DIAGNOSTIC METHODS AND COMPOSITIONS FOR TREATMENT OF CANCER

Field of the Invention

[00001] The present invention is directed to methods for identifying patients that will benefit from treatment with a VEGF antagonist, *e.g.*, an anti-VEGF antibody.

Background of the Invention

[00002] Measuring expression levels of biomarkers (*e.g.*, secreted proteins in plasma) can be an effective means to identify patients and patient populations that will respond to specific therapies including, *e.g.*, treatment with VEGF antagonists, such as anti-VEGF antibodies.

[00003] There is a need for effective means for determining which patients will respond to which treatment and for incorporating such determinations into effective treatment regimens for patients with VEGF antagonist therapies, whether used as single agents or combined with other agents.

Summary ~~of the Invention~~

[00004] The present ~~invention~~ disclosure provides methods for identifying patients who will benefit from treatment with a VEGF antagonist, such as an anti-VEGF antibody. These patients are identified based on expression levels of the following genes: DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1).

[00005] ~~The invention~~In one aspect there is provide~~d~~s a method~~s~~ of determining whether a patient is likely to respond to treatment with a VEGF antagonist, the method~~s~~ ~~including~~comprising: (a) detecting expression of at least one of the following genes, DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), in a biological sample obtained from the patient prior to any administration of a VEGF antagonist to the patient; (b) comparing the expression level of the at least one gene to a reference expression level of the at least one gene, wherein a change in the level of expression of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment with a VEGF antagonist; and~~,~~ ~~optionally,~~ (c) informing the patient that they have an increased likelihood of being responsive to treatment with a VEGF antagonist. In some embodiments, the methods can instead optionally

include (c) informing the patient that they do not have an increased likelihood of being responsive to treatment with a VEGF antagonist if, for example, no change in the level of expression of the at least one gene is detected in the patient sample relative to the reference level.

[00006] ~~The invention also~~In one aspect there is provided~~s~~ a method~~s~~ of optimizing therapeutic efficacy of an anti-cancer therapy for a patient, the method~~s~~ ~~including~~comprising: (a) detecting expression of at least one of the following genes, DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), in a biological sample obtained from the patient prior to any administration of a VEGF antagonist to the patient; (b) comparing the expression level of the at least one gene to a reference expression level of the at least one gene, wherein a change in the level of expression of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment with a VEGF antagonist; and~~,~~ ~~optionally,~~ (c) providing a recommendation to the patient that the anti-cancer therapy ~~include~~ comprise a VEGF antagonist. In some embodiments, the methods can instead optionally include (c) providing a recommendation to the patient that the anti-cancer therapy is not a VEGF antagonist if, for example, no change in the level of expression of the at least one gene is detected in the patient sample relative to the reference level.

[00007] In these methods, the patient can be in a population of patients being tested for responsiveness to a VEGF antagonist and the reference level can be the median level of expression of the at least one gene in the population of patients.

[00008] ~~Also included in the invention are~~ In one aspect there is provided a method~~s~~ of monitoring whether a patient who has received at least one dose of a VEGF antagonist will respond to treatment with a VEGF antagonist, the method~~s~~ ~~including~~comprising: (a) detecting expression of at least one of the following genes, DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), in a biological sample obtained from the patient following administration of the at least one dose of a VEGF antagonist; (b) comparing the expression level of the at least one gene to a reference level, which ~~can be~~is the expression level of the at least one gene in a biological sample obtained from the patient prior to administration of the VEGF antagonist to the patient, wherein a change in the expression level of the at least one gene in the sample obtained following administration of the VEGF antagonist relative to the reference level identifies a patient who will respond to treatment with a VEGF antagonist; and~~, optionally,~~ (c) informing the patient that they have an increased likelihood of being responsive to treatment with a VEGF antagonist. In some embodiments, the methods can instead include (c) informing the patient that they may not be

responsive to treatment with a VEGF antagonist if, for example, no change in the level of expression of the at least one gene is detected in the sample obtained following administration of the VEGF antagonist relative to the reference level.

[00009] In the methods described above, the change in level of expression of the at least one gene in the patient sample can be an increase or a decrease relative to the reference level.

[00010] Expression of the at least one gene in the biological sample obtained from the patient can be detected by measuring, for example, mRNA and/or plasma protein levels.

[00011] The biological sample can be, for example, tumor tissue, such as a tumor biopsy, or a blood plasma sample.

[00012] The methods of the ~~invention~~ disclosure can further include detecting expression of at least a second, third, fourth, or further of the genes in a biological sample from the patient.

[00013] The VEGF antagonist can be an anti-VEGF antibody, such as bevacizumab.

[00014] The patient can have an angiogenic disorder. For example, the patient can have a cancer selected from the group consisting of: colorectal cancer, breast cancer, lung cancer, glioblastoma, and combinations thereof.

