Review

Biological Psychiatry

The Pleiotropic MET Receptor Network: Circuit Development and the Neural-Medical Interface of Autism

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ABSTRACT

People with autism spectrum disorder and other neurodevelopmental disorders (NDDs) are behaviorally and medically heterogeneous. The combination of polygenicity and gene pleiotropy—the influence of one gene on distinct phenotypes—raises questions of how specific genes and their protein products interact to contribute to NDDs. A preponderance of evidence supports developmental and pathophysiological roles for the MET receptor tyrosine kinase, a multifunctional receptor that mediates distinct biological responses depending upon cell context. MET influences neuron architecture and synapse maturation in the forebrain and regulates homeostasis in gastrointestinal and immune systems, both commonly disrupted in NDDs. Peak expression of synapse-enriched MET is conserved across rodent and primate forebrain, yet regional differences in primate neocortex are pronounced, with enrichment in circuits that participate in social information processing. A functional risk allele in the *MET* promoter, enriched in subgroups of children with autism spectrum disorder, reduces transcription and disrupts socially relevant neural circuits structurally and functionally. In mice, circuit-specific deletion of *Met* causes distinct atypical behaviors. MET activation increases dendritic complexity and nascent synapse number, but synapse maturation requires reductions in MET. MET mediates its specific biological effects through different intracellular signaling pathways and has a complex protein interactome that is enriched in autism spectrum disorder and other NDD candidates. The interactome is coregulated in developing human neocortex. We suggest that a gene as pleiotropic and highly regulated as *MET*, together with its interactome, is biologically relevant in normal and pathophysiological contexts, affecting central and peripheral phenotypes that contribute to NDD risk and clinical symptoms.

Keywords: Forebrain, Gastrointestinal systemic, Immune system, Protein interactome, Symptom heterogeneity, Synapse development

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder (NDD) affecting 1%–2% of children (1). Diagnosis of ASD is based on two behaviorally defined criteria: 1) dysfunction in social interaction and communication, and 2) restricted repetitive behavior, including hyper- or hyporeactivity to sensory input (2). Described more than 70 years ago by Kanner (3), the nature and severity of clinical presentation is highly heterogeneous. There has been more recent attention to another layer of heterogeneity, the medical and psychiatric co-occurring disturbances expressed by most individuals with ASD. Multiple comorbid conditions have been described, including gastrointestinal (GI) disturbances (GIDs), immunological dysfunction, sleep abnormalities, epilepsy, motor deficits, generalized anxiety disorder, attention-deficit/hyperactivity disorder, and aggression (4–6).

Although a diagnosis of ASD is based on clinical observation using categorical measures, there is a growing consensus that understanding the genetic contribution and underlying pathophysiology of complex NDDs will be better served using a dimensional approach, with each dimension, or endophenotype, ranging along a continuum from typical to atypical (7,8). This approach recognizes that 1) distinct neural circuitry underlies different phenotypes; for example, language, social interaction, and behavioral inflexibility; 2) alterations in a single dimension will cross categorical diagnoses; for example, impairments in social interactions are observed in many DSM-5 disorders; and 3) co-occurring psychiatric conditions or shared traits across conditions probably arise from shared genetic and environmental burdens. In such a scheme, co-occurring medical conditions that likely share disruptions in common biological pathways define subpopulations of individuals with ASD, facilitating the identification of specific genetic and environmental contributions to the cause of the disorder. Further, a focus solely on identifying genome-wide disease risk (usually small risk effect size) will miss identifying factors that contribute to biological dimensions that may be vulnerable in particular categorically defined disorders. A similar approach has benefited several fields of

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medicine, recently emphasized in studies of psychiatric disorders (9).

The concept of pleiotropy and studies of the underlying complex biology of ASD heterogeneity raises the question of how specific genes may contribute. This review focuses a biological lens on basic and clinical studies of the MET receptor tyrosine kinase, which is an important regulator of development and cellular homeostasis in organs in which it is expressed (10). *MET* is a category 2 risk gene on Simons Foundation Autism Research Initiative Gene (SFARIgene, https://gene.sfari.org/autdb/GS_Home.do). A functional promoter variant reduces *MET* transcription and is enriched in ASD. This has led to extensive interdisciplinary studies, reviewed here (Supplemental Table S1), demonstrating the biological significance of dysregulation of MET expression in the context of typical and atypical neurodevelopment. We also describe MET function in peripheral systems relevant to ASD, particularly GI and immune systems. We also review studies that place MET functionally in the broader context of specific gene and protein networks implicated in NDDs.

