Center for Therapeutic Innovation and Department of Psychiatry and Behavioral Sciences, University of Miami, Miami FL 33136, USA. cwahlestedt@med.miami.edu

Abstract

This lecture will primarily be concerned with long noncoding natural antisense RNAs which regulate gene expression through several distinct mechanisms including modulation of chromatin regulator protein complexes. Notably, inhibition/perturbation of endogenous natural antisense transcripts by AntagoNATs, *in vitro* (1) or *in vivo* (2), often reveals discordant regulation and results in locus specific up-regulation of conventional (protein-coding) gene expression.

References

1. Katayama S, … and Wahlestedt C. Antisense transcription in the mammalian transcriptome. *Science* 309:1564–1566, 2005.
2. Modarresi F, Faghihi MA, Lopez-Toledano MA, Fatemi RP, Magistri M, Brothers SP, van der Brug MP and Wahlestedt C. Natural antisense inhibition results in transcriptional de-repression and gene up-regulation. *Nature Biotechnology*, 25;30:453–9, 2012.
3. Wahlestedt C. Targeting noncoding RNA to therapeutically up-regulate gene expression. *Nature Reviews Drug Discovery* 12:433–46, 2013.
4. Yamanaka Y, Faghihi MA, Magistri M, Alvarez-Garcia O, Lotz M, Wahlestedt C. Antisense RNA controls sense transcript expression through interaction with a chromatin-associated protein, HMGB2. *Cell Rep*, 11:967–976, 2015.

Speaker 3: Iiris Hovatta, Finland

Title: Gene-environment interaction in microRNA expression of a mouse model for anxiety and depression

Gene-environment interaction in microRNA expression of a mouse model for anxiety and depression

Kalevi Trontti, Ingrid Balcells, Ewa Sokolowska, Iiris Hovatta
Department of Biosciences, University of Helsinki, Finland

Abstract

MicroRNAs (miRNAs) are small non-coding RNAs that function in the post-transcriptional regulation of gene expression. A single miRNA can target hundreds of genes, often within the same biological pathway. miRNAs have been suggested as putative drug targets as by manipulating the levels of a single miRNA it may be possible to affect the expression levels of hundreds of target genes within the same biological pathway. The role of individual miRNAs in various neurobiological functions, such as development of the nervous system, synaptic plasticity, and neurodegeneration has recently been revealed. Also, specific miRNAs have been associated with psychiatric phenotypes, including human anxiety disorders [1, 2]. Psychosocial stress is an important environmental risk factor for anxiety disorders and major depression. We have investigated the effect of genetic background on brain gene and miRNA expression profiles after psychosocial stress. We used chronic social defeat paradigm to induce anxiety and depression-like behavior in two inbred mouse strains, C57BL/6 and DBA/2. Based on the social preference test conducted after social defeat, we divided the mice into stress susceptible and resilient groups. Of the C57BL/6 mice 61.5 % and of the DBA/2 mice 11.8 % were resilient to stress. To investigate how genetic background affects the transcriptomic response to stress, we carried out miRNA-seq [3] and RNA-seq in ventral hippocampus and medial prefrontal cortex of the stress susceptible, resilient and control mice of the two strains. In C57BL6/J mice, we found 10 and 0 miRNAs being differentially expressed (nominal p<0.01, FC>1.5 or <-1.5) in control vs. susceptible and control vs. resilient animals, respectively. In DBA/2J mice, 7 and 4 miRNAs were differentially expressed in control vs. susceptible and control vs. resilient mice, respectively. We next carried out bioinformatic target predictions for these miRNAs using TargetScan [4] to identify their putative target mRNAs. We analyzed these target genes in the Ingenuity Pathway Analysis system to identify biological pathways the miRNAs and genes are involved in. Interestingly, the pathways we identified were mostly different in the two strains. In conclusion, our data suggest that genetic background influences the susceptibility and resiliency to chronic stress on the behavioral level. Furthermore, it has a large effect on the brain transcriptomic response to stress as most of the miRNAs that were differentially expressed due to stress were different in the two strains and were predicted to target a different set of genes and biological pathways.

