Autism - Open Access
ISSN: 2165-7890

Smith and Powell, Autism 2012, S1
DOI: 10.4172/2165-7890.S1-002

Review Article Open Access

Mice with Impaired Met Tyrosine Kinase Signaling Demonstrate Characteristics Relevant to Autism

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Abstract

Variants of MET, a receptor tyrosine kinase which binds the ligand Hepatocyte growth factor (HGF), have been linked to elevated risk for developing autism spectrum disorders (ASD) in humans. Though best known as a proto-oncogene, *MET* also plays important roles during normal development, including the development of the central nervous system. Recent studies in several mouse lines have shown that mice with reduced HGF-Met signaling have altered profiles of interneurons in the cortex, striatum, and hippocampus. Alterations in neuronal development, particularly in the cerebral cortex, may contribute to the pathology of developmental disorders, including autism. Other studies have shown changes in excitatory signaling in the Met-deficient cortex. Interestingly, mice with deficient Met signaling also show behavioral alterations characteristic of autism. Here we review anatomical and behavioral findings in mice with altered HGF - Met signaling.

Keywords: HGF; MET; Interneuron; Forebrain; Attentional set-shifting; Reversal learning; Seizure; Plaur

Abbreviations

ADI-R	Autism Diagnostic Interview, Revised
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
CA1	Cornu Ammonis 1
CA3	Cornu Ammonis 3
CR	Calretinin
Dlx5/6	Distal-less homeobox 5/6
EEG	Electroencephalogram
Emx1	Empty spiracles homeobox 1
EN2	Engrailed 2
EPSC	Excitatory postsynaptic potential
GABA	Gamma aminobutyric acid
Gad67	Glutamic acid decarboxylase 67
GE	Ganglionic eminence
HGF	Hepatocyte growth factor
HOXA1	Homeobox A1
MSN	Medium spiny neuron
NF1	Neurofibromin 1
NrCAM	Neuronal cell adhesion molecule
OFC	Orbital frontal cortex
PV	Parvalbumin
PI3K	Phosphoinositol 3 kinase
PLCγ	Phospholipase C gamma
RAS	Rat sarcoma
Six3	Sine oculis-related homeobox 3
SNP	Single nucleotide polymorphism
SRS	Social Responsiveness Scale
SST	Somatostatin
tPA	Tissue-type plasminogen activator
uPA	Urokinase plasminogen activator
uPAR/*PLAUR*	Urokinase plasminogen activator receptor protein/gene
WT	Wild type

Introduction

Met is a tyrosine kinase receptor which binds the high-affinity ligand hepatocyte growth factor (HGF) [1]. Both Met and HGF are initially produced as single-chain pro-proteins, which are subsequently processed into their mature forms by proteolytic cleavage [2]. In the case of HGF, this is accomplished by enzymes such as matriptase [3], HGF activator [4], tissue-type plasminogen activator (tPA, gene: *Plat*) [5] or urokinase-type plasminogen activator (uPA, gene: *Plau*) [6]. The proteolytic activity of uPA is increased upon binding to its receptor (uPAR, gene:*Plaur*) [7]. Upon binding to HGF, Met auto-phosphorylates creating a multi-substrate docking site for a number of adaptor proteins [8]. Downstream targets of HGF-Met signaling include PI3K, RAS, and PLCγ [8]. Potentially owing to this diverse array of downstream targets, Met signaling has been implicated in cellular processes as varied as

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Received August 30, 2012; **Accepted** September 10, 2012; **Published** September 13, 2012

Citation: Smith JM, Powell EM (2012) Mice with impaired Met Tyrosine Kinase Signaling demonstrate characteristics relevant to autism. Autism S1:002. doi:10.4172/2165-7890.S1-002

proliferation, migration, survival, the formation of neuronal processes [9-19].

Both Met and HGF are expressed in the developing brain in rodents [19-25] as well as primates [26, 27]. In mice, HGF and Met expression are detectable as early as E11.5. Expression of both HGF and Met is found in the cortical ventricular zone, and later in the cortical plate [15]. HGF is also expressed in the proliferative zone of the ganglionic eminence [15]. Met expression remains high from late embryonic through early post-natal development in the mouse [24,25,28] and at the corresponding ages in primate [27]. At late embryonic and early post-natal stages, Met transcript is also found in the amygdala, septum, and hippocampus [24]. Expression of both HGF and Met persists in the adult brain, albeit at reduced levels [19-22,24,29]. HGF-Met signaling may therefore participate in multiple phases of neurodevelopment. Furthermore, HGF and Met expression are found in multiple areas thought to be affected in autism spectrum disorders (ASD).

