Review

The molecular basis of cognitive deficits in pervasive developmental disorders

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Persons with pervasive developmental disorders (PDD) exhibit a range of cognitive deficits that hamper their quality of life, including difficulties involving communication, sociability, and perspective-taking. In recent years, a variety of studies in mice that model genetic syndromes with a high risk of PDD have provided insights into the underlying molecular mechanisms associated with these disorders. What is less appreciated is how the molecular anomalies affect neuronal and circuit function to give rise to the cognitive deficits associated with PDD. In this review, we describe genetic mutations that cause PDD and discuss how they alter fundamental social and cognitive processes. We then describe efforts to correct cognitive impairments associated with these disorders and identify areas of further inquiry in the search for molecular targets for therapeutics for PDD.

Normal early childhood development requires a myriad of molecular and cellular processes that are exquisitely balanced and tightly regulated. In contrast, in pervasive developmental disorders (PDD), normal neurodevelopment is either delayed or severely compromised (DSM-IV, American Psychiatric Association 2000). The ICD-10 nomenclature of the World Health Organization (WHO) designates this set of conditions as Autism Spectrum Disorders (ASD), a more frequently used term (WHO 2004). It is estimated that early onset intellectual disability (ID), which is highly co-morbid with an existing PDD diagnosis, affects ~1% of the global population. PDD is perhaps the most expensive of all human disorders, outpacing cancer and psychiatric diseases (Ropers 2010) because the affected individual requires a combination of behavioral and clinical therapy as well as long-term care. The current diagnostic and statistical manual of mental disorders IV (DSM-IV) defines PDD as an umbrella category comprising five major conditions: (1) autism, including both genetic and idiopathic causes; (2) Asperger's Syndrome; (3) Rett's Syndrome; (4) childhood disintegrative disorder (CDD), a rare, regressive late-onset developmental delay with unknown functional basis; and (5) PDD-NOS, which encompasses atypical autistic cases.

An individual is diagnosed with PDD when behavioral abnormalities are observed in any one or all of the three core domains: social development, communication, and repetitive behavior/obsessive interests (Baron-Cohen 2004). This "triad of deficits" can be thought of as an overall "problem" in social cognition. The severity of the condition may range from inability to process simple cues such as gaze fixation to complex operations such as biologic motion sensing, triadic attention sharing, and behavioral requesting (McPartland et al. 2011). The intellectual quotient (IQ) of individuals with PDD varies across a broad range, but is a strong predictor of the expression of the disorder, the level of cognitive abilities observed, and treatment outcomes (Baron-Cohen 2004). A plethora of imaging studies conducted with autistic and nonautistic children in a variety of contexts have helped identify several key difficulties with higher order cognitive processing. First, it is believed that deficits occur due to altered development of key brain areas involved in the processing of social and operational information (see McPartland et al. 2011 for details).

Second, there is mounting evidence that points to altered connectivity between these regions and other brain areas responsible for the expression of social behavior, anxiety, and emotional responses. It is here that nonhuman models (mainly mouse) of cognitive dysfunction hold promise, because genetic manipulations that alter the connectivity and architecture of discrete brain areas can be done with relative ease. However, the major challenge has been to recreate cognitive dysfunction in these models of PDD.

The three major criteria that have made mice the system of choice to model cognitive dysfunction associated with PDD are: (1) the relative ease of manipulating genes, (2) a reasonably good approximation of human behaviors, and (3) mice are a social species that engage in a variety of social interactions, parenting, communal nesting, and aggressive territory marking behaviors (Crawley 2007). In the past decade, behavioral neuroscientists have worked intensely with clinical experts on PDD to devise a large battery of tests that measure social interactions and the expression of stereotypic behavior. These tests are being used extensively to characterize a myriad of gene-behavior questions related to autism and associated PDDs (see Silverman et al. 2010a for a detailed review). The expression of empathy and the attributing of "theory of mind" capabilities to nonhuman species has become an intensely debated topic. Recent findings demonstrate that rodents may have some form of "emotional contagion-like or empathy-like responses" (Ben-Ami Bartal et al. 2011; Panksepp and Lahvis 2011), which if shown to be impaired in PDD models reliably, will considerably aid future research. Meanwhile, traditional tests of learning and memory are being utilized routinely to assess the cognitive outcomes of gene manipulations in mouse models of PDD. These include spatial learning and memory using the Morris water maze (MWM), Y-maze, and T-maze; emotional and associative memory using passive avoidance and fear conditioning paradigms, and attention-related sensorimotor gating using paired pulse inhibition (PPI), go/no go tests, and multiple choice serial reaction tests (Crawley 2007; Bishop and Lahvis 2011). A point to be noted is that these tests measure operational learning and memory, which often is impaired only when there is mild to profound mental retardation accompanying a PDD diagnosis in humans.

