EDITORIAL

Shifting the Paradigm for Autism Treatments

Autism is a heterogeneous disorder with a number of monogenetic and polygenetic causes that have been well-characterized including fragile X syndrome (FXS), tuberous sclerosis, fragile premutation involvement, phenylketoneuria, 15 q 11-13 duplication, 16p11.2 duplication, and mutations in NGLN3,4, phosphatase and tensin homolog (PTEN), and SHANK3 to name a few. With advances in molecular biology, the neurobiological underpinnings of many of these disorders have been elucidated, leading to many commonalities across disorders, such as oxidative stress/mitochondrial dysfunction, imbalance of inhibitory-excitatory systems (through GABA and glutamate pathways), immune dysregulation, upregulation of the mammalian target of rapamycin (mTOR) system, and down regulation of PTEN. Many of these mechanisms are discussed in the overview of Bent and Hendren (page 232) with a particular emphasis on immune dysregulation in autism. This theme is further developed by Careaga, Van de Water, and Ashwood (page 283) in which a detailed look from immunologists links cytokine/chemokine changes, auto-antibodies and CNS inflammation to subtypes of autism. Subsequently Chez and Guido-Estrada (page 293) discuss early treatment studies of immune dysfunction in autism, which will hopefully lead the way for further controlled trials in subgroups of autism with specific immune biomarkers.

Knowledge of the dysregulation of certain pathways in specific genetic causes of autism has now led to targeted treatments that may be generally applicable to idiopathic causes of autism. Therefore, single gene causes of autism are now guiding targeted treatments that have the potential to reverse cognitive, social, and behavioral abnormalities that have been demonstrated in mouse models for these disorders. This is a new age of treatment based on knowledge of neurochemistry, metabolic pathways, and other biomarkers rather than symptom-based diagnoses. We hope that this special issue will stimulate new research based on these new models.

The lineup of single gene articles includes the review by de Vries (page 275) who describes the animal studies of tuberous sclerosis in which documentation of upregulation of mTOR took place. This translational research subsequently led to the targeted use of rapamycin to lower mTOR activation and reverse some of the neuro-

biological abnormalities in tuberous sclerosis. There are several other genetic disorders that lead to upregulation of mTOR, including neurofibromatosis, craniofacial cardiac syndrome, Costello syndrome, and even FXS.^{1,2} FXS is the most common single gene cause of autism. The protein that is missing or deficient in FXS, FMRP, is important for RNA transport, RNA stabilization, and regulation of translation for many hundreds of mRNAs important for synaptic plasticity.³ In the absence of FMRP, there is dysregulation of many proteins that are linked to autism, including PTEN, GABA A and B receptors, metabotropic glutamate receptor 5 (mGluR5), PP2A, APP, PAK3, Arc, and SHANK3. P13K, CYFIP1 and 2, NGL3 and 4, Herc2 (located at 15q11-13), Rai1 (located at 17p11.2), Maz, Sez612 (both located at 16p11.2), several cytokines and chemokines, and also mRNAs.³⁻⁵ Currently targeted treatments for FXS that serve to lower protein expression in the mGluR5 pathway are being studied because this pathway is associated with excessive long-term depression, which is the weakening of synaptic connections through internalization of AMPA receptors. These controlled trials of mGluR5 antagonists in FXS and in idiopathic autism are detailed in the Wang et al. article in this issue (page 264).

Another single gene disorder that can lead to autism if not treated early on by dietary interventions is PKU. Frye and colleagues (page 241) outlined the use of BH4 (Kuvan), which is remarkably helpful in PKU, and they have studied this in autism cohorts, because BH4 is a cofactor in a number of reactions that are important for the production of Ldopa, 5HT, and tyrosine, in addition to being an antioxidant. This is another example of how one medication for a specific disorder may be helpful for many patients who experience dysregulation of neurotransmitters and oxidative stress. We are just beginning to consider the use of BH4 for other neurodevelopmental disorders.

Tourette syndrome is a disorder with at least three genes currently associated with its presence. Tourette syndrome is also associated with auto-antibody production after strep infections, supporting a gene-environment or epigenetic cause. The use of micro-array technology is giving us new insights into this interaction and thus new treatments as described by Liao and Sharp in this issue (page 302).

Green and Hollander's report (page 250) on the many studies of oxytocin that enhance social interactions and affiliative behavior in animals and in humans, especially those with autism. This exciting treatment may be another type that has the potential to help neurodevelopmental disorders with social deficits, including FXS and Prader-Willi syndrome.

Finally, the medical comorbidities article by Bauman (page 320) reminds us that autism can affect many organ systems beside the brain. The metabolic complications, including the high rate of mitochondrial disorders or even mild mitochondrial dysfunction, will lead the way to new treatments that are just now being investigated, and will also lead to an appreciation for environmental toxins that may be additive to the phenotype of autism. Such mechanisms can tie into the immune dysfunction that is common to many disorders, including those with the fragile X premutation involvement that can also lead to autism. Use of hormonal treatments is mentioned in the Bauman article (page 320), which also discusses treatments for seizure disorders, sleep difficulties, and gastrointestinal disturbances.

Our hope is that this special issue will stimulate further translational research and targeted treatments based on recently understood mechanisms of action for children and adults affected with ASD and related neurodevelopmental disorders.

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