

through IL-1 family receptors, including IL-36R and IL1RALP1, and serves as an immune checkpoint by dampening inflammation (Veerdonk et al., 2017). In particular, IL-38 is shown to reduce the production of inflammatory cytokines, which can play key roles in an effective anti-tumor response. In addition, IL-38 secreted from apoptotic tumor cells can suppress macrophage and T cell responses *in vitro* (Mora et al., 2016). Similarly, IL-38 expression has been shown to correlate with poor prognosis in patients with lung adenocarcinoma as well as correlate with PDL1 expression (Takada et al., 2017). However, conflicting evidence has been reported in non small cell lung cancer, where lower expression of IL-38 correlates with poor prognosis (Wang et al., 2018). IL-38 may serve as an immunosuppressive cytokine within the tumor microenvironment and thus blocking IL-38 signaling may trigger an effective anti-tumor response (Fig. 2).

Summary

[0010] In some examples the present disclosure relates to discovery of the role of the IL-38 cytokine in various cancers. Accordingly, in some examples, provided herein are antibodies that specifically bind to and inhibit IL-38 that are effective for treatment of cancer. In some examples, the antibody that specifically binds to IL-38 comprises the CDR sequences of M3. In some examples, the antibody that specifically binds to IL-38 comprises a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:24, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 25, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:60. In some examples, the antibody that specifically binds to IL-38 comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:98 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:101. In some examples, the cancer is selected from the group consisting of head and neck squamous cell carcinoma (HNSC), esophagus cancer (ESCA), squamous cell cancer of the lung (LUSC), cancer of the cervix (CESC), bladder cancer (BLCA), skin cutaneous melanoma (SKCM), prostate adenocarcinoma (PRAD), gastroesophageal carcinoma, cervical squamous cell carcinoma, cervical squamous cell carcinoma, skin squamous cell carcinoma, basal cell carcinoma, skin cutaneous melanoma, lung adenocarcinoma, endocervical adenocarcinoma, bladder urothelial carcinoma and prostate adenocarcinoma and lung adenocarcinoma (LUAD).

[0011] This disclosure relates to antibodies specific for human interleukin-38 (IL-38), including isolated antibodies, or antigen-binding fragments thereof, which contain at least 3, at least 4, at

least 5, at least 6, at least 7, or at least 8 optionally contiguous amino acids of at least one complementary-determining region (CDR) contained within the variable heavy chain (VH) amino acid sequences of: SEQ ID NO: 22, SEQ ID NO: 27, SEQ ID NO: 32, SEQ ID NO: 37, SEQ ID NO: 42, SEQ ID NO: 47, SEQ ID NO: 52, SEQ ID NO: 2, or SEQ ID NO: 7; and/or contained within the variable light chain (VL) amino acid sequences of: SEQ ID NO: 57, SEQ ID NO: 62, SEQ ID NO: 67, SEQ ID NO: 72, SEQ ID NO: 77, SEQ ID NO: 82, SEQ ID NO: 4, or SEQ ID NO: 9.

[0012] More particularly, the CDRs of an antibody of the disclosure, or antigen-binding fragment may contain at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 optionally contiguous amino acids of: the VH CDR1 amino acid sequences of SEQ ID NOS: 23, 28, 33, 38, 43, 48, 53, or 15; the VH CDR2 amino acid sequences of SEQ ID NOS: 24, 29, 34, 39, 44, 49, 54, or 16; the VH CDR3 amino acid sequences of SEQ ID NOS: 25, 30, 35, 40, 45, 50, 55, or 17; the VL CDR1 amino acid sequences of SEQ ID NOS: 58, 63, 68, 73, 78, 83, or 18; the VL CDR2 amino acid sequences of SEQ ID NOS: 59, 64, 69, 74, 79, 84, or 19; and/or the VL CDR3 amino acid sequences of SEQ ID NOS: 60, 65, 70, 75, 80, 85, or 20.

[0013] Antibodies of the disclosure, or antigen-binding fragments thereof, partially or fully blocks, inhibits, or neutralizes a biological activity of IL 38. Accordingly, methods of the disclosure include methods of inhibiting tumor growth or metastasis in an individual afflicted by tumor growth and/or metastasis by administering a therapeutically effective amount of a composition comprising the antibody or an antigen-binding fragment thereof, to the individual for treatment in which the antibody of the disclosure, or an antigen-binding fragment thereof, partially or fully blocks, inhibits, or neutralizes a biological activity of IL-38 that promotes or sustains tumor growth and/or metastasis.

[0013a] In one aspect, the present disclosure refers to use of a composition comprising an antibody that binds to IL-38 in the manufacture of a medicament for treating cancer in an individual, wherein the antibody comprises

- a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:98 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:101;

- a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:22 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:57;

- a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:7 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:10;

- a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:87 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:92;

- a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:27 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:57;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:37 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:67;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:42 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:72;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:47 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:77;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:32 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:62;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:52 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:82; or

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:4.

[0013b] In one aspect, the present disclosure refers to an isolated antibody that specifically binds to IL-38 comprising

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:87 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:92.

[0013c] In one aspect, the present disclosure refers to an isolated antibody that specifically binds to IL-38 comprising

a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:98 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:101; or

a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:87 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:92.

[0013d] In one aspect, the present disclosure refers to an isolated antibody that specifically binds to IL-38 comprising

i) a comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 101;

ii) a comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 102;

iii) a comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 103;

iv) a VH comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 104;

v) a VH comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 105;

vi) a VH comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 106;

xxviii) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:104;

xxix) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:105; or

xxx) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:106.

[0013e] In one aspect, the present disclosure refers to a composition comprising the antibody disclosed herein.

[0013f] In one aspect, the present disclosure refers to nucleic acid(s) encoding the antibody disclosed herein.

[0013g] In one aspect, the present disclosure refers to a vector comprising the nucleic acid(s) disclosed herein.

[0013h] In one aspect, the present disclosure refers to a host cell comprising the nucleic acid disclosed herein or the vector disclosed herein.

[0014] The disclosure of PCT Application No. PCT/US2020/044260 is incorporated herein in its entirety.

Brief Description of the Figures

[0015] Fig. 1 is a representation of a co-crystal structure of an Interleukin-1 (IL-1) receptor complex (RCSB PDB file number 3O4O) visualized using PyMol. The co-crystal comprises IL-1Beta, Interleukin-1 receptor type 2 (IL-1R2), and Interleukin-1 receptor accessory protein (IL-1RAP). IL-1R2 and IL-1RAP are depicted in black and light gray cartoons, respectively. IL-1Beta is depicted in medium gray ribbon. Residues of IL-1Beta depicted in spheres are those predicted to be within 4 Angstroms of either IL-1R2 or IL-1RAP.