References

1. Issler O, Chen A. Determining the role of microRNAs in psychiatric disorders. Nat Rev Neurosci. 2015 Apr;16(4):201–12.
2. Muiños-Gimeno M, Espinosa-Parrilla Y, Guidi M, Kagerbauer B, Sipilä T, Maron E, Pettai K, Kananen L, Navinés R, Martín-Santos R, Gratacòs M, Metspalu A, Hovatta I, Estivill X. Human microRNAs miR-22, miR-138-2, miR-148a, and miR-488 are associated with panic disorder and regulate several anxiety candidate genes and related pathways. Biol Psychiatry. 2011 Mar 15;69(6):526–33.
3. Juhila J, Sipilä T, Icay K, Nicorici D, Ellonen P, Kallio A, Korpelainen E, Greco D, Hovatta I. MicroRNA expression profiling reveals miRNA families regulating specific biological pathways in mouse frontal cortex and hippocampus. PLoS One. 2011;6(6):e21495.
4. Agarwal V, Bell GW, Nam JW, Bartel DP. Predicting effective microRNA target sites in mammalian mRNAs. Elife. 2015 Aug 12;4.

Speaker 4: Gustavo Turecki, Canada

Title: Regulation of aggressive and impulsive behaviours by a novel lincRNA

Labonté B[1,2], Maussion G[1], Yerko V[1], Yang J[1], Golden SA[2], Suderman M[3], Navarro L[4], Checknita D[1], Gigek C[1], Lopez JP[1], Neve RL[5], Russo SJ[2], Côté G[6], Meaney MJ[1,7], Mechawar N[1], Nestler EJ[2], *Turecki G*[1]
[1]McGill Group for Suicide Studies, Department of Psychiatry, McGill University, Montreal, Quebec, Canada [2]Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA. [3] School of Social and Community Medicine, University of Bristol, Bristol, UK. [4]Unitat de Genètica Molecular Institut de Biomedicina de València, Valencia, Spain. [5]Department of Brain and Cognitive Science, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. [6]Philippe-Pinel Institute of Montreal, University of Montreal [7]Department of Pharmacology, McGill University, Montreal, Quebec, Canada. [7]Ludmer Centre for Neuroinformatics and Mental Health, McGill University, Montreal, Quebec, Canada.

Abstract

High impulsive and aggressive traits associate with poor behavioural self-control and are important predictors of suicide risk. At present, the regulation of these disruptive behavioural traits is poorly understood. Here, we studied the hippocampus of suicides with high impulsive-aggressive traits and identified and characterized a novel long intergenic non-coding RNA (lincRNA), which we called MAOA-Associated lincRNA (MAALIN),

due to its ability to regulate the expression of the monoamine oxidase A (MAOA) gene. Using 3 different human cohorts combining brain tissue, neurons and blood samples, we reported consistent hypomethylation in MAALIN's promoter across tissues. In suicide brains, MAALIN's promoter hypomethylation was associated with higher MAALIN and lower MAOA expression. MAALIN's methylation levels were also inversely correlated with measures of impulsivity and aggression behaviors in humans. Luciferase assays confirmed the regulatory role of DNA methylation on MAALIN's expression. Finally, we used viral mediated gene transfer in mouse brain and showed that MAALIN regulates several indices of aggressive and impulsive behaviours. In conclusion, our findings suggest that changes in DNA methylation patterns allows the expression of a novel lincRNA which, the brain, modulates impulsive and aggression behaviors by interfering with MAOA expression.

S8: Novel approaches to the identification of biomarkers for psychiatric disorders

Chair: Elizabeth Scarr, Australia
Co-Chair: Seunghee Won, Republic of Korea

Speaker 1: Elizabeth Scarr, Australia

Title: Identifying markers for the schizophrenia syndrome

Elizabeth Scarr & Brian Dean
University of Melbourne & Florey Institute of Neuroscience and Mental Health

Abstract

Psychiatry is one of the few areas of medicine that does not have an array of diagnostic tests at its disposal. Part of the reason for this deficit is the complexity of the disorders being dealt with; therefore diagnosis, treatment and recovery management all depend heavily on the knowledge and experience of the treating clinician. In order to support this expertise, a great deal of effort is being invested in the quest for biomarkers for different aspects of the disorders such as diagnosis, stratification for treatment and assessing treatment responsivity.