So how did the view that PDD has a genetic basis come about? Work by eminent psychiatrists and psychologists like Rutter, Wing, and Baron-Cohen to name a few, in the 1960–1980s, laid the groundwork for the codification of PDD, put forth

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theories to explain the observed deficits, and categorized the large variation in behavioral abnormalities observed (Rutter 1970; Rutter and Bartak 1973; Wing 1981; Baron-Cohen 2010). At this point, treating PDD was considered solely the purview of behavioral interventionists because it was deemed largely intractable to medical treatment. Meanwhile, many genetic conditions such as fragile X syndrome, tuberous sclerosis complex, neurofibromatosis, and Down syndrome were being similarly medically and molecularly characterized, and co-morbidities with PDD were observed. These observations helped introduce the notion that many neurodevelopmental deficits in PDD might be due to altered molecular function and/or architecture of neural systems. Thus, by the turn of the 21st Century, the unifying hypothesis was that autism and other PDDs have a strong genetic basis, and that it was time to consider the condition and treatment from a genetic and molecular point of view.

The shifting views of PDD came at a moment when tremendous innovation and progress in molecular genetics and cell biology already had been achieved. Not only was the human genome sequenced, uncovering a plethora of de novo mutations and copy-number variations in PDD, but the functions of many proteins were being discovered with the help of animal models where one could study the effects of gene deletion and overexpression. In parallel, the cell biology of transcription, translation, protein trafficking, metabolism, and perhaps most importantly, signaling pathways in the context of neuronal and circuit function had been studied in great detail. We now are witnessing a convergence of causality, with multiple syndromic conditions impacting common molecular and cellular processes as well as many candidate genes altered in PDD identified as mediators of these processes (Kelleher and Bear 2008; Hoeffer and Klann 2010). Though this phenomenon augurs well for therapies that target common affected pathways in PDD, the information on how cognitive abnormalities are rectified by manipulating molecular processes oftentimes get lost amidst the sea of “rescue” studies that focus on rectifying signaling and neuronal markers rather than behavioral abnormalities. This review is organized according to pathways that are vital to normal neuronal function at a cellular and molecular level and how disruption of these processes in PDD are associated with social and cognitive dysfunction. The aim of this review is to describe the current state of (1) mouse models of human genetic syndromes co-morbid with PDD that are available and successfully mimic the social and cognitive behavioral abnormalities of PDD; (2) how these social and cognitive behaviors (largely limited to cortical areas of the brain) are disturbed by the molecular and cellular abnormalities; and (3) identify gaps in our current understanding that require further attention.

DNA regulation

The genetic bases of several PDD associated conditions frequently involve mutations in genes involved in DNA regulation. These include homeobox pattern regulators like *Aristaless*, *Hox1A*, and *SATB2*; epigenetic enzymes including *EHMT1* and DNA-binding proteins including *NSD1* and nuclear factor 1/X (Betancur 2011; van Bokhoven 2011). The most intensely studied condition involving improper DNA regulation as the core molecular abnormality is Rett Syndrome (RTT), which is caused by the loss of *Mecp2*, a transcription factor that binds methyl CpG modifications on DNA (Chen et al. 2001; Guy et al. 2001). RTT is one of the five main divisions of the PDD category in DSM IV. However, it is proposed to be excluded in DSM-V because patients often display autistic traits only briefly during early childhood and the RTT diagnosis is essentially etiologic rather than behavioral (www.dsm5.org). Complete deletion of *Mecp2* is embryonic

