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Cristina A. Ghiani, *University of California Los Angeles*
[Victor Faundez](#), *Emory University*

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Cellular and Molecular Mechanisms of Neurodevelopmental Disorders

Cristina A Ghiani^{1,#} and Victor Faundez²

¹Departments of Pathology & Laboratory Medicine and Psychiatry & Biobehavioral Sciences, Intellectual and Developmental Disabilities Research Center, University of California Los Angeles, Los Angeles, California 90095, USA

²Department of Cell Biology and the Center for Social Translational Neuroscience, Emory University, Atlanta, GA 30322, USA

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Neurodevelopmental disorders are a group of affections whose onset and clinical expression occur during infancy/childhood or adolescence, and for which disease mechanisms are still largely a mystery. These disorders include autism and schizophrenia spectrum disorders, intellectual disability, and attention deficit hyperactivity disorder. Some of them are the focus of this issue. Neurodevelopmental disorders have a strong genetic basis, but causal environmental factors have also been identified. These predisposition factors may interact during brain developmental vulnerability windows to cause disease in ways that are not clearly understood yet (Maynard et al., 2001; Rappoport et al., 2012; Farrell et al., 2015; Charman and Chakrabarti 2016; Davis et al., 2016).

Brain development is a continuous highly regulated process with pre- and postnatal windows of high vulnerability (Marco et al., 2011; Silbereis et al., 2016). Hence, a limited insult during one of these windows may alter the trajectory of brain development in individuals with susceptible genomes causing subtle abnormalities and conferring a predisposition to develop, for example, schizophrenia spectrum disorders in late adolescence/young adulthood (Maynard et al., 2001; Fatemi and Folsom, 2009; Rappoport et al., 2012; Piper et al., 2012; Davis et al., 2016). These windows of susceptibility may explain why neurodevelopmental disorders sometimes have overlapping clinical features, commonly co-occur, and why the same mutation may end up associated with different mental illnesses. In fact, most neurodevelopmental disorders do not have a *Bona Fide* gene (Chisholm et al., 2015; Farrell et al., 2015; O'Donovan and Owen, 2016).

#Address correspondence to: Cristina A Ghiani, Department of Pathology & Laboratory Medicine, UCLA, NRB Ste 260, 635 Charles E Young Dr Sth, Los Angeles, CA 90095, USA, Phone: (310)7944960, Cghiani@mednet.ucla.edu.

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The complexity of these affections often leaves physicians fumbling in the dark when diagnosing cases that do not fit precisely into categorical diagnoses. At the same time, spotty knowledge about disease mechanisms hinders and slows down the development of better targeted therapeutic molecules or interventions. Even though our cellular and molecular understanding of neurodevelopmental disorder pathogenesis is still incomplete, we believe that the recent advancements in genomics, patient-derived neuronal cultures, and novel mouse genetic models have positioned the field at the cusp of revolutionary developments in diagnosis and treatment. We sought to assemble an ‘In Focus’ issue to present the foundations for this optimistic view of the future. This issue covers some of the work done and in progress on neurodevelopmental disorders, their aetiology, underlying mechanisms, and potential therapeutics.

The biological plausibility of some experimental models might be questionable or has not been fully explored, however, several reproduce brain morphological abnormalities and the associated behavioural and cognitive deficits described in affected individuals. Thus, *in vitro*, *ex vivo* and *in vivo* models made possible to study discrete aspects of the pathophysiological mechanisms underlying developmental neuropsychiatric disorders, otherwise, limited to post-mortem samples obtained after years of disease and treatments. Albeit, animal models have proven valuable to examine the consequence of aberrant expression of specific genes associated with neurodevelopmental disorders, still no single model completely recapitulates human disease presentation. Hence, the usage of more than one model is a necessity.

