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HYPOTHESIS

Biological Diagnosis of Depression: A Biomarker Panel from Several Nonspecial Indicators Instead of the Specific Biomarker(s)

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Abstract: It is a consensus that the diagnosis efficiency of depression is rather low in clinic. The traditional way of diagnosing depression by symptomatology is flawed. Recent years, a growing body of evidence has underlined the importance of physiological indicators in the diagnosis of depression. However, the diagnosis of depression is difficult to be like some common clinical diseases, which have clear physiological indicators. A single physiological index provides limited information to clinicians and is of little help in the diagnosis of depression. Thus, it is more rational and practical to diagnose depression with a biomarker panel, which covers a few non-specific indicators, such as hormones, cytokines, and neurotrophins. This open review suggested that biomarker panel had a bright future in creating a new model of depression diagnosis or at least providing a reference to the existing depression criteria. The viewpoint is also the future of other psychiatric diagnosis.

Keywords: biological diagnosis, biomarker, depression, nonspecial indicator, panel

Introduction

The diagnosis of depression has long been a subject of controversy. According to Diagnostic and Statistical Manual of Mental Disorders (DSM)-5[1] and the International Statistical Classification of Diseases and Related Health Problems (ICD)-11,[2] diagnosis of depressive disorders relies mostly on the evaluation of relatively subjective clinical symptoms, including anhedonia, depressed mood, and altered cognitive function. Depression patients are supposed to meet at least five of nine symptoms during a 2-week period on the basis of DSM-5 criteria. However, obstacles exist when the criteria were applied in clinical practice. On one hand, a recurring problem derives from unavoidably inaccurate assessment of patients' depressive symptoms.[3,4] Therapists cannot always form a uniform medical result when the diagnostic criteria are based on the subjective indicators and clinical experience. Those with mild emotional disorder or regularly low spirits are likely to be diagnosed as major depressive disorder, while those who are seriously ill are able to receive a mild diagnosis.[5] On the other hand, the depression criteria have long been accused of inaccurate for unable to reflect the underlying biology of depression. The disease which we call "major depressive disorder" may actually be a mixture of multiple disorders with individual underlying biological causes that need different treatments.[6] A number of scales are used to estimate the severity of depression, including HAMD, BDI and MADRS. However, differences between self-report and scale scores and multi-dimensionality weighting of individual symptoms may affect the results of measurement.[7] Hence, it is rational to obtain help from objective laboratorial biomarkers when confirming depression diagnosis. Diagnosing mental neuropsychiatry disorders with objective indicators is an international trend and common goal.[8,9]

Biomarkers at a Crossroads

The past decade has seen spectacular progress in neuroscience. A growing body of evidence has shown that multiple biological contributing factors were able to be presumed biomarkers for depression, including HPA (Hypothalamic-

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Pituitary-Adrenal) axis, thyroid function and thyroid autoimmunity, cytokines and inflammatory markers, markers of oxidative stress, neurotrophins, and markers in genetics and genomics.[10–14] However, these putative biomarkers reflect only a few aspects of biological characteristics of depressive patients and sometimes could be inconsistent with current diagnostic criteria or disease severity.[15,16] Though considerable efforts have been made to clarify the pathogenesis of depression, no clear single special biomarker of depression has ever been identified. Meanwhile, both symptoms and biomarker changes are also found as part of other psychiatric diseases. Actually, it is difficult to form a one-to-one correspondence between depressive symptoms and one specific biomarker. The similar symptoms may be attributed to different biomarkers.[17] Furthermore, changes in one biomarker often cause changes in other indicators, and then cause a cascade reaction. It is difficult to indicate which indicator is the most important one. Generally, it still has a long way to go to find a one-size-fit-all biomarker with high sensitivity and specificity.

A Biomarker Panel Instead of a Single or Specific Biomarker

Despite of the fact that considerable progress has been made in searching for convincing diagnostic biomarkers, none of them could be widely accepted in clinical practice.[18,19] Since the utility of a single biomarker to serve as a clinical diagnosis of depression runs into a stone wall, we may rethink if it is rational and practical to diagnose depression with only one specific biomarker. Thus, an idea of developing a biomarker panel just comes to our mind. That is to say, coverage of a few non-specific indicators, such as hormones, cytokines, and neurotrophins, may add a relatively specific diagnosis of depression, or at least provide a reference to the existing depression criteria. Although a single specific biomarker may provide a succinct and clear diagnosis, the predictive ability tends to be increased when several non-specific biomarkers are assembled together.[20] Instead of depending on the result from a single biomarker, an approach to using aggregate score or creating predictive algorithm of several biomarkers would be more applicable. However, one major obstacle is that it still remains dispute about which biomarkers should be involved in the biomarker panel.[21]

Although a variety of biomarkers have already been confirmed to be potential predicators by clinical researches and meta-analysis,[22–24] it is really hard work for us to select eligible ones and integrate all the potential indicators into diagnostic criteria. An alternative approach is to select the most typical biomarkers to profile diverse mechanisms of depression. These most crucial indicators serve as "the headrope" of the overall network according to the "Gang Ju Mu Zhang" hypothesis.[25] That is to say, if we successfully take hold of the key indicators which comprise the headrope, the function of mind may switch to a balanced situation. What we should do next is to find out "the headrope" according to different pathogenesis of depression.