lethal; therefore, multiple lines of conditional knockout mice have been generated targeting *Mecp2* in specific neuronal subpopulations as well as knockin mice with full-length *Mecp2*-containing, RTT-specific mutations (for review, see Calfa et al. 2011). Mice carrying a *Mecp2* truncation exhibited increased confrontation tendency in the tube test of social interaction (Shahbazian et al. 2002). However, these mice displayed normal fear-conditioning responses and MWM performance. Abnormal home-cage behavior, nesting, and social approach have been reported for another mouse model with RTT mutation *Mecp2*-308, with no differences in either aggression or exploration of novel inanimate stimuli (Moretti et al. 2006). Interestingly, conditional deletion of *Mecp2* in specific brain areas resulted in specific behavioral phenotypes. For example, a forebrain-specific deletion of *Mecp2* exhibited increased anxiety and social behavior, whereas acquisition and consolidation of associative fear memory remained intact (Gemelli et al. 2006). Deletion of *Mecp2* in dopaminergic and noradrenergic neurons did not result in cognitive defects, but severely impaired locomotion (Samaco et al. 2009). Serotonergic system-targeted silencing of *Mecp2* caused increased aggression, while deletion of *Mecp2* in the amygdala resulted in heightened anxiety and impaired associative fear memory (Adachi et al. 2009; Hutchinson et al. 2012). Interestingly, increasing the gene dosage of *Mecp2* via duplication causes a severe form of PDD called MECP2 duplication syndrome, and model mice with global increases in the protein exhibited increased anxiety, impaired contextual fear memory, and deficits in novel object recognition (Collins et al. 2004; Na et al. 2012). Finally, targeted deletion of *Mecp2* in GABAergic neurons recapitulated all of the social impairments associated with RTT (Chao et al. 2010). Therefore, cognitive dysfunction in RTT may be due to problems in local populations of inhibitory neurons. At present, none of the experimental approaches have fully reversed RTT-associated cognitive phenotypes, although breathing and locomotor impairments have been rescued in RTT model mice (see Guy et al. 2007; Calfa et al. 2011). Social interaction impairments and increased anxiety due to duplication of *Mecp2* have been counteracted successfully by decreasing *Crh* and its receptor (Samaco et al. 2012).

Rubinstein-Taybi syndrome (RTS) is an uncommon autosomal dominant syndrome that is associated with PDD-like features and is caused by mutations in the CREB-binding protein 2 (*CREB-BP 2*) gene (Betancur 2011). CREB-BP 2 is a ubiquitously expressed histone acetyltransferase with scaffolding, transcription-factor recognition, and transcription regulation functions. Because its primary association is with CREB, CREB-BP 2 interacts with a wide variety of transcription factors and has been shown to be vital for synaptic plasticity and neurodevelopment (Josselyn 2005). Transgenic mice expressing truncated *CREB-BP 2* exhibit impaired spatial learning in the MWM and defective contextual fear memory, but normal cued fear memory (Wood et al. 2005a). An earlier study showed that these mice display enhanced anxiety, impaired novel object recognition, and sensorimotor gating deficits (Alarcón et al. 2004). To model effects of impaired CREB-BP function during development, mice haploinsufficient for *CREB-BP 2* were generated and it was demonstrated that neonates have altered ultrasonic vocalizations (USVs), indicating a role for this enzyme in early cognitive development (Wang et al. 2010a). Precisely how the function of CREB-binding proteins are functionally linked to intellectual deficits associated with RTS has not been determined. However, inhibiting HDAC activity can ameliorate certain behavioral phenotypes displayed by RTS model mice, while either increasing cAMP signaling with Rolipram or transgenic expression of a constitutively truncated CREB-binding protein results in deficits in MWM and contextual fear conditioning tasks (Bourtchouladze et al. 2003; Alarcón et al. 2004; Wood et al. 2005a).

RNA regulation

Being highly polarized with extensive elaborations, neurons face a supply-chain problem of delivering newly synthesized proteins to the appropriate synaptic locations in response to rapid, activity-dependent changes in signaling cascades. To overcome this problem, neurons utilize the phenomenon of local axonal and dendritic translation in close proximity to synaptic sites. Therefore, mRNA trafficking and translational control impacts not only synaptic plasticity, but neural circuits as well, and these processes have been found to be dysregulated in a subset of PDDs (Liu-Yesucevitz et al. 2011). The most extensively studied of this type of PDD is fragile X syndrome (FXS), which is caused by an uncontrolled expansion of CGG repeats at the 5' end of the *Fmr1* gene, causing promoter hypermethylation and subsequent loss of expression of fragile x mental retardation protein (FMRP). FMRP mediates different aspects of RNA metabolism, including trafficking of RNP particles, translation of specific mRNA transcripts via regulation of translation initiation and elongation, and targeted degradation via the RISC complex (Jin et al. 2004; Park et al. 2008; Kao et al. 2010; Melko and Bardoni 2010). FXS model mice, where the *Fmr1* gene has been deleted, have been exhaustively studied and shown to display the "triad of deficits" features associated with PDD (Gross et al. 2012). Intriguingly, most pharmacological and genetic rescue strategies have opted to evaluate hyperactivity, motor skill learning, and the seizure susceptibility of FXS model mice, with only recent reports highlighting the effect of such molecular manipulations on social interactions (Mines et al. 2010; Goebel-Goody et al. 2012; Rotschafer et al. 2012). In spite of our current insights into the pathophysiology of FXS, no treatment strategy has as yet attempted to rescue disease phenotypes by regulating translational control elements directly. Current therapeutic efforts are focused on manipulating cell surface receptors and signaling kinases far upstream of translation (Gross et al. 2012). FMRP is a member of the RNA-binding protein family, of which mutations in another member, *Fmr2* or *AFF-2*, causes FRAXE condition, which is one of the most common forms of nonsyndromic X-linked mental retardation (Stettner et al. 2011). Because *Fmr2* knockout mice show impaired fear conditioning, it is likely that dysregulated RNA metabolism also is responsible for many features of FRAXE (Gu et al. 2002). In the future, it may be pertinent to explore strategies involving direct modulation of translation regulatory elements to holistically address impairments observed in FXS, FRAXE, and related conditions.

