is a human antibody. In certain examples the antigen binding protein is a monoclonal antibody. In certain examples the antigen binding protein is of the IgG1-, IgG2- IgG3- or IgG4-type. In certain examples the antigen binding protein is coupled to a labeling group.

[0006] In certain examples the antigen binding protein is an antibody or a fragment thereof. In certain examples the antibody comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein the CDRL1 comprises a sequence selected from the group consisting of SEQ ID NOs: 4, 10, 16, 22, 28, 34, 40, 46, 52, 58, 64, 70, 76, 82, 88, 94, 100, 106, 112, 118, 124, and 130; the CDRL2 comprises a sequence selected from the group consisting of SEQ ID NOs: 5, 11, 17, 23, 29, 35, 41, 47, 53, 59, 65, 71, 77, 83, 89, 95, 101, 107, 113, 119, 125, and 131; the CDRL3 comprises a sequence selected from the group consisting of SEQ ID NOs: 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120, 126, and 132; the CDRH1 comprises a sequence selected from the group consisting of SEQ ID NOs: 136, 142, 148, 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, 214, 220, 226, 232, 238, 244, 250, 256, and 262; the CDRH2 comprises a sequence selected from the group consisting of SEQ ID NOs: 137, 143, 149, 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, 215, 221, 227, 233, 239, 245, 251, 257, and 263; and the CDRH3 comprises a sequence selected from the group consisting of SEQ ID NOs: 138, 144, 150, 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, 216, 222, 228, 234, 240, 246, 252, 258, and 264.

[0007] In certain examples the antibody comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein each CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, respectively, comprises a sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 138; SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 144; SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150; SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 154, SEQ ID NO: 155, and SEQ ID

NO: 156; SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 160, SEQ ID NO: 161, and SEQ ID NO: 162; SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 166, SEQ ID NO: 167, and SEQ ID NO: 168; SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 172, SEQ ID NO: 173, and SEQ ID NO: 174; SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 178, SEQ ID NO: 179, and SEQ ID NO: 180; SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 184, SEQ ID NO: 185, and SEQ ID NO: 186; SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 190, SEQ ID NO: 191, and SEQ ID NO: 192; SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 196, SEQ ID NO: 197, and SEQ ID NO: 198; SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 202, SEQ ID NO: 203, and SEQ ID NO: 204; SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 208, SEQ ID NO: 209, and SEQ ID NO: 210; SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 214, SEQ ID NO: 215, and SEQ ID NO: 216; SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 220, SEQ ID NO: 221, and SEQ ID NO: 222; SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 226, SEQ ID NO: 227, and SEQ ID NO: 228; SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 232, SEQ ID NO: 233, and SEQ ID NO: 234; SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 238, SEQ ID NO: 239, and SEQ ID NO: 240; SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 244, SEQ ID NO: 245, and SEQ ID NO: 246; SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 250, SEQ ID NO: 251, and SEQ ID NO: 252; SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 256, SEQ ID NO: 257, and SEQ ID NO: 258; and SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 262, SEQ ID NO: 263, and SEQ ID NO: 264.

[0008] In certain examples the antigen binding protein is an antibody or a fragment thereof, and wherein the antibody or fragment thereof comprises a light chain variable region comprising a sequence selected from the group consisting of SEQ ID NOs: 267, 271, 275, 279, 283, 287, 291, 295, 299, 303, 307, 311, 315, 319, 323, 327, 331, 335, 339, 343, 347, and 351 and a heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NOs: 268, 272, 276, 280, 284, 288, 292, 296, 300, 304, 308, 312, 316, 320, 324, 328, 332, 336, 340, 344, 348, and 352.

[0009] In certain examples the antigen binding protein is an antibody or a fragment thereof, and wherein the antibody or fragment thereof comprises a combination of a light chain variable region and a heavy chain variable region selected from the group consisting of a light chain variable region comprising SEQ ID NO: 267 and a heavy chain variable region comprising SEQ ID NO: 268; a light chain variable region comprising SEQ ID NO: 271 and a heavy chain variable region comprising SEQ ID NO: 272; a light chain variable region comprising SEQ ID NO: 275 and a heavy chain variable region comprising SEQ ID NO: 276; a light chain variable region comprising SEQ ID NO: 279 and a heavy chain variable region comprising SEQ ID NO: 280; a light chain variable region comprising SEQ ID NO: 283 and a heavy chain variable region comprising SEQ ID NO: 284; a light chain variable region comprising SEQ ID NO: 287 and a heavy chain variable region comprising SEQ ID

