EBioMedicine 68 (2021) 103362

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Circular RNAs as putative biomarkers for depression diagnosis and treatment

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ARTICLE INFO

Article History:
Received 12 April 2021
Accepted 13 April 2021
Available online xxx

Major depressive disorder (MDD) is a prevalent psychiatric disorder associated with significant global burden for individuals, families, and society at large [1]. MDD is frequently chronic and resistant to treatment. Despite the availability of numerous effective treatments, the majority of depressed individuals remain undertreated and treatment outcomes remain unsatisfactory, with insufficient numbers of adequately treated individuals achieving symptomatic remission, and many requiring multiple treatment trials [2]. Clinicians currently have little biologically-based guidance available to aid them in effectively matching depressed individuals with the treatment that is most likely to benefit them, nor is it currently possible to accurately predict the development of depression in those who may be at risk. These issues have led the field to expeditiously identify and evaluate potential biomarkers that may allow for meaningful prediction of disease onset and course, as well as greater precision and targeted treatment approaches for individuals with depression.

Several individual biomarker candidates have emerged in recent years and have shown promising associations with characteristics of depression and prediction of treatment response, but none as yet are routinely utilized as part of clinical care. The symptomatic heterogeneity associated with depressive disorders, coupled with the vast numbers and complexity of associated biologic, neurochemical, and physiologic processes has made progress slow, albeit steady [3]. Thus, the field is still in the very preliminary stages of evaluation of putative biomarker candidates to inform the clinical care of depression, with subsequent investigations needed to establish potential clinical utility, as well as the need for integration of multiple and/or multimodal biomarkers to increase precision.

Circular RNAs, or circRNAs, have increasingly gained attention as promising biomarker targets to inform disease diagnosis and prognosis. CircRNAs are long non-coding RNAs that are closed in a circular formation due to covalent joining of backspliced exons from a single pre-mRNA [4,5]. CircRNAs are involved in a wide variety of biologic functions, including regulation of cell proliferation, direct and indirect regulation of gene transcription, regulation of protein function, and sequestration of microRNA [4–6].

Accumulating evidence supports the use of circRNAs as meaningful biomarkers for cancer diagnosis and prognosis across multiple cancer types [7], as well as for multiple immune-related diseases [4]. Emerging evidence has also implicated potential roles for circRNAs in psychiatric disease, including schizophrenia, bipolar disorder, and MDD [6,8]. CircRNAs have also been associated with cognition and neuroplasticity, and despite having several overlapping functions, circRNAs can be differentiated from linear RNAs by their stability and continuity in involvement with cellular functions, leading to them being informally referred to as "memory molecules" (p. 3, [9]).

The recent publication by Shi and colleagues in *EBioMedicine* [10] examines the potential relevance and suggested eventual clinical utility of circRNAs in the context of diagnosing and treating MDD. The investigators first identified circRNAs that were differentially expressed in depressed individuals compared to healthy controls; as these circRNAs are derived from the FKBP8 and MBNL1 genes, they were referred to as circFKBP8 and circMBNL1. The investigators next confirmed differential expression of the identified circRNAs in a validation sample. Depressed participants in the validation sample then received active or sham repetitive transcranial magnetic stimulation (rTMS) treatment, and those who received 4 weeks of active rTMS had significantly higher levels of circFKBP8 compared to those receiving sham treatment. Furthermore, circFKBP8 was negatively correlated with both self- and clinician-rated depressive symptoms, and positively correlated with serum brain derived neurotrophic factor (BDNF) levels. In addition, both circFKBP8 and circMBNL1 expression was positively correlated with amplitude of low frequency fluctuations (ALFFs) in the right orbital middle frontal gyrus in MDD patients, as assessed by functional magnetic resonance imaging (fMRI).

While there is certainly much additional work to be done with respect to identifying a clear role for circRNAs in diagnosis and treatment of depression, studies such as that presented by Shi et al. [10] highlight important associations observed between circRNAs and depression that warrant further examination. Importantly, the

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103337.
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https://doi.org/10.1016/j.ebiom.2021.103362
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investigators' examination of the relationship between circRNAs, depressive symptoms and treatment response, and associated biomarkers of depression (i.e., serum BDNF levels and neuronal activity as assessed by ALFF), demonstrate the multifaceted approach that is needed to ultimately identify clinically useful biomarkers. The authors appropriately suggest caution in the interpretation of their results and the need for subsequent investigation. This is important given that existing evidence regarding circRNAs potentially involved in MDD and other psychiatric disorders has been inconsistent across studies, and the biologic relevance of these associations is not readily clear.

The complexity and characterization of how circRNAs function and their relevance to psychiatric disorders is still being elucidated. However, comprehensive examination of circRNAs in MDD, such as that provided by Shi and colleagues, demonstrates multi-modal and novel analytic approaches that can advance the field and move us closer to attaining clinically useful biomarkers to guide depression detection and treatment.

Author contribution

Dr. Greer developed, wrote, and edited the manuscript.

Declaration of Competing Interest

Dr. Greer has received research funding from NARSAD and contracted research support from Janssen Research & Development, LLC. She has received honoraria and/or consultant fees from H. Lundbeck A/S and Takeda Pharmaceuticals International, Inc.

Acknowledgements

The author thanks the Center for Depression Research and Clinical Care and University of Texas Southwestern Medical Center Department of Psychiatry for support.

References

[1] Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet (London, England) 2017;390(10100):1211–59.
[2] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163(11):1905–17.
[3] Strawbridge R, Young AH, Cleare AJ. Biomarkers for depression: recent insights, current challenges and future prospects. Neuropsychiatr Dis Treatment 2017;13:1245–62.
[4] Xie R, Zhang Y, Zhang J, Li J, Zhou X. The role of circular RNAs in immune-related diseases. Front Immunol 2020;11:545.
[5] Yu CY, Kuo HC. The emerging roles and functions of circular RNAs and their generation. J Biomed Sci 2019;26(1):29.
[6] Gan H, Lei Y, Yuan N, Tang K, Hao W, Ma Q, et al. Circular RNAs in depression: biogenesis, function, expression, and therapeutic potential. Biomed Pharmacother 2021;137:111244.
[7] Wang M, Xie F, Lin J, Zhao Y, Zhang Q, Liao Z, et al. Diagnostic and prognostic value of circulating CircRNAs in cancer. Front Med 2021;8:649383.
[8] Zimmerman AJ, Hafez AK, Amoah SK, Rodriguez BA, Dell'Orco M, Lozano E, et al. A psychiatric disease-related circular RNA controls synaptic gene expression and cognition. Mol Psychiatry 2020;25(11):2712–27.
[9] Zajaczkowski EL, Bredy TW. Circular RNAs in the brain: a possible role in memory? Neurosci: Rev J Bring Neurobiol, Neurol Psychiatry 2020:1073858420963028.
[10] Shi Y SR, Wang Z, Zhang H, Zhu J, Yue Y, Zhao Y, Zhang Z. Potential clinical value of circular RNAs as peripheral biomarkers for the diagnosis and treatment of major depressive disorder. EBioMedicine 2021 doi:10.1016/j.ebiom.2021.103337.