Other translation regulators also have been implicated in the pathophysiology of PDD, including eukaryotic initiation factor 4E (eIF4E) (Neves-Pereira et al. 2009), faulty RNA editing mechanisms of serotonin receptor type 2C (Morabito et al. 2010) leading to Prader-Willi-like features, and defects in correct splicing machinery contributing to some forms of Angelman and Down syndromes (Sartori et al. 2008; Shi et al. 2008). In summary, though the concept of dysregulated RNA translation and dynamics is well established in the etiology of multiple PDD conditions, the precise contribution of these molecular processes in cognition remains to be comprehensively demonstrated.

Metabolism and energetics

Behavioral research focusing on metabolic disruptions has lagged despite early indications that nearly 5% of all PDD cases are caused by inborn errors of metabolism (Manzi et al. 2008). For example, individuals with Lesch-Nyhan's Syndrome (LNS), which is caused by a deficiency of the hypoxanthine-guanine-phosphoribosyl-transferase (HGPRT) enzyme that plays a key role in the purine

salvage pathway, displays multiple behavioral phenotypes that include self-mutilating behavior and mental impairment (Nyhan et al. 2000). Although a mouse model of HGPRT deficiency exists, neurological phenotypes have not been studied extensively (Bertelli et al. 2009; Ceballos-Picot et al. 2009). Another syndrome with defective nucleotide metabolism is adenylosuccinate lyase deficiency (ADSL), which presents with global developmental delay akin to Angelman syndrome, including severe speech deficits, seizures, happy disposition, hyperactivity, and stereotypies (Gitiaux et al. 2009). Biotinidase deficiency is known to be associated with autism (Betancur 2011), with the first neurological assessments of a mouse model being conducted recently (Pindolia et al. 2011). In contrast, errors in cholesterol metabolism and the association with PDD have been extensively studied. This may be due to the well-established importance of lipid-protein interactions in signaling, trafficking, and synaptic transmission, and because of the role of cholesterol in myelination and neurite development (Korade and Kenworthy 2008). Inhibitors of cholesterol synthesis have been shown to affect acquisition of conditioned eyeblink response in rats (Xu et al. 1998; O'Brien et al. 2002). The clinical correlate of these studies is Smith-Lemli-Opitz syndrome (SLOS), which is caused by the genetic deletion of 7-dehydrocholesterol reductase gene resulting in an inability to convert 7-dehydrocholesterol to cholesterol. There is an extremely high prevalence of autism in SLOS patients (Sikora et al. 2006) and SLOS mouse models are available (Xu et al. 2011). Therefore, it will be very relevant to investigate the cognitive dysfunctions in SLOS model mice.

In contrast to metabolic impairments, the relationship between oxidative stress, mitochondrial function, and cognition has been studied widely (see Massaad and Klann 2011 for detailed review). Multiple studies have focused on the effects of reactive oxygen species (ROS) and mitochondrial dysfunction on several forms of memory (Hu et al. 2009; Otte et al. 2011), but there are very few reports involving the role of either mitochondrial-derived or other sources of ROS in social interactions or behavioral inflexibility (Zhuravliova et al. 2009; Rammal et al. 2010; Kamat et al. 2011). An insightful study was done by Roubertoux et al. (2003), which demonstrated a striking effect of mitochondrial DNA polymorphism (and presumably mitochondrial dysfunction) on cognition in mice. Over the past few years, evidence has been mounting that ROS and oxidative stress play a critical role in the manifestation of PDD. Numerous examples have been recorded of humans suffering from either syndromic or idiopathic PDD who show elevated levels of mitochondrial ROS and bioenergetic stress markers such as high levels of circulating lactate, pyruvate, carnitine, and ubiquinone (Palmieri et al. 2010; Chauhan et al. 2011; Sajdel-Sulkowska et al. 2011; Frustaci et al. 2012; Rossignol and Frye 2012). It is speculated that 20% of all autistic cases may be caused to some extent by mitochondrial dysfunction, and a large number of de novo mutations implicated in PDD affect either mitochondrial genes or nuclear origin genes encoding proteins involved in the electron transport chain and other oxidation-related processes (see Dhillon et al. 2011 for the multiple ways in which mitochondrial and oxidative dysfunction is associated with PDD). Well-studied monogenetic PDD conditions such as FXS and RTT have high levels of oxidative stress, and there is evidence of a partial rescue of biochemical markers and nonverbal communication in RTT patients with the administration of ω -3 polyunsaturated fatty acids (Ross-Inta et al. 2010; Leoncini et al. 2011; De Felice et al. 2012). "Metabolomics" and oxidative stress are fast-emerging subdisciplines in PDD; however, the precise role of mitochondria and ROS in cognitive dysfunction remains to be unraveled, as does the efficacy of treatments based on antioxidants.