[00015] The methods described above can further include a step of administering a VEGF antagonist (e.g., an anti-VEGF antibody, such as, for example, bevacizumab) to the patient.

[00016] ~~The invention also includes~~In one aspect there is provided a method~~s~~ for selecting a therapy for a particular patient in a population of patients being considered for therapy, the method~~s~~ ~~including~~comprising: (a) detecting expression of at least one of the following genes, DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), in a biological sample obtained from the patient prior to any administration of a VEGF antagonist to the patient; (b) comparing the expression level of the at least one gene to a reference expression level of the at least one gene, wherein a change in the level of expression of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment with a VEGF antagonist;, and (c) selecting a therapy ~~including~~ comprising a VEGF antagonist if the patient is identified as likely to respond to treatment with a VEGF antagonist and~~, optionally,~~ recommending to the patient the selected therapy ~~including~~ comprising a VEGF antagonist; or (d) selecting a therapy that does not ~~include~~ comprise a VEGF antagonist if the patient is not identified as likely to respond to treatment with a VEGF antagonist and~~, optionally,~~ recommending to the patient the selected therapy that does not ~~include~~ comprise a VEGF antagonist.

[00017] In these methods, the patient can be in a population of patients being tested for responsiveness to a VEGF antagonist and the reference level can be the median level of expression of the at least one gene in the population of patients.

[00018] ~~Also included in the invention are~~In one aspect there is provided a method~~s~~ for selecting a therapy for a patient who has received at least one dose of a VEGF antagonist, the method~~s~~ ~~including~~comprising: (a) detecting expression of at least one of the following genes, DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), in a biological sample obtained from the patient following administration of the VEGF antagonist; (b) comparing the expression level of the at least one gene to a reference level, which is the expression level of the at least one gene in a biological sample obtained from the patient prior to administration of the VEGF antagonist to the patient~~,~~; wherein a change in the level of expression of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment with a VEGF antagonist, and (c) selecting a therapy ~~including~~ comprising a VEGF antagonist if a change in the expression level of the at least one gene is detected in the sample obtained following administration of the VEGF antagonist and~~, optionally,~~ recommending to the patient the selected therapy ~~including~~ comprising a VEGF antagonist; or (d) selecting a therapy that does not ~~include~~ comprise a VEGF antagonist if no change in the expression level of the at least one gene is detected in the sample obtained following administration of the VEGF antagonist and~~, optionally,~~ recommending to the patient the selected therapy that does not ~~include~~ comprise a VEGF antagonist.

[00019] In the two methods described above, the change in level of expression of the at least one gene in the patient sample can be an increase or a decrease relative to the reference level.

[00020] The methods can further include detecting expression of at least a second, third, fourth, or further of the genes in the biological sample from the patient.

[00021] Further, the therapy of (d) can be an agent selected from the group consisting of: an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, a cytotoxic agent, and combinations thereof.

[00022] The methods can further include: (e) administering an effective amount of a VEGF antagonist to the patient if the patient is identified as likely to respond to treatment with a VEGF antagonist. The VEGF antagonist can be an anti-VEGF antibody, such as bevacizumab.

[00023] In addition, the methods can further include administering an effective amount of at least a second agent. For example, the second agent can be selected from the group

consisting of: an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, a cytotoxic agent, and combinations thereof.

[00024] ~~Also included in the invention are~~In one aspect there is provided a method~~s~~ for diagnosing an angiogenic disorder in a patient, the method~~s~~ ~~including~~ comprising the steps of: (a) detecting the expression level of at least one of the following genes, DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), in a sample obtained from the patient prior to any administration of a VEGF antagonist to the patient; and (b) comparing the expression level of the at least one gene or biomarker to a reference level of the at least one gene,~~;~~ wherein a change in the level of expression of the at least one gene in the patient sample relative to the reference level identifies a patient having an angiogenic disorder; and~~, optionally,~~ (c) informing the patient that they have an angiogenic disorder. In some embodiments, the methods can instead include (c) informing the patient that they may not have an angiogenic disorder if, for example, no change in the level of expression of the at least one gene is detected in the patient sample relative to the reference level.

[00025] These diagnostic methods can also include a step of administering a VEGF antagonist to the patient if identified as having an angiogenic disorder. The VEGF antagonist can be, for example, an anti-VEGF antibody, such as, e.g., bevacizumab.

[00025a] In one aspect, there is provided a kit for determining whether a patient may benefit from treatment with a VEGF antagonist, the kit comprising:

(a) polypeptides or polynucleotides capable of determining the expression level of at least one of the following genes: DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1); and

(b) instructions for use of the polypeptides or polynucleotides to determine the expression level of at least one of DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), wherein a change in the level of expression of the at least one gene relative to a reference level indicates that the patient may benefit from treatment with a VEGF antagonist.