GENETIC STUDIES: ASSOCIATION OF THE MET TYROSINE KINASE RECEPTOR WITH ASD

ASD is a polygenic disorder. Multiple rare de novo and inherited variations that are enriched in the ASD population have been identified (11–13). These represent a modest fraction of ASD diagnoses, with common heritable variations representing the largest component of genetic risk (14). Our laboratory identified genetic association, in multiplex families, of a common promoter variant, rs1858830, in the gene encoding the MET receptor tyrosine kinase with ASD (15). The association of this and other variants has been replicated across independent cohorts (16–19). However, there are two important facts to emphasize in our and others' genetic findings. First, the promoter variant individually has a small effect on ASD risk. Second, the promoter variant, like the majority of genetic findings in ASD, does not reach genome-wide significance across populations selected solely on an ASD diagnosis. Rather, the *MET* contribution to ASD risk likely occurs in unique subgroups of children, and moreover, the variant alone is not sufficient to cause ASD. Thus, the common promoter variant is likely one of a number of genetic and specific environmental factors that result in ASD. The variant is nonetheless functional. The *G*-to-*C* single nucleotide polymorphism results in a striking 50% decrease in promoter activity (20). Given that the promoter variant may be more biologically influential in ASD subpopulations, how might one identify clinically relevant subgroups across the autism spectrum? Attempts to do this with ASD diagnostic tools have not succeeded (21). We have used a different approach, examining subgroups for genetic risk by focusing on biomedical phenotypes (Figure 1). The strategy takes advantage of the pleiotropic nature of *MET*, which, in addition to its role in brain development, has demonstrated functions in systems vulnerable in ASD, including GI (22,23) and immune (24,25). The *MET C* allele is enriched in children with ASD and co-occurring GIDs (26) and is associated in mothers with the expression of ASD-associated antibodies that react with fetal brain proteins (27). In individuals with ASD from families with GID, the *MET C* allele also is associated with more disrupted social communication (28). This observation is consistent with the strong link between the most common types of GID in ASD and increased social impairment and lack of expressive language (29). Further, siblings in a family pedigree with a rare functional mutation in *MET* that generates haploinsufficiency have either ASD or social communication deficits (30). Finally, a subgroup of children who are homozygous for the *MET C* allele and whose mothers had been exposed to high levels of air pollution during pregnancy are at an increased risk for ASD (31).

REGULATION OF MET EXPRESSION: BIOLOGICAL SIGNIFICANCE

Because gene dysregulation is central to human disease (32), including ASD and psychiatric disorders (33), and cell type–specific regulation of gene expression likely defines the most vulnerable circuits in ASD (34), we have focused on defining precisely spatial, temporal, and evolutionary regulation of MET expression in the developing brain (35–38). Spatial and temporal mapping of transcript and protein in the developing rodent forebrain revealed low levels of MET expression prenatally. *Met* is not expressed in progenitor and migratory zones of neocortex and subcortical structures (36,38), a pattern distinct from stem and migrating cell expression during peripheral organ development (39). During the first postnatal week, there is a dramatic increase in MET expression in discrete forebrain regions, including neocortex, hippocampus, and subcortical limbic regions, with levels remaining elevated through the second postnatal week (36,40). This corresponds to the early and peak periods of process outgrowth and synaptogenesis. In these regions, MET is expressed in excitatory projection neurons, with no in vivo evidence of expression in interneurons, astrocytes, or oligodendrocytes, consistent with the failure to alter interneuron development in $Met^{fx/fx}/Dlx5/6^{Cre}$ mice (38). This latter point is important because MET expression may occur ectopically in some cells placed in culture or after injury. This occurs in cultured ganglion eminence, which gives rise to interneurons. The cells that generate interneurons respond to the MET receptor ligand, hepatocyte growth factor (HGF), in vitro, but in contrast to our initial interpretation (41), this signaling would not operate for cortical interneurons in vivo because they lack *Met*. There also is no evidence for *MET* expression in prenatal human ganglion eminence, dorsal pallial progenitors, or any migrating neurons (35), as well as in our own and GENSAT Met^{GFP} mice (42). However, we note a report that $Met^{fx/fx}/Dlx5/6^{Cre}$ mice on a different background exhibit neocortical interneuron decreases (43), though without direct evidence of ganglion eminence or interneuron *Met* expression in vivo using in situ hybridization colabeling. At later stages of cortical development, ligand-activated phosphorylated MET expression rapidly declines during synapse refinement (36,40).

In developing rhesus monkey, three striking findings emerged: 1) the temporal pattern of MET expression is conserved, with peak expression also occurring during the period of rapid process outgrowth and synapse formation (37); 2) subcortical and hippocampal expression patterns are similar between rodent and primate; and 3) there are substantial