Genetic Association of Autism with the Met Signaling Pathway

ASD is characterized by language and communication deficits as well as restricted interests and repetitive or stereotyped behaviors. Multiple neuroanatomical abnormalities have been observed in the brains of autistic patients [32-38]. Genetics are thought to play a role in the etiology of ASDs, as they are highly heritable [39-44], although environmental influences could also play important roles [43,45]. A number of genetic syndromes include autistic-like features or are associated with an increased risk of ASD, including Prader-Willi [46,47] Fragile X [48,49], and Rett syndromes [50], as well as tuberous sclerosis [51].While multiple genomic regions have been linked with autism risk a particularly strong candidate is a region on chromosome 7q [52], which contains putative autism susceptibility genes such as *EN2, HOXA1, WNT2*, and *NrCAM* [53-58]. Chromosome 7q also contains the *MET* gene, located at 7q31 [59], as well as *HGF*, located at 7q21.1 [60]. Several *MET* variants have been shown to increase risk for ASDs [61-66]. One SNP in particular, rs1858830, has been found to be associated with the co-occurrence of autism with gastrointestinal conditions [63]. Another gene involved in HGF signaling, *PLAUR* (which encodes uPAR, and is found on chromosome 19q13) [67], has also been associated with autism. The T allele of the *PLAUR* promoter variant rs344781 is associated with a 1.93 relative risk for ASD [62]. While some studies examining *MET* association with autism have failed to replicate the association of individual SNPs [64], evidence for the association of the gene as a whole is strong, especially when combined with the association of related genes.

In addition to genetic association, a number of *MET* variants have been shown to be functionally significant. The C allele of rs1858830 has been shown to reduce *MET* promoter activity [61]. *MET* protein levels are also reduced post-mortem in temporal cortex from autistic patients compared to controls [68]. A few *MET* variants have even been shown to have functional consequences at the level of behavior. The C allele of rs1858830 is also associated with social and communication scores on the ADI-R, ADOS, and SRS [69]. The C allele of rs2237717 and the G allele of rs42336 have been associated with altered facial emotion perception [70], which is altered in ASD. Given the repeated association of *MET* with autism, and the potential association of other genes in the pathway, it is highly likely that dysregulation of HGF-MET signaling could contribute to the pathology of ASD, in at least a subset of affected individuals.

Consequences of Altered Met Signaling

While *MET* is well validated as a risk gene for autism [61,63,70-72], only a few studies have examined the effects of loss of Met function in animals. This is likely due at least in part to the embryonic lethality of constitutive knockouts. Met function appears to be required for proper placental [73] and liver development [74], and therefore global Met knockout mice die early during gestation. In order to avoid this, groups have used Cre-*loxP* recombination strategies to inactivate Met specifically in cells expressing Cre recombinase [19,23,75,76,].

The *Dlx5/6-Cre* driver inactivates Met ($Met^{fx/fx}/Dlx^{Cre}$ mice) in post-mitotic GABAergic neurons originating in the Ganglionic Eminence (GE). GABAergic neurons from the GE become the inhibitory interneurons of the cerebral cortex, hippocampus, amygdala, and striatum, as well as the medium spiny neurons of the striatum [77]. The $Met^{fx/fx}/Dlx^{Cre}$ mice show increased numbers of parvalbumin (PV) and somatostatin (SST) positive interneurons in the striatum, as well as a reduction in PV interneuron numbers in the sensorimotor and orbitofrontal cortex, but not in visual cortex [19]. Furthermore, at more caudal levels of the striatum, a greater percentage of the population of PV positive interneurons was found in medial (associative), and fewer in lateral (sensorimotor) regions of the striatum than in control mice. Loss of Met function in embryonic interneurons therefore seems to affect the migration of GABAergic interneurons both within the striatum and between the embryonic striatum and cortex.

Hippocampal interneurons are also generated from the ganglionic eminence and appear to be affected by loss of Met signaling. Fewer PV and calretinin (CR) positive interneurons were found in the CA3 region of the hippocampus in $Met^{fx/fx}/Dlx^{Cre}$ mice than in controls. Mice in which Met was inactivated in the proliferative zones of the ganglionic eminence using a *Six3-Cre* driver ($Met^{fx/fx}/Six3^{Cre}$ mice) showed a similar loss of PV and CR cells in CA3, but further showed a loss of CR interneurons throughout the hippocampus, and an increase in PV interneurons in the dentate gyrus [23]. Alterations in the number of interneurons in the hippocampus of $Met^{fx/fx}/Dlx^{Cre}$ mice are likely due to a migration defect similar to that seen for cortical and striatal interneurons in these animals. Deficits in the $Met^{fx/fx}/Six3^{Cre}$ mice could also be due to changes in the specification of different subtypes of interneuron. It is unlikely that the deficit in $Met^{fx/fx}/Six3^{Cre}$ mice is due to decreased proliferation of interneurons, as similar a similar pattern of GABA staining found in the hippocampus [23].