Stumbling Blocks in Selecting Candidate Biomarkers

The idea of a biomarker panel has ever been discussed before. Schmidt et al highlighted the need for a depression biomarker panel to improve the predictive power.[17] A putative biomarker panel based on clinical and pre-clinical data for depression has been proposed by Brand et al.[26] A total of 16 strong markers have been included: reduced gray matter volume, circadian and sleep-wake cycle changes, increased saliva cortisol, hypothalamic–pituitary–adrenal (HPA) axis hyperactivation, thyroid dysfunction, reduced dopamine, 5-hydroxyindoleacetic acid or noradrenaline, increased glutamate, decreased cAMP and MAPK/ERK pathway activity, increased superoxide dismutase and lipid peroxidation, increased pro-inflammatory cytokines, alterations in kynurenine pathway markers, polymorphisms in 5-HT, BDNF, and tryptophan, and abnormal insulin secretion. However, this biomarker panel was just an idea based on previous comprehensive research with unknown sensitivity and specificity. It has not been verified in other studies. Other studies also tried to analyze the blood of depression patients by means of omics to find the biomarker panel.[27,28] Nevertheless, these panels all had limitations and could not be applied on a large scale.

The researches to date have explored multiple biomarkers that are closely associated with depression. However, these abundant potentially useful biomarkers pose a great challenge for us to determine which ones should be included in the panel. The activity of these biomarkers may have the ability of predicting the mental status of depressed individuals, but the evidence is not always consistent. This inconsistent arises from several reasons. Some biomarkers are significantly effective in only a certain group of patients. The present diagnostic criteria, including DSM-V, would lead to a syndrome which is highly heterogenous. Owing to the fact that biomarkers take effect through a variety of ways, some markers are

likely to be epiphenomena of other factors, rather than main factors. Another obstacle on the way to form a biomarker panel is that, owing to different genetic compositions, it is difficult to predict the influence of environmental factors on different individuals' state of minds. Besides, testing the effect of a new biomarker panel require a large sample size of subjects in order to guarantee the reliability and validity.

A Biomarker Panel in the Future

Despite twists and turns on the road ahead, the prospects are bright. As great advances have been made in technology, it is now possible to develop a reliable model. The large-scale use of big data has the possibility to make key breakthroughs in the course of development of a biomarker panel, such as exploring optimal biomarkers, verifying the reliability and validity, and heterogeneity identification.[29] New algorithm analysis will also assist in the application of big data. Li et al proposed two efficient and effective computational methods based on flux analysis and reaction–reaction network approach for the identification of potential metabolic biomarkers.[30] These two methods were helpful to analyze the gene expression data in two pairs of samples in disease/normal state, and then discover the genes that may become potential biomarkers. Imaging and machine learning methodologies have the potential of prompting the development of the biomarkers that are selected by big data.[31]

In addition to technological advancements, we are supposed to commit to create subsets of the panel. The biomarker panel should be a biomarker collection, which contains multiple subsets of different subtypes of depression. Patients are supposed to be diagnosed by the panel and then divided into subsets in the collection according to the report results. The biomarker panel should be conducive to not only the diagnosis of depression but the separation of patients into different subsets. This method is helpful in screening the changed biomarkers and further determine which antidepressants the patients are more sensitive to.

As discussed previously, the accuracy of a new biomarker panel was 80–90% able to distinguish between MDD and control groups.[32] The new technology makes it possible to develop a biomarker panel with such a high accuracy. We suggest creating a panel of biomarkers measured by an aggregate score or predictive algorithm to improve the predictive power of depression, the classification of MDD subtypes, as well as measure treatment response.

Conclusion

Collectively, we need to change our mind and improve the application of biological indicators in the diagnosis of depression. According to current data, a broad panel of biomarkers instead of a single or specific biomarker(s) hold some promise as specific diagnosis indicators of depression. The biomarker panel could include representative markers in inflammatory indicators, neurotrophins, HPA axis et al. Referred to inflammatory indicators, it is concluded that CRP, IL-1, IL-6 and TNFα maybe the biomarkers of the depression according to the reports of our laboratory and others.[33] New technologies, such as big data and algorithm analysis, are supposed to be applied in discovering more potential markers. Despite twists and turns on the road ahead, there is always a bright prospect ahead. The viewpoint is also the future of other psychiatric diagnosis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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