At present, human Induced Pluripotent Stem Cells (hiPSCs) derived from individuals with specific mental illnesses are regarded as highly promising to study the aetiopathophysiology of neurodevelopmental disorders. As reviewed by Dr Zhexing Wen (this issue, 2017), hiPSCs represent a big step forward in comparison to classical *in vitro* models, and offer a highly controlled method not only to study disease mechanism(s), but to also test potential new drug treatments, which are in critical need. hiPSCs can be differentiated into different neuronal cell populations relevant to a specific disease, and should faithfully recapitulate human pathology, furthering our knowledge on specific cellular and molecular defects, a great aid to concurrent preclinical animal studies, human genetic and imaging studies. Even though hiPSCs and derived organoids still present several limitations, these systems are the best window to access neural tissue from diseased patients for experimentation. Now we are not limited to post-mortem brain samples, thus removing a major obstacle to the study of disease mechanism(s) and the development of effective therapeutic and diagnostic strategies. Nevertheless, hiPSCs will not substitute either preclinical studies or animal models for studying disease mechanism(s) as the behavioural essence of mental illness is out of reach for *ex vivo* experimental systems. Among the limitations to still be overcome are lack of cell type homogeneity, and even when assembled tridimensionally, it is not yet possible to study neural circuits and brain areas connectivity (Ebert et al., 2012; Young-Pearse and Morrow, 2016). Besides, studying the cytoarchitectural abnormalities in the available animal models may also provide important information on critical processes occurring during proper brain development.

The effects of stressors and insults during periods of high vulnerability of brain development have been broadly studied (Marco et al., 2011). Among the insults known to impact this finely tuned process, leading to life-long cognitive and behavioural deficits, are modifications of the “*in utero*” environment, for instance maternal infections and the consequent rise in pro-inflammatory cytokines (Fatemi and Folsom, 2009; Meyer and Feldon, 2010; Harvey and Boksa, 2012). Several animal models have been developed to investigate the link(s) between the increase in pro-inflammatory cytokines in foetuses and the cellular and molecular alterations in their brain, which result in cognitive and behavioural deficits in young adults (Meyer et al., 2009). In line with this hypothesis, Fatemi and colleagues (this issue, 2017) discuss their and others’ work on the effects of a viral infection during pregnancy on brain development, quite a timely topic. The model developed by this group analyses the postnatal effects of an injection of the human influenza virus H1N1 at embryonic day 16, corresponding to about second trimester of gestation in human, on the expression levels of the products of genes linked to autism and schizophrenia spectrum disorders. Interestingly, they show that the pathways of genes such as Reelin and Fragile X mental retardation protein (FMRP), are altered also in the cerebellum of the offspring at different postnatal ages, suggesting that the complex phenotype observed in these patients might be due to more than one dysfunctional brain region and disorganised communication among brain areas, i.e. common defective brain circuits (Sahin and Sur, 2015).

The onset of a number of neurodevelopmental disorders is during adolescence, another critical period for brain development when synaptic pruning and maturation occur in the cerebral cortex. The adolescent brain is a fascinating puzzle highly vulnerable to stressors that can trigger the emergence of psychiatric dysfunctions in genetically predisposed individuals (Guyer et al., 2016; Tottenham and Galvan, 2016). Gourley and colleagues (this issue, 2017) provide evidence that different parts of the prefrontal cortex undergo structural refinements at specific times. Dendritic and synaptic pruning and remodelling take place earlier in the excitatory neurons of the deep layers of the medial prefrontal cortex than in the orbital prefrontal regions. Furthermore, the expression levels of key cytoskeleton regulatory factors vary between the medial and orbital prefrontal cortex throughout adolescence, but such difference is lost by young adulthood. These modifications in synaptic architecture in the prefrontal cortex are skewed by drugs of abuse, opening the door to understand how environmental factors and genomes interact at a specified critical developmental window when adult behaviours are set (DePoy and Gourley, 2015).