Transport

Studies of the cell biology of the endoplasmic reticulum (ER) and the Golgi apparatus and their functions, which include post-translational modifications, protein folding, and protein trafficking, has resulted in a wealth of knowledge concerning how the cell manages the protein assembly line and delivery of proteins to the appropriate locations (Lodish et al. 2008). There are numerous examples of how impaired post-translational processing, protein folding, and protein trafficking underlie inherited human diseases (Hebert and Molinari 2007) including lung emphysema, cardiac arrhythmia, liver failure, and Parkinson's disease. Among PDDs, there are fewer examples, usually in rare genetic syndromes that have some overlap with autism (Betancur 2011). The most direct association of a PDD-candidate gene and protein trafficking comes from studies of oligophrenin 1 (OPHN1). OPHN1 is a member of the BAR domain superfamily that organize membrane curvature and signaling assemblies on membranes (Qualmann et al. 2011). *OPHN1* knockout mice were shown to display deficits in spatial memory and social interactions (Khelifaoui et al. 2007). Another candidate gene for PDD is calcium-dependent activator protein for secretion 2 (*CADSP2*), which mediates exocytosis of dense core vesicles by interaction with ARF-family GTPases (Sadakata et al. 2012). Alternative splicing of *CADSP2* mRNA has been reported in autistic individuals, and *CADSP2* knockout mice were shown to exhibit impaired social interaction, hyperactivity, hesitation to explore a novel object, and most importantly, maternal neglect of newborns (Sadakata et al. 2007). Unfortunately, there is a paucity of studies aimed at evaluating the effect of improper protein trafficking on cognition in PDD.

There is evidence that correct protein trafficking is important for cognition. For example, deletion of the glutamate receptor interacting protein GRIP in mice results in impairments in PPI, novel object recognition, and sociability (Mejias et al. 2011). In addition, recent studies strongly suggest that insulin-like growth factor 2 (*IGF2*) enhances memory consolidation (Alberini and Chen 2012). *IGF2* has been implicated in Beckwith–Wiedemann and Silver–Russell syndromes, and in most cases, signals via the *IGF2* receptor, a mannose-6-phosphate receptor that is important for transporting lysosomal acid hydrolase precursors from the Golgi apparatus to the lysosome (Laureys et al. 1988; Kent et al. 2008). Deletion of dysbindin-1 protein, which plays a role in the post-endocytic trafficking of G-protein-coupled receptors (Marley and von Zastrow 2010), results in hyperactivity and deficits in spatial learning (Cox et al. 2009; Karlsgodt et al. 2011). Moreover, the molecular mechanisms underlying the cognitive deficits in individuals with mutations in the neuroligins may stem from their abnormal trafficking. It was shown that mutations in both neuroligin 3 and neuroligin 4 that are associated with PDD cause improper folding of each protein, resulting in ER retention and stress (Zhang et al. 2009; Fujita et al. 2010). ER stress also appears to play a role in tuberous sclerosis complex (TSC). Disruption of the *TSC1/TSC2*, which enhances mTORC1 signaling, results in ER stress, which is thought to be a response to limit mTORC1 activity (Di Nardo et al. 2009). Therefore, though we have extensive knowledge of how protein folding and trafficking is executed and regulated, it is only very recently that its role in relation to PDD is being identified and appreciated.

Signaling and cell-to-cell communication

The synapse has been the primary focus of understanding the molecular architecture in neuronal systems. Not surprisingly, this has generated a wealth of information, not only about signaling pathways underlying synaptogenesis, synapse maturation, and synap-

tic plasticity, but also regarding mechanisms that allow the pre- and post-synaptic structures to interact. Neurological disorders involving dysregulated proteins in the synaptic proteome has been implicated in over 100 human diseases (Grant 2012), of which PDDs are a prominently represented subset. Of these, behavioral data examining cognitive function is available for only a handful of the genetic mutations associated with PDD, although in some cases, knockout mouse models exist. Table 1 lists the molecules that have a high correlation to PDD and other related disabilities, and the current state of literature regarding their association with cognitive deficits in the mutant mice for each gene product.

