

X₂₈ is P or A or C or D or E or H or K or S or T or V or W,

X₂₉ is L or G or R, and

X₃₀ is T or I or R, with the proviso that X₁ to X₃₀ cannot be T, H, T, N, P, S, H, Y, E, S, Y, F, A, M, W, G, V, S, A, A, W, A, S, H, H, F, T, P, L and T, respectively, at the same time and up to three of X₁ to X₁₆ can be other than T, H, T, N, P, S, H, Y, E, S, Y, F, A, M, W, and G, respectively, at the same time, and up to five of X₁₇ to X₃₀ can be other than V, S, A, A, W, A, S, H, H, F, T, P, L and T, respectively, at the same time; and the antibody or antibody fragment has a higher binding affinity to Axl protein at a value of a pH in a range of 5.8 to 7.0 of a tumor microenvironment in comparison with the binding affinity to Axl protein at a different value of the pH in a range of 7.0 to 7.6 that occurs in a non-tumor microenvironment.

[0010] Disclosed is that, the isolated heavy chain variable region polypeptide is combined with an isolated light chain variable region that includes three complementarity determining regions L1, L2, and L3 sequences, wherein:

the L1 sequence is KASQDX₁₇X₁₈SX₁₉VX₂₀ (SEQ ID NO: 4);

the L2 sequence is X₂₁X₂₂X₂₃TRX₂₄T (SEQ ID NO: 5); and

the L3 sequence is QEX₂₅X₂₆SX₂₇X₂₈X₂₉X₃₀ (SEQ ID NO: 6),

wherein

X₁₇ is V or D or G or N or W,

X₁₈ is S or V,

X₁₉ is A or L or M,

X₂₀ is A or D or N or Q,

X₂₁ is W or F,

X₂₂ is A or I or N or P or Q,

X₂₃ is S or D,

X₂₄ is H or D,

X₂₅ is H or C or F or I or L or Q or S or T or V or Y,

X₂₆ is F or C or D or E or G or N or S,

X₂₇ is T or C or P,

X₂₈ is P or A or C or D or E or H or K or S or T or V or W,

X₂₉ is L or G or R, and

X₃₀ is T or I or R.

[0010a] In another example, there is provided an isolated polypeptide that specifically binds to Axl protein, said polypeptide comprising an light chain variable region including three complementarity determining regions having L1, L2, and L3 sequences, wherein:

(a) the L1 sequence is KASQDX₁₇X₁₈SX₁₉VX₂₀ (SEQ ID NO: 4);

(b) the L2 sequence is X₂₁X₂₂X₂₃TRX₂₄T (SEQ ID NO: 5); and

(c) the L3 sequence is QEX₂₅X₂₆SX₂₇X₂₈X₂₉X₃₀ (SEQ ID NO: 6),

wherein

X₁₇ is V or D or G or N or W,

X₁₈ is S or V,

X₁₉ is A or L or M,

X₂₀ is A or D or N or Q,

X₂₁ is W or F,

X₂₂ is A or I or N or P or Q,

X₂₃ is S or D,

X₂₄ is H or D,

X₂₅ is H or C or F or I or L or Q or S or T or V or Y,

WHAT IS CLAIMED IS:

1. An antibody or antibody fragment that specifically binds to Axl protein, said antibody or antibody fragment comprising a heavy chain variable region including three complementarity determining regions and a light chain variable region including three complementarity determining regions, said heavy chain complementarity determining regions having H1, H2, and H3 sequences, wherein:

- (a) the H1 sequence is $X_1GX_2X_3MX_4$ (SEQ ID NO: 1);
- (b) the H2 sequence is LIKX₅SNGGTX₆YNQKFKG (SEQ ID NO: 2); and
- (c) the H3 sequence is $GX_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}DYX_{15}X_{16}$ (SEQ ID NO: 3),

wherein

- X₁ is T or A or W,
- X₂ is H or A,
- X₃ is T or I,
- X₄ is N or I,
- X₅ is P or N,
- X₆ is S or I or T,
- X₇ is H or D or E or P or R or W,
- X₈ is Y or N,
- X₉ is E or A or D or F or G or H or I or L or M or N or R or V or Y,
- X₁₀ is S or D or M or N or Q,
- X₁₁ is Y or C or E or P,
- X₁₂ is F or E or N or S or T or V,
- X₁₃ is A or D or G or L or Y,
- X₁₄ is M or E or F,
- X₁₅ is W or A or D or H or L or N or P or R or T, and
- X₁₆ is G or H; and

said light chain complementarity determining regions having L1, L2, and L3 sequences, wherein:

