INTEGRATING 'OMICS' APPROACHES TO PRIORITISE NEW PATHOGENETIC MECHANISMS FOR MENTAL DISORDERS

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Neuropsychopharmacology research is between a rock and a hard place. The rock is the historical, but slow, hypothesis-driven approach, where discovery occurs by testing candidate mechanisms in already well-known biological models. The hard place is the innovative, but overwhelming, hypothesis-free approach, where 'omics' analyses of everything that is analysable generates a deluge of data implicating hitherto unknown mechanisms. So, either we have little data on things we already know, or too much data and cannot find the needle in a haystack. One solution is to mix apples and oranges: integrating cross-species and cross-tissues 'omics' data to find mechanisms that recur across different experimental and clinical models. The idea has been used with remarkable success. And yes, we will finish with the proverbs now.

Niculescu et al. (2000) first developed and used such an approach, which they called Convergent Functional Genomics. More recently, the approach has been used by them to help prioritize genes from GWAS of bipolar disorder (Patel et al. 2010), integrating GWAS findings, transcriptomics data on postmortem human brain and blood, and studies in animal models, in order to identify top-genes supported by all approaches. They identified six genes (ARNTL, MBP, BDNF, NRG1, RORB and DISC1) which are involved in relevant biological processes, such as circadian rhythm, connectivity and neuroplasticity. They used a similar strategy for schizophrenia (Ayalew et al., 2012). Interestingly, this strategy could be done with publically available data rather than being based on novel experimental findings.

In 2013, we studied transcriptomics data from the hippocampus of adult prenatally stressed rats (an established animal model of depression with high glucocorticoid levels) and from a human neuronal stem cell line (that we treated with a concentration of cortisol that reduces neurogenesis) (Anacker et al., 2013). We found that TGFβ-SMAD2/3 and Hedgehog signaling are reduced in both models: TGFβ-SMAD2/3 promotes neurogenesis (and has been found to be reduced in depressed patients), while Hedgehog promotes neuronal differentiation (and has not been studied in depressed patients yet). Similarly, Malki et al. (2016) studied transcriptomics from the prefrontal cortex of mice bred for high aggressive behavior and from the brain of zebrafish exposed to aggressive social encounters. They identified seven genes shared in both datasets, including HDAC4, which has genetic variants associated with aggressive behavior in mental retardation, and it is targeted by valproic acid, a pharmacological treatment for aggressive behavior. Finally, Luoni

et al. (2016) studied methylome analyses performed in multiple models of early life stress: rats exposed to prenatal stress (prefrontal cortex); human newborns exposed to stress in pregnancy (cells from the umbilical cord); and rhesus monkeys exposed to stressful rearing conditions (peripheral blood and prefrontal cortex). Their top gene was Ank3, a gene with a strong association for psychiatric disorders; and they also demonstrated an interaction between functional genetic variants within Ank3 gene and obstetric complications on working memory in humans. While these studies are predominantly 'comparative' in their nature, this cross-species and cross-tissues approach can be used to produce 'integrative' findings when it generates novel lists of overlapping or functionally-related genes through statistical or bioinformatic analysis.

With the collapse of R&D in mental health by pharmaceutical companies, convergent/integrative 'omics' approach represents a unique opportunity for the scientific community to mine existing datasets as well as data from experimental and clinical models, in order to prioritise targets for the psychotropic medications of the future.

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