Degradation

Activity-dependent breakdown of “memory proteins” coupled with the synthesis of new ones is believed to be critical for the appropriate expression of synaptic plasticity, neural connectivity, and ultimately, memory consolidation. It has been known for nearly 60 yr that proper protein synthesis is required for memory consolidation, but it is only in the past decade that the importance of protein degradation in memory formation has been realized (Lopez-Salon et al. 2001; Lee et al. 2008). Protein degradation can occur via three routes: (1) the ubiquitin-proteasome system (UPS) that degrades the majority of short-lived proteins, (2) lysosomal degradation that targets organelles and membrane proteins, and (3) autophagy, a specialized process in which bulk cytoplasmic content is engulfed within double-membrane vesicles and then targeted to lysosomes (Bingol and Sheng 2011). Disruption of each of these three processes has been implicated in the pathophysiology of human diseases, but only the UPS has been shown thus far to be affected in PDD (Tai and Schuman 2008; Betancur 2011). The prime example of a PDD caused by disruption of the UPS is Angelman syndrome (AS), which most often occurs when the UPS executor protein ubiquitin ligase E6-AP, also known as *UBE3A*, is absent due to mutations in the maternal copy of the *UBE3A* gene (Lalande and Calciano 2007).

Cognitive problems in AS individuals include language impairments, happy demeanor, hyperexcitability, and severe developmental delays (Pelc et al. 2008). AS mouse models with a deletion of *UBE3A* alone were reported to have deficits in spatial memory in the MWM and in contextual fear memory along with increased seizure susceptibility (Jiang et al. 1998; Miura et al. 2002). Genetic enhancement of CaMKII activity in AS model mice prevents deficits in spatial memory in the MWM, contextual fear memory, and reduces susceptibility to audiogenic seizures (van Woerden et al. 2007). In addition, impairments in contextual fear memory in AS model mice recently was shown to be counteracted by suppressing neuregulin1-Erb4 signaling (Kaphzan et al. 2012). Interestingly, some social behavior and anxiety features in AS may not be due to the lack of *UBE3A* expression alone, but may also require deletions of additional genes on chromosome 15 that are known to occur in 70% of AS patients (Jiang et al. 2010; Allensworth et al. 2011). Interestingly, transgenic mice with increased expression of *UBE3A*, which models duplications and triplications of *15q11-13*, where the *UBE3A* gene resides, were shown to have defective social interactions and a lower frequency of ultrasonic vocalizations (Smith et al. 2011). A related PDD condition of X-linked Angelman-like syndrome caused by mutations in the *Slc9a6* gene is reported to have disruptions in endosomal–lysosomal functions (Strømme et al. 2011). Additional components of the degradation machinery have been linked to decreased cognitive ability. For example, mice with a deletion of *ubiquitin C-terminal hydrolase L3* gene (*Uchl3*) display impaired passive avoidance behavior and working memory (Wood et al. 2005b). Future research focused on directly

Table 1. Proteins involved in signaling networks and cell-to-cell communication with a high correlation to PDD