NO: 288; a light chain variable region comprising SEQ ID NO: 291 and a heavy chain variable region comprising SEQ ID NO: 292; a light chain variable region comprising SEQ ID NO: 295 and a heavy chain variable region comprising SEQ ID NO: 296; a light chain variable region comprising SEQ ID NO: 299 and a heavy chain variable region comprising SEQ ID NO: 300; a light chain variable region comprising SEQ ID NO: 303 and a heavy chain variable region comprising SEQ ID NO: 304; a light chain variable region comprising SEQ ID NO: 307 and a heavy chain variable region comprising SEQ ID NO: 308; a light chain variable region comprising SEQ ID NO: 311 and a heavy chain variable region comprising SEQ ID NO: 312; a light chain variable region comprising SEQ ID NO: 315 and a heavy chain variable region comprising SEQ ID NO: 316; a light chain variable region comprising SEQ ID NO: 319 and a heavy chain variable region comprising SEQ ID NO: 320; a light chain variable region comprising SEQ ID NO: 323 and a heavy chain variable region comprising SEQ ID NO: 324; a light chain variable region comprising SEQ ID NO: 327 and a heavy chain variable region comprising SEQ ID NO: 328; a light chain variable region comprising SEQ ID NO: 331 and a heavy chain variable region comprising SEQ ID NO: 332; a light chain variable region comprising SEQ ID NO: 335 and a heavy chain variable region comprising SEQ ID NO: 336; a light chain variable region comprising SEQ ID NO: 339 and a heavy chain variable region comprising SEQ ID NO: 340; a light chain variable region comprising SEQ ID NO: 343 and a heavy chain variable region comprising SEQ ID NO: 344; a light chain variable region comprising SEQ ID NO: 347 and a heavy chain variable region comprising SEQ ID NO: 348; and a light chain variable region comprising SEQ ID NO: 351 and a heavy chain variable region comprising SEQ ID NO: 352.

[0010] In one aspect the present disclosure is directed to a nucleic acid molecule encoding an antibody or fragment thereof according to the present disclosure. In one example the the nucleic acid molecule is operably linked to a control sequence.

[0011] In one aspect the present disclosure is directed to a vector comprising a nucleic acid molecule according to the present disclosure.

[0012] In one aspect the present disclosure is directed to a host cell comprising a nucleic acid molecule according to the present disclosure.

[0013] In one aspect the present disclosure is directed to an antibody or fragment thereof produced by a host cell of the present disclosure.

[0014] In one aspect the present disclosure is directed to a method of making an antibody or fragment thereof according to the present disclosure, comprising the step of preparing the antibody or fragment thereof from a host cell that secretes the antibody.

[0015] In one aspect the present disclosure is directed to a pharmaceutical composition comprising at least one antibody or fragment thereof according to the present disclosure, and a pharmaceutically acceptable excipient.

[0016] In one aspect the present disclosure is directed to an isolated antigen binding protein that competes for binding to human Jagged1 with an antibody or fragment thereof according to the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIGS. 1A-1F. FIGS. 1A through 1D show periodic acid-Schiff/alcian blue staining of unstimulated ALI cultures untreated or treated with IgG1 (10ug/ml) or anti-Jag-1 15D11.1 (10ug/ml or 1ug/ml). FIGS. 1E through 1F show quantification of goblet cell number and percent mucin

CLAIMS

What is claimed is:

1. An isolated antigen binding protein that specifically binds to a Jagged1 polypeptide, wherein the antigen binding protein is an antibody or a fragment thereof, and wherein the antibody comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein each CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, respectively, comprises a sequence selected from SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 230, SEQ ID NO: 231, and SEQ ID NO: 232.
2. The isolated antigen binding protein of claim 1, wherein the human Jagged1 has a sequence comprising SEQ ID NO: 353.
3. The isolated antigen binding protein of claim 1 or 2, wherein the antigen binding protein is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof.
4. The isolated antigen binding protein of claim 3, wherein the antibody fragment is a Fab fragment, a Fab' fragment, or a F(ab')₂ fragment.
5. The isolated antigen binding protein of claim 3, wherein the antigen binding protein is a human antibody.
6. The isolated antigen binding protein of claim 3, wherein the antigen binding protein is a monoclonal antibody.
7. The isolated antigen binding protein of claim 3, wherein the antigen binding protein is of the IgG1-, IgG2-, IgG3- or IgG4-type.
8. The isolated antigen binding protein of claim 7, wherein the antigen binding protein is of the IgG1- or the IgG2-type.
9. The isolated antigen binding protein of claim 3, wherein the antigen binding protein is coupled to a labeling group.
10. The isolated antigen binding protein of claim 3, wherein the antigen binding protein is an antibody or a fragment thereof, and wherein the antibody or fragment thereof comprises a combination of

a light chain variable region comprising SEQ ID NO: 7 and a heavy chain variable region comprising SEQ ID NO: 8.

11. A nucleic acid molecule encoding the antibody or fragment thereof according to claim 3 or claim 10.

12. The nucleic acid molecule according to claim 11, wherein the nucleic acid molecule is operably linked to a control sequence.

13. A vector comprising a nucleic acid molecule according to claim 12.

14. A host cell comprising the nucleic acid molecule according to claim 13.

15. An antibody or fragment thereof produced by the host cell of claim 14.

16. A method of making the antibody or fragment thereof according to claim 3 or claim 10, comprising the step of preparing the antibody or fragment thereof from a host cell that secretes the antibody.

17. A pharmaceutical composition comprising at least one antibody or fragment thereof according to claim 3 or claim 10, and pharmaceutically acceptable excipient.

18. An isolated antigen binding protein that competes for binding to human Jagged1 with an antibody or fragment thereof of claim 3 or claim 10.

19. Use of an antigen binding protein according to claim 3 or claim 10 that specifically binds to Jagged1 in the manufacture of a medicament for treating a subject with a condition related to lung disease, comprising that a therapeutically effective amount of the antigen binding protein is to be administered to the subject.

20. The use of claim 19, wherein the subject is a mammal.

21. The use of claim 19, wherein the subject is human.

22. The use of claim 19, wherein the therapeutically effective amount of the antigen binding protein is to be administered to the subject by nebulization.

23. The use of claim 19, wherein the therapeutically effective amount of the antigen binding protein is to be administered to the subject by subcutaneous injection.