[00026] The ~~invention~~ disclosure also features kits for determining whether a patient may benefit from treatment with a VEGF antagonist, the kit including (a) compounds (e.g., polypeptides or polynucleotides (e.g., PCR primers or probes)) capable of determining the expression level of at least one of the following genes: DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and

stromal derived growth factor (SDF1) and, optionally, (b) instructions for use of the polypeptides or polynucleotides to determine the expression level of at least one of DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), wherein a change in the level of expression of the at least one gene relative to a reference level indicates that the patient may benefit from treatment with a VEGF antagonist. In some embodiments, the polypeptides are antibodies.

[00027] These and other embodiments are further described by the detailed description that follows.

13. The method of claim 1, 2, or 3, wherein the VEGF antagonist is an anti-VEGF antibody.

14. The method of claim 13, wherein the anti-VEGF antibody is bevacizumab.

15. The method of claim 1, 2, or 3, wherein the patient has an angiogenic disorder.

16. The method of claim 15, wherein the patient has cancer selected from the group consisting of: colorectal cancer, breast cancer, lung cancer, glioblastoma, and combinations thereof.

17. The method of claim 1, 2, or 3, ~~further comprising administering~~wherein a VEGF antagonist is to be administered to the patient.

18. The method of claim 17, wherein the VEGF antagonist is an anti-VEGF antibody.

19. The method of claim 18, wherein the anti-VEGF antibody is bevacizumab.

20. A method for selecting a therapy for a particular patient in a population of patients being considered for therapy, the method comprising:

(a) detecting expression of at least one of the following genes, DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), in a biological sample obtained from the patient prior to any administration of a VEGF antagonist to the patient;

(b) comparing the expression level of the at least one gene to a reference expression level of the at least one gene, wherein a change in the level of expression of the at least one gene in the patient sample relative to the reference level identifies a patient who is likely to respond to treatment with a VEGF antagonist; and

(c) selecting a therapy comprising a VEGF antagonist if the patient is identified as likely to respond to treatment with a VEGF antagonist and recommending to the patient the selected therapy comprising a VEGF antagonist; or

(d) selecting a therapy that does not comprise a VEGF antagonist if the patient is not identified as likely to respond to treatment with a VEGF antagonist and recommending to the patient the selected therapy that does not comprise a VEGF antagonist.

27. The method of claim 26, further comprising detecting expression of at least a fourth of said genes in the biological sample from the patient.

28. The method of claim 20 or 21, wherein the therapy of (d) is an agent selected from the group consisting of: an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, a cytotoxic agent, and combinations thereof.

29. The method of claim 20 or 21, ~~further comprising~~wherein:

(e) ~~administering~~ an effective amount of a VEGF antagonist is to be administered to the patient if the patient is identified as likely to respond to treatment with a VEGF antagonist.

30. The method of claim 29, wherein the VEGF antagonist is an anti-VEGF antibody.

31. The method of claim 30, wherein the anti-VEGF antibody is bevacizumab.

32. The method of claim 31, ~~further comprising administering~~wherein an effective amount of at least a second agent is to be administered.

33. The method of claim 32, wherein the second agent is selected from the group consisting of: an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, a cytotoxic agent, and combinations thereof.

34. A method for diagnosing an angiogenic disorder in a patient, the method comprising the steps of:

(a) detecting the expression level of at least one of the following genes, DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), in a sample obtained from the patient prior to any administration of a VEGF antagonist to the patient; and

(b) comparing the expression level of the at least one gene or biomarker to a reference level of the at least one gene, wherein a change in the level of expression of the at least one gene in the patient sample relative to the reference level identifies a patient having an angiogenic disorder; and

(c) informing the patient that they have an angiogenic disorder.

35. The method of claim 34, ~~further comprising administering~~wherein a VEGF antagonist is to be administered to the patient if identified as having an angiogenic disorder.

36. The method of claim 35, wherein the VEGF antagonist is an anti-VEGF antibody.

37. The method of claim 36, wherein the anti-VEGF antibody is bevacizumab.

38. A kit for determining whether a patient may benefit from treatment with a VEGF antagonist, the kit comprising:

(a) polypeptides or polynucleotides capable of determining the expression level of at least one of the following genes: DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1); and

(b) instructions for use of the polypeptides or polynucleotides to determine the expression level of at least one of DLL4, angiopoietin 2 (Angpt2), NOS2, Factor V, Factor VIII (AHF), EGFL7, EFNA3, PGF, ANGPTL1, SELP, Cox2, Fibronectin (FN_EIIIB), ESM1, and stromal derived growth factor (SDF1), wherein a change in the level of expression of the at least one gene relative to a reference level indicates that the patient may benefit from treatment with a VEGF antagonist.