Molecule	Type of PDD	Mouse model phenotypes	Rescue strategies	Reference
Signaling, receptors, and ion channels				
<i>Angiotensin receptor II type 2 (AGTR2)</i>	Nonsyndromic X-linked ID	Cognitive: ↓ spatial memory in MWM ↓ performance one-way active avoidance task Social: not known		Maul et al. 2008
<i>AMPA Receptor 3 (GRIA3)</i>	Nonsyndromic X-linked ID	Cognitive: no effect in MWM and Y-maze Social: ↑ social interaction and aggression		Betancur 2011; Adamczyk et al. 2012
<i>B-Raf, K-Ras</i>	Cardio-facio-cutaneous syndrome, Noonan syndrome, Castello syndrome	KO model exists, but no behavioral analysis at this time	MEK inhibitor ameliorated the embryonic lethality and cardiac defects	Nava et al. 2007; Chen et al. 2010; Wu et al. 2011
<i>Ca²⁺ channel, voltage-gated, α1C (CACNA1C)</i>	Timothy syndrome	Cognitive: ↑ tone-cued and contextual fear Social: ↓ USVs ↓ social approach, preference and exploration	Not examined in neuronal systems Deletion of AKAP150 rescues arrhythmias	Splawski et al. 2004; Bader et al. 2011; Cheng et al. 2011
<i>Cyclin-dependent protein Kinase-like 5 CDKL5</i>	Rett Syndrome-like with spasms and ID	No behavioral analysis at this time		Weaving et al. 2004
<i>Fibroblast Growth Factor Receptor 1 (FGFR1)</i>	Autism	Cognitive: ↓ spatial memory in MWM ↓ PPI in FGFR1 Tg Social: ↓ interaction No effect on grooming in FGFR1 Tg	Agonists to FGFR1 ↑ social memory and ↓ anxiety Qietiapine ↑ social interaction in FGFR1 Tg	Zhao et al. 2007; Klejbor et al. 2009; Rudenko et al. 2010; Rubenstein 2011
<i>Neurofibromin 1</i>	Neurofibromatosis	Cognitive: ↑ radial arm maze errors ↓ performance in delayed nonmatch to sample task Social: not known, but NF1 mediates depressive behaviors	Picrotoxin administration normalizes working memory deficits	Shilyansky et al. 2010; Li et al. 2012
<i>Phosphatase and Tensin Homolog on Chromosome 10 (PTEN)</i>	PTEN hamartoma syndrome, Lhermitte-Duclos disease	Cognitive: ↓ PPI ↑ seizure susceptibility Social: ↓ social approach ↓ social recognition and novelty discrimination ↓ nesting behavior ↑ anxiety	5-d rapamycin treatment for 4 wk improved anxiety, seizure, and social phenotypes	Kwon et al. 2006; Zhou et al. 2009
<i>Rac/cdc42 GEF</i>	X-linked ID	Cognitive: ↓ reversal learning in MWM		Ramakers et al. 2012
<i>Shank 1/2/3</i>	Autism, Asperger syndrome, Phelan-McDermid syndrome	Cognitive: Shank 1 KO—no deficits Shank 2 KO—not known Shank 3 KO—↓ NOR, no effect in MWM, fear conditioning, ↑ PPI startle latency, probability Social: Shank 1—↓ social interaction, ↓ USVs, ↑ anxiety Shank 2 KO—not known Shank 3 KO—↓ juvenile reciprocal interaction, ↓ social investigation, ↑ aggressive episodes, ↑ grooming, no effect in three chambered social arenas		Bozdagi et al. 2010; Kumar 2010; Silverman et al. 2010b; Wang et al. 2010b; Bangash et al. 2011; Wöhr et al. 2011; Yang et al. 2012
<i>Sodium channel, voltage-gated, type I, α (SCN1A)</i>	Dravet syndrome with PDD	↑ myoclonic seizures		Ogiwara et al. 2007
<i>Solute carrier family 9 (sodium/hydrogen exchanger), member 6 (SLC9A6)</i>	Angelman-like syndromic X-linked ID	Cognitive: No changes in spatial object memory Other behaviors not examined as yet		Strømme et al. 2011

(continued)

Table 1. *Continued*

Molecule	Type of PDD	Mouse model phenotypes	Rescue strategies	Reference
<i>Synaptic Ras GTPase activating protein 1 (SYNGAP1)</i>	Nonsyndromic ID	Cognitive: ↓ working and reference memory ↓ spontaneous alternation in T-maze No change in object recognition ↑ execution of learned operant behavior ↓ PPI Social: ↓ social memory and social isolation		Muhia et al. 2009, 2010; Guo et al. 2009
<i>Tuberous Sclerosis 1/2 (TSC)</i>	Tuberous Sclerosis	Cognitive: ↓ context fear discrimination ↑ errors of quadrant crossing in MWM Social: ↓ social novelty and interaction Altered USVs	Acute rapamycin treatment improved context discrimination and MWM performance	Ehninger et al. 2008, 2012; Young et al. 2010; Chévere-Torres et al. 2012
Cell-to-cell communication				
<i>Neurexin1 (NRX 1)</i>	Autism, ID, Pitt–Hopkins-like syndrome-2	Cognitive: ↑ responsiveness and habituation to novelty ↓ startle in 80–100 dB range in PPI Social: ↑ grooming behavior ↓ nesting behavior		Etherton et al. 2009; Laarakker et al. 2012
<i>Contactin-associated protein-like 2 (CNTNAP2)</i>	Cortical dysplasia-focal epilepsy syndrome and Pitt–Hopkins-like syndrome-1	Cognitive: ↑ seizures Social: ↓ USVs ↓ social interaction ↓ nesting behavior	Risperidone relieves abnormal nesting behavior	Peñagarikano et al. 2011
<i>Dystrophin (DMD)</i>	Duchenne and Becker Muscular Dystrophy	Cognitive: ↓ spatial and object recognition		Vaillend and Ungerer 1999, 2004
<i>Neurexins (NLG 1, 2, 3, and 4)</i>	Autism, X-linked ID (NLG-4)	Cognitive: NLG1 Tg: ↓ memory acquisition in MWM NLG3 R451C Tg: ↑ performance MWM Social: NLG1 Tg: ↓ or altered USVs NLG3 R451C Tg: ↓ social interaction behaviors NLG2 KO: ↑ anxiety NLG2 Tg: ↓ sociability NLG3 KO: ↓ USV, social novelty preference NLG4 KO: ↓ reciprocal social interaction	↑ NLG1 improved social behaviors in Fmr1 KO	Tabuchi et al. 2007; Hines et al. 2008; Jamain et al. 2008; Blundell et al. 2009; Radyushkin et al. 2009; Dahlhaus and El-Husseini 2010; Dahlhaus et al. 2010; Fischer and Hammerschmidt 2011