- (a) the L1 sequence is KASQDX₁₇X₁₈SX₁₉VX₂₀ (SEQ ID NO: 4);
- (b) the L2 sequence is X₂₁X₂₂X₂₃TRX₂₄T (SEQ ID NO: 5); and
- (c) the L3 sequence is QEX₂₅X₂₆SX₂₇X₂₈X₂₉X₃₀ (SEQ ID NO: 6),

wherein

- X₁₇ is V or D or G or N or W,
- X₁₈ is S or V,

X₁₉ is A or L or M,
 X₂₀ is A or D or N or Q,
 X₂₁ is W or F,
 X₂₂ is A or I or N or P or Q,
 X₂₃ is S or D,
 X₂₄ is H or D,
 X₂₅ is H or C or F or I or L or Q or S or T or V or Y,
 X₂₆ is F or C or D or E or G or N or S,
 X₂₇ is T or C or P,
 X₂₈ is P or A or C or D or E or H or K or S or T or V or W,
 X₂₉ is L or G or R, and
 X₃₀ is T or I or R, with the proviso that X₁ to X₃₀ cannot be T, H, T, N, P, S, H, Y, E, S, Y, F, A, M, W, G, V, S, A, A, W, A, S, H, H, F, T, P, L and T, respectively, at the same time and up to three of X₁ to X₁₆ can be other than T, H, T, N, P, S, H, Y, E, S, Y, F, A, M, W, and G, respectively, at the same time, and up to five of X₁₇ to X₃₀ can be other than V, S, A, A, W, A, S, H, H, F, T, P, L and T, respectively, at the same time; and the antibody or antibody fragment has a higher binding affinity to Axl protein at a value of a pH in a range of 5.8 to 7.0 of a tumor microenvironment in comparison with the binding affinity to Axl protein at a different value of the pH in a range of 7.0 to 7.6 that occurs in a non-tumor microenvironment.

2. An anti-Axl antibody or antibody fragment of claim 1, in which only one of X₁ to X₁₆ can be other than T, H, T, N, P, S, H, Y, E, S, Y, F, A, M, W, G, respectively, and only one of X₁₇ to X₃₀ can be other than V, S, A, A, W, A, S, H, H, F, T, P, L and T, respectively.

3. The antibody or antibody fragment of claim 1, wherein the heavy chain variable region is encoded by a DNA sequence selected from sequences of SEQ ID NOS: 11-13.

4. The antibody or antibody fragment of claim 1, wherein the light chain variable region is encoded by a DNA sequence selected from SEQ ID NOS: 7-10.

5. The antibody or antibody fragment of claim 1, wherein the heavy chain variable region is encoded by SEQ ID NO: 12 and the light chain variable region is encoded by SEQ ID NO: 9.

6. The antibody or antibody fragment of claim 1, wherein the heavy chain variable region is encoded by SEQ ID NO: 13 and the light chain variable region is encoded by SEQ ID NO: 10.
7. The antibody or antibody fragment of claim 1, wherein the heavy chain variable region is encoded by SEQ ID NO: 11 and the light chain variable region is encoded by SEQ ID NO: 7.
8. The antibody or antibody fragment of claim 1, wherein the heavy chain variable region is encoded by SEQ ID NO: 11 and the light chain variable region is encoded by SEQ ID NO: 8.
9. The antibody or antibody fragment of claim 1, wherein the heavy chain variable region is encoded by SEQ ID NO: 13 and the light chain variable region is encoded by SEQ ID NO: 7.
10. The antibody or antibody fragment of claim 1, wherein the heavy chain variable region is encoded by SEQ ID NO: 12 and the light chain variable region is encoded by SEQ ID NO: 8.