Over the decades, countless studies have assessed the levels of gene expression in the form of messenger RNA levels in samples from people with psychiatric disorders, particularly schizophrenia. However, until recently (1), few investigators have attempted to assess the potential of this data for use as biomarkers.

Our recent microarray study, using post-mortem brain tissue from people with schizophrenia and people with no history of psychiatric illness was analysed using a range of predictive models. At the first level the modelling was used to distinguish samples from people with schizophrenia from the control group. A series of 100 markers was identified that achieved this goal with an overall accuracy of up to 1.0. The validity of these markers has been assessed in two separate cohorts of samples from people with schizophrenia and control subjects. The second level of analysis was to determine whether a similar approach could be used to separate the subjects with schizophrenia into two distinct subgroups – one with low levels of muscarinic M1 receptors and the other with levels of muscarinic M1 receptors similar to those seen in control subjects. A battery of 97 markers achieved this with an overall accuracy of up to 1.0.

The uses of these potential biomarkers are quite different. The first will be of most use in people who are in the prodromal phase of the disorder – facilitating their rapid identification and subsequent therapeutic program. The second set of markers will be useful for the stratification of people, initially for clinical trials of the selective M1 ligands that are currently in development and, once these drugs are available, for the identification of people who will most benefit from such targeted therapy.

Reference

(1) Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T, et al. Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. Mol Psychiatry 2013 Feb;18(2):206–14.

Speaker 2: Kotaro Hattori, Japan

Title: Altered protein patterns in cerebrospinal fluid of psychiatric disorders

Kotaro Hattori[1,2], Miho Ota[1], Hiroshi Kunugi[1]
[1]Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Japan [2]Medical Genome Center, National Center of Neurology and Psychiatry, Japan

Abstract

Cerebrospinal fluid (CSF) is derived from the brain tissue as well as the choroid plexus, and is in continuity with the brain interstitial fluid. Molecules released from brain cells can directly diffuse into the CSF. There are established CSF biomarkers for brain disorders. For example, tau, phosphorylated tau, and Abeta42 levels in CSF are useful biomarkers in the diagnosis of Alzheimer's disease, although levels of these molecules in peripheral blood are not of clinical use. To explore such biomarkers in psychiatric disorders, we have been collecting CSF samples from patients with schizophrenia, major depressive disorder (MDD), bipolar disorder, and normal controls. We have thus far collected more than 700 samples for research. To develop a biomarker for the psychiatric disorders, we have performed both targeted and untargeted approaches on the CSF samples. For the untargeted approach, we conducted an aptamer-based proteomics analyses which measured 1129 proteins with high accuracy in a selected sample of 30 patients with schizophrenia, 30 with MDD, 16 with bipolar disorder and 30 controls, matched for age and sex. One of the top candidate proteins for MDD in the analyses was fibrinogen. An approximately one fourth of the MDD patients had an excessively high level of CSF fibrinogen. By using fibrinogen ELISA, we obtained similar results in an independent sample set consist of 36 MDD and 30 controls. We then confirmed the high fibrinogen patients in a total of 384 subjects. We also found that fibrinogen levels reduced after electroconvulsive therapy. When MRI brain imaging data were combined, the diffusion tensor imaging analysis revealed white matter tract abnormalities in the patients with a high fibrinogen level but not in the patients with a normal fibrinogen level or in the control subjects. Our results point to a subgroup of MDD represented by increased CSF fibrinogen and white matter tract abnormalities. Omics approaches on CSF samples may be a promising strategy to elucidate biomarkers and brain pathophysiology of psychiatric diseases. The omics database we are creating would also be useful for a number of neurological diseases.

References

Hattori et al., Increased cerebrospinal fluid fibrinogen in major depressive disorder, Sci Rep. 5:11412, 2015

Ogawa et al., Reduced cerebrospinal fluid ethanolamine concentration in major depressive disorder. Sci Rep. 5:7796, 2015