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each miRNA can target hundreds of genes, often within the same
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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 prefer-
ence 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/ mice, we found 10 and 0 miRNAs being differentially
expressed (nominal p<0.01, FC>1.5 or <-1.5) in control vs. sus-
ceptible and control vs. resilient animals, respectively. In DBA/2
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 sug-
gest 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 pre-
dicted to target a different set of genes and biological pathways.

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Speaker 4: Gustavo Turecki, Canada
Title: Regulation of aggressive and impulsive
behaviours by a novel lincRNA
Regulation of aggressive and impulsive
behaviours by a novel lincRNA
Kalevi Trontti, Ingrid Balcells, Ewa Sokolowska, Iiris Hovatta
Department of Biosciences, University of Helsinki, Finland
Abstract
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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 responsibility.

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.

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Speaker 2: Kotaro Hattori, Japan
Title: Altered protein patterns in cerebrospinal fluid of psychiatric disorders
Kotaro Hattori1, Miho Ota1, Hiroshi Kunugi1
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2Medical 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.

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