Key: (↑) increased; (↓) decreased; (MWM) Morris water maze; (USV) ultrasonic vocalization; (KO) knock-out; (Tg) knock-in or overexpression; (PPI) sensorimotor gating using paired-pulse inhibition paradigm.

regulating the UPS and lysosomal activity to ameliorate symptoms of Angelman syndrome and related conditions may be fruitful due to the strong causal relationship between dysregulated proteolytic mechanisms and PDDs.

Summary

It is now seems obvious that PDD in humans can be caused by genetic mutations, and mouse models serve as a critical tool for dissecting the social and cognitive dysfunction involved in these disorders. However, it is important to remember that basic research is focused primarily on syndromic forms of PDD that represent a minority of individuals afflicted with PDD. In addition, DSM IV and related manuals do not categorize many frequently studied syndromes under PDD. Instead, these conditions are defined as genetic syndromes associated with a “high-risk” of an accompanying PDD diagnosis. This may be because psychiatric diagnostic modules such as DSM IV are organized according to

behavioral abnormalities rather than molecular mechanisms. In the future, devising a unified form of classification should help to mitigate the confusion prevalent regarding the precise definitions of such spectrum disorders.

The evaluation of social and cognitive deficits in mouse models of PDD were devised and standardized fairly recently. Thus, we now are witnessing an explosion of work characterizing the social and cognitive impairments in a variety of mouse models of syndromic autism. In some cases such as RTT, FXS, and AS, viable therapeutic options that could improve the quality of life of individuals with these syndromes are possible in the near future. Learning- and memory-based metrics such as MWM and fear conditioning have yielded important results in many other models (AS, RBS, etc.). However, certain key concerns persist that impede a more holistic advancement of the field.

First, there is a critical need to appreciate that genes underlying PDD work in concert and not in isolation. Therefore, not only do mutations of a gene and abnormal expression of the protein product affect the most direct cellular process/signaling pathway

in which it is implicated, but they most certainly will have secondary effects in other processes/pathways as well. Because cognition is an outcome of the sum total of the function of neurons either autonomously or in a circuit, understanding the proteome, interactome, or metabolome in specific brain regions may offer additional targets through which therapeutic interventions can be designed. Second, because multiple effector molecules often impinge on a common cellular operation, as is the case with FMRP, PTEN, TSC1/2, mTORC1, eIF4E for translation (Kelleher and Bear 2008; Hoeffer and Klann 2010), it is possible that common cognitive deficits could be targeted via control of a common molecular pathway, such as a translational control molecule rather than an individual target for each. Third, it may be necessary to shift from intensely focused efforts on a handful of conditions such as RTT, FXS, and AS to PDDs associated with mitochondrial dysfunction because these likely represent a much larger set of afflicted individuals. On a related note, there is a paucity of data examining the role of oxidative stress in social cognition deficits in PDD, which is in contrast to studies of mouse models of aging and neurodegenerative disease (Massaad and Klann 2011). As was discussed earlier, in addition to mitochondrial dysfunction, altered DNA regulation and protein transport appear to play important roles in the manifestation of specific cognitive disruptions in mouse models of PDD, which should provide additional molecular targets for intervention (Sakurai et al. 2008). It is surprising that in some cases of PDD, such as Ras mutant mice modeling Noonan syndrome, well-developed mouse models are available that are being actively examined in fields outside of neuroscience, but have yet to be examined in detail for cognitive dysfunction. A final challenge is modeling gene-environment interactions that likely underlie the majority of idiopathic PDD cases, including CDD and PDD-NOS. Increasingly, experts in the field are recommending whole-genome assessments for all PDD cases, making it vital to have information on how perturbing each node of the interacting network impacts behavioral measures.

In summary, PDD represents a continuum of disorders caused by genetic mutations that results in impaired intracellular processes, triggering alterations in neuronal and circuit function, which ultimately impacts a number of behaviors. The utilization of mouse models to identify molecular targets represents the next wave of novel therapeutics for treatment of PDD.

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