In order to examine the functions of Met in the developing cortex, a similar system has been employed using Cre recombinase expressed under the control of the *Emx1* promoter to inactivate Met in excitatory neurons and glia of the cerebral cortex and hippocampus. Notably, this system does not directly ablate Met function in cortical GABAergic interneurons, which originate in the ganglionic eminence [76,78] found that pyramidal neurons in layers 2 and 3 of the anterior cingulate cortex of $Met^{fx/fx}/Emx1^{Cre}$ mice showed significant alterations in dendritic arbor. $Met^{fx/fx}/Emx1^{Cre}$ neurons showed reduced apical dendritic arbor length distal to the cell body, and increased basal dendritic arbor length proximal to the cell body. These differences appear to be primarily due to changes in branching complexity. Since the distal apical dendritic arbor of pyramidal neurons receives distinct synaptic inputs from the basal and proximal apical arbor [79], this could result in changes in synaptic connectivity. No difference was found in the number of dendritic spines between $Met^{fx/fx}/Emx1^{Cre}$ and control mice, but an increase in the volume of spine heads was observed [80]. Interestingly, striatal medium spiny neurons (MSNs), were also found to show increases in both dendritic arbor length and spine head volume. Alterations in

MSNs would suggest that loss of Met signaling in cortical pyramidal neurons may have effects on cells targeted by cortical efferents, as striatal MSNs are not targeted by the *Emx1-Cre* driver [78]. As spine structure is closely related to function, and spines are the main target of glutamatergic synapses, alterations in spine head volume could produce changes in excitatory neurotransmission [81]. Indeed, alterations in excitatory neurotransmission have been shown in the cortex of $Met^{fx/fx}/Emx1^{Cre}$ mice. In the anterior cingulate cortex of $Met^{fx/fx}/Emx1^{Cre}$ mice, stimulation layer 2/3 pyramidal neurons produced stronger excitatory post-synaptic potentials (EPSCs) in layer 5B corticostriatal projection neurons [82].While changes in EPSC amplitude in this population could be due to either presynaptic or postsynaptic alterations, no difference was found in paired pulse ratios between $Met^{fx/fx}/Emx1^{Cre}$ mice and controls, suggesting that at least some presynaptic parameters (i.e. release probability) are unaltered by loss of Met signaling. In contrast, no changes in EPSCs were found in corticopontine projection neurons after stimulation in layer 2/3 [82], further suggesting that the increased connection strength in corticostriatal neurons is likely due to post-synaptic mechanisms.

Alterations in cortical connectivity in $Met^{fx/fx}/Emx1^{Cre}$ mice reflect some changes seen in ASD. Altered cortical connectivity is thought to play a role in the etiology of ASD [83], including local hyperconnectivity (as demonstrated in $Met^{fx/fx}/Emx1^{Cre}$ mice) as well as long-range hypoconnectivity.That hyperconnectivity in the $Met^{fx/fx}/Emx1^{Cre}$ mice appears specific to corticostriatal projection neurons is significant, as both corticostriatal structural [84] and functional connectivity [85,86] have been shown to be altered in ASD. Furthermore, there is some evidence of an association between changes in striatal functional connectivity and repetitive behavior in children with ASD [86].

Unlike $Met^{-/-}$or $Hgf^{-/-}$mice which die before embryonic day 12 [74,87], $Plaur^{-/-}$ mice live to adulthood [88]. These mice exhibit reduced HGF levels [25,89] suggesting reduced HGF-Met signaling, and possible alterations to HGF mediated developmental processes. HGF has been reported to facilitate forebrain GABAergic interneuron migration [89,90]. Several studies have found decreased numbers of GABAergic interneurons in the brains of $Plaur^{-/-}$ mice [25,28,91,92]. Fewer GABA positive cells were found in the cingulate and parietal cortex of $Plaur^{-/-}$ mice than in WT mice [28]. In a parallel study, $Gad67^{+}$ cells were found to be decreased in the parietal cortex, as well as in the dentate gyrus and the CA1 region of the hippocampus [91]. No change in either GABA or Gad67 staining was observed in occipital cortex [28,91]. Among GABAergic interneurons, PV expressing cells seem to be preferentially affected in $Plaur^{-/-}$ mice. Decreases in PV^{+} interneurons have been noted in the frontal areas, including the anterior cingulate [28], and orbital frontal cortex (OFC) [92], and parietal cortex, in particular in somatosensory areas [25,28,91],as well as in the striatum (Bissonette et al., 2010). In the hippocampus, however, the PV^{+} population is unaffected, and there is a reduction in somatostatin^{+} (SST^{+}) cells in the dentate gyrus and CA1[91]. In the cases of the somatosensory and orbital frontal cortical regions and the striatum, over expression of HGF in astrocytes restored the numbers of PV^{+} interneurons [25,92], suggesting that the decrease in HGF levