METHODS FOR DIAGNOSING AND ASSESSING TREATMENT FOR CUSHING'S SYNDROME

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/163,130, filed on May 18, 2015, the contents of which are hereby incorporated in the entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Glucocorticoids (GCs) are a class of steroid hormones that bind to and activate the glucocorticoid receptor (GR), which is present in almost every vertebrate cell. The GR is pleiotropic and regulates a variety of important pathways in the vertebrate organism, for example, metabolism, immunity, and development. As such, detection of GR activity or regulation can be used to diagnose a variety of different vertebrate diseases, or assess a clinical or biochemical response to treatments that modulate GR activity.

[0003] For example, detection of GR activity or regulation can be used for detection of various forms of Cushing's syndrome. As another example, glucocorticoid receptor antagonists (GRAs) can be administered to a patient to treat a number of different diseases and conditions, and detection of a change in GR activity in response to administration of the GRA can indicate or assess a clinical or biochemical response to the treatment. However, current methods and compositions for assessing GR activity suffer from one or more of the following insufficiencies: high cost, low sensitivity, low specificity, high false positive rate, or high false negative rate. Therefore, there remains a need for improved methods and compositions for detection of GR activity.

BRIEF SUMMARY

[0003a] In one aspect of the present disclosure, there is provided an in vitro method for assessing a biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject suffering from Cushing's syndrome, wherein said GRA is selected from mifepristone and CORT125134, the method comprising:

a) measuring a first or activity of 51 kDa FK506 binding protein (FKBP5 protein) in a first sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring FKBP5 binding activity by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before the GRA is administered to the subject;

b) measuring a second activity of FKBP5 protein in a second sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the GRA is administered to the subject; and

c) comparing the first and second activities,

wherein a reduction in the activity of FKBP5 protein in the second sample by at least 50% as compared to said first activity indicates the biochemical response to the GRA.

[0003b] In yet another aspect of the present disclosure, there is provided an in vitro method for assessing a biochemical response in a human subject to administering to the subject a medical or surgical therapy for treatment of hypercortisolemia, said subject suffering from hypercortisolemia, the method comprising:

a) measuring a first activity of 51 kDa FK506 binding protein (FKBP5 protein) in a first sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring FKBP5 binding activity by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before administering the medical or surgical therapy for treatment of hypercortisolemia to the subject;

b) measuring a second activity of FKBP5 protein in a second sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the medical or surgical therapy for treatment of hypercortisolemia is administered to the subject; and

c) comparing the first and second amounts, activities, or expression levels,

wherein a reduction in the activity of FKBP5 protein in the second sample by at least 50% as compared to said first activity indicates the biochemical response to the medical or surgical therapy for treatment of hypercortisolemia.

[0004] The present disclosure provides a method for assessing a clinical or biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject, the method comprising: a) measuring a first amount, or activity of 51 kDa FK506 binding protein

WHAT IS CLAIMED IS:

1. An in vitro method for assessing a biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject suffering from Cushing's syndrome, wherein said GRA is selected from mifepristone and CORT125134, the method comprising:

a) measuring a first activity of 51 kDa FK506 binding protein (FKBP5 protein) in a first sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring FKBP5 binding activity by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before the GRA is administered to the subject;

b) measuring a second activity of FKBP5 protein in a second sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the GRA is administered to the subject; and

c) comparing the first and second activities, wherein a reduction in the activity of FKBP5 protein in the second sample by at least 50% as compared to said first activity indicates the biochemical response to the GRA.

2. The in vitro method of claim 1, wherein the first sample is obtained prior to administering multiple doses of GRA to the subject, and the second sample is obtained after administering the multiple doses of GRA to the subject.

3. The in vitro method of claim 1 or 2, wherein the GRA administered to the subject comprises mifepristone.

4. The in vitro method of claim 1 or 2, wherein the GRA administered to the subject comprises CORT125134.

5. The in vitro method of any of claims 1 to 4, wherein the first or second samples comprise whole blood, or a fraction thereof, or wherein the first or second samples comprise nasal epithelial scraping samples, or wherein the first and second samples comprise whole blood, or a fraction thereof.

6. The in vitro method of any of claims 1 to 5, wherein the patient a) is in need of administration of the glucocorticoid receptor antagonist (GRA); b) has elevated levels of cortisol; or c) has cancer and the first and second samples comprise tumor cells.

7. The in vitro method of claim 1, wherein the first and second samples comprise whole blood, or a fraction thereof.

8. The in vitro method of any of claims 1 to 7, wherein the method comprises administering an increased amount of GRA to the subject in the absence of a detected reduction in the activity of FKBP5 protein in the second sample.

9. An in vitro method for assessing a biochemical response in a human subject to administering to the subject a medical or surgical therapy for treatment of hypercortisolemia, said subject suffering from hypercortisolemia, the method comprising:

a) measuring a first activity of 51 kDa FK506 binding protein (FKBP5 protein) in a first sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring FKBP5 binding activity by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before administering the medical or surgical therapy for treatment of hypercortisolemia to the subject;

b) measuring a second activity of FKBP5 protein in a second sample obtained from the subject, wherein said measuring consists of measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample or of measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample, and wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the medical or surgical therapy for treatment of hypercortisolemia is administered to the subject; and

c) comparing the first and second amounts, activities, or expression levels,

wherein a reduction in the activity of FKBP5 protein in the second sample by at least 50% as compared to said first activity indicates the biochemical response to the medical or surgical therapy for treatment of hypercortisolemia.

10. The in vitro method of claim 9, wherein the medical or surgical therapy for treatment of hypercortisolemia is selected from the group consisting of: inhibition of steroidogenesis, administration of an ACTH modulator, GRA administration, transsphenoidal surgery, repeat transsphenoidal surgery, unilateral adrenalectomy, bilateral adrenalectomy, radiotherapy, resection of a non-pituitary ACTH-secreting tumor, treatment with a peptide receptor radionuclide therapy, and combinations thereof, wherein the method comprises administering an additional medical or surgical therapy for treatment of hypercortisolemia in an absence of a detected reduction in the amount or activity of FKBP5 protein or reduction in the expression level of the gene encoding FKBP5 protein in the second sample.