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ACTA PSYCHOPATHOLOGICA

An Integrated systems biology approach identifies causal pathways and neuronal subtypes associated with phasic changes in major depressive disorder

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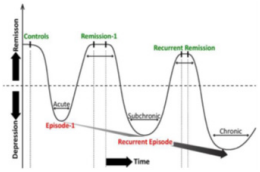
Abstract

Statement of the problem: MDD is characterized by heterogeneous symptoms, including low mood, anhedonia and cognitive impairments. The course of the disease often follows a periodic trajectory (Fig1), which includes recurrent episodes of increasing severity, duration, and progressive resistance to antidepressants, separated by gradually shortening partial or full remission phases, often leading to chronic and treatment-resistance depression with deteriorating functional fitness. Notably, studies so far have majorly focused on the differences between control and MDD subjects. Molecular changes in different phases of the MDD largely remains unknown. Methodology & theoretical orientation: To address this issue we performed RNAseq of 90 post-mortem subgenual anterior cingulate cortex tissue samples obtained from one control (n=20) and four MDD cohorts in 1) first episode of depression (n=20); 2) remission state after first episode (n=15); 3) recurrent stages of depressive episode (n=20) and 4) remission stages after recurrent episodes (n=15). Integrating with the available single cell RNAseq and drug based transcriptomic profile using machine learning and network biology approaches we looked for cell specific molecular changes, causal biological pathways, and drug molecules and their targets involved in MDD. Findings: Genes and biological pathways associated with the different phases of MDD and their cellular correlates were first characterized. A subset of CRH, VIP and SST positive interneuron neuron showed significant association with the disease trajectory (p-value<3x10-3). Using causal probabilistic Bayesian network, we then showed that MDD is associated with biological changes that include immune system process (FDR<8.67x10-3), cytokine response (FDR<4.79x10-27), and oxidative stress components (FDR<2.05x10-3). Drugs and their associated target proteins which replicates or reverses the expression profiles of the causal pathways were mostly those with antidepressant and antipsychotic properties. Conclusion & Significance: These findings support established clinical evidence of MDD at a molecular level and outlines a novel method of drug discovery by targeting disease-causing pathways.



Biography

Shukla with his expertise both in experimental and computational biology is interested in understanding the causal links to different psychiatric illnesses and developing a unified theory explaining the similarities and differences between them. His research interests are shaped by 1) models (both theoretical and animal) explaining the disease mechanisms 2) cellular micro-circuitry changes in psychiatric disorders 3) bio-statistical and machine learning approaches and 4) drug-discovery and repositioning advances for a translational output. Over the past ten years, his research agenda focuses on leveraging these approaches for a better understanding of psychiatric disorders. Dr Shukla did his PhD from National institute for Basic biology, Japan (2009-14) and postdoctoral training from the University of Toronto, Canada (2014-19). Starting June 2019, he joined as Assistant Professor at the University of Toledo, USA.

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Citation: Rammohan Shukla, An Integrated systems biology approach identifies causal pathways and neuronal subtypes associated with phasic changes in major depressive disorder, Neuroimmunology 2020, Paris, February 19-20, 2020, PP. 33

Acta Psychopathologica 2020
ISSN:2469-6676