PL.04. Plenary lecture

PL.04.01 Epigenetics as a potential mechanism for intervention

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The traditional aetiological strategy to understanding the causes of psychiatric disease, such as schizophrenia, bipolar disorder and major depression, has focussed on the interplay between genetic (DNA) and environmental factors. There are, however, numerous epidemiological, clinical, and molecular peculiarities associated with complex behavioural phenotypes that are hard to explain using traditional DNA- and environment-based approaches. For example, discordance between monozygotic twins, late age of onset, sexual dimorphism, parental-origin effects, and significant fluctuation of disease course suggest that epigenetic factors may also play a role in disease aetiology [1]. In addition to uncovering the primary mechanisms of psychiatric disease, epigenetics may offer new treatment approaches. In our laboratory we perform large scale epigenome-wide DNA modification studies in major psychiatric disease. We collected evidence that detection of epimutations can be confounded by epigenetic heterogeneity, large but uncommon epimutations, tissue- and cell-specific effects, epigenetic outliers, DNA sequence impact on epigenetic variation, age effects (heteroscedasticity), and the presence of small epigenetic differences over extended genomics regions. We explored new analytical avenues and report findings by employing tools that have not been previously applied to psychiatric epigenomic studies, including several types of methylome networks, which may uncover systemic epigenomic changes in the diseased cell. We performed a series of studies differentiating the main types of DNA modification, and detected that such differentiation may be critical for the discovery of the molecular mechanisms of synaptogenesis and alternative splicing and their role in psychiatric disease [2]. Finally, in collaboration with the Structural Genomics Consortium (Toronto), we have launched testing of small molecules that modulate histone modification – controlling proteins for their psychotropic and therapeutic potential.

References

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PL.05. Plenary lecture

PL.05.01 Role of GABA neurons in schizophrenia

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Schizophrenia (SZ) involves the ingrowth of amygdala fibers during the equivalent of late adolescence when they form contacts with GABAergic interneurons within the trisynaptic pathway [1]. The expression of GAD_{67} by interneurons located in stratum oriens of sectors CA3/2 involves a complex network of genes that control their functional integrity, possibly through kainate receptors [2]. In SZ, abnormalities of the GAD_{67} system probably contribute to the inability of hippocampal GABA cells to provide appropriate modulation of trisynaptic circuitry. Rodent modeling for these postmortem findings suggests that there may be two functionally different types of interneurons involved: an ***inhibitory*** type that suppresses the activity of excitatory pyramidal neurons and a ***disinhibitory*** type that inhibits the latter via GABA-to-GABA interactions. The amygdala projections to both seem to require GluR6 and 7 subunits [3]; but, a pre-synaptic action on GABA cell activity at the stratum oriens-CA3/2 locus through a GluR5 subunit influence involving axo-axonic contacts also exists. When disturbances in these connections occur, they may not only affect the regulation of GAD_{67}, but also the functional integrity of interneurons at this locus. By using sophisticated molecular approaches to manipulate the regulation of genes found to be abnormal in GABA cells, it may be possible to return the set-point of GAD_{67} expression to normal and re-establish the appropriate activation of the trisynaptic path in patients with schizophrenia and other psychotic disorders.

References

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