As mentioned above, a *Bona Fide* gene or genetic defect for a specific neurodevelopmental disorder is still to be identified. Emerging evidence strongly suggests that these are “non-single” gene diseases, some of which share risk factors with other pathologies (Crawley et al., 2016; Farrell et al., 2015; O’Donovan and Owen, 2016). Among the genetic aberrations considered the strongest risk factors for schizophrenia spectrum disorders and other developmental neuropsychiatric disorders are copy number variants (CNVs; Joobar and Boksa, 2009; Rappoport et al., 2012; Torres et al., 2016). Because of their size, CNVs affect the function(s) of multiple genes. Mulle and colleagues (this issue, 2017) discuss how these multiple aberrations make it difficult to study the mechanism(s) underlying the behavioural and cognitive deficits, as each gene may contribute to one phenotype or more. This complex

interplay makes extremely complicated to treat these individuals, especially their cognitive deficits, the hardest to be treated. Hence, it is critical to unravel mechanisms elicited by hemideficiencies spanning multiple genes to develop better interventions. This complex mutation is further compounded since single CNVs confer risk for more than one neurodevelopmental disease. For instance, Mulle and colleagues (this issue, 2017) discuss the recently identified 3q29 microdeletion, which has been linked to increased risk to develop bipolar disorders, autism and schizophrenia spectrum disorders. This suggests that loci outside the 3q29 microdeletion may modify its phenotypic outcomes. Alternatively, microdeletions may underscore common mechanisms of disease spanning multiple mental affections. In aid, new technologies, such as CRISPR-Cas9-dependent genome editing, are now providing tools to dissect and, thus, study the effects of a single CNV in human isogenic cells.

Development of effective drug therapies has been quite slow, and made difficult by co-occurrence of disorders such as schizophrenia and autism spectrum disorders, and by our limited understanding of why these diseases co-occur (Chilshom et al., 2015). Many signalling pathways and mechanisms have been explored in search for new drugs, mostly based on genetic associations. Gross and colleagues (this issue, 2017) review evidence for an involvement of faulty phosphoinositide metabolism in autism spectrum disorders and other neurodevelopmental syndromes. Mutations in the enzymes involved in the metabolism of these crucial components of the plasma membrane, such as the phosphoinositide-3-phosphatase PTEN, have been associated with certain forms of autism. Targeting these pathways has been shown to be effective in certain forms of cancer, opening the door to the opportunity of exploring and developing new interventions for autism spectrum disorders as well.

In line with using models and drugs available, as well as knowledge from other diseases to develop better treatment for developmental neuropsychiatric disorders is the paper by Lavin and colleagues (this issue, 2017). The authors report improvement of cognitive functions and memory by using the sphingolipid Fingolimod in a well-studied mouse model lacking the dysbindin-containing complex Biogenesis of lysosome-organelle complex-1 (BLOC-1). Dysbindin was associated with schizophrenia (Straub et al., 2002) and later found to be part of BLOC-1 in tissues such as liver (Li et al., 2003) and brain (Ghiani et al., 2010) as well as in invertebrates (Mullin et al., 2015). Even though the genetic association between dysbindin and schizophrenia has not been proven strong (Straub et al, 2002; Farrell et al., 2015), several reports have pointed out that this complex may play a role in brain function and, most importantly, including its development (Ryder and Faundez, 2009; Ghiani and Dell' Angelica 2011; Mullin et al., 2011). Lavin and colleagues bring into the picture the important link between decreased levels of BDNF (Brain derived neurotrophic factor) and cognitive impairments (Mariga et al., 2016), and the possibility that by pharmacologically restoring BDNF expression with Fingolimod, some of the cognitive deficits can be rescued in individuals affected by developmental neuropsychiatric disorders. These are important findings since this molecule has been reported to be beneficial in preventing brain atrophy and cognitive dysfunctions in individuals with relapsing-remitting multiple sclerosis (Groves et al., 2013; Sanford, 2014; Fonseca, 2015). Thus, the prospect is bright for additional therapeutic applications of Fingolimod to treat cognitive defects in diverse mental illnesses.

In conclusion, the biological models utilised for the study of neurodevelopmental disorders offer new light and possibilities despite their limitations. These models and approaches are and will continue to further our knowledge on the underlying the aetiopathogenesis and the pathophysiology of developmental neuropsychiatric disorders, although, the latter can still differ in humans and animal models. We look forward to a promising future in the understanding of mechanisms, the development of drug treatments and interventions for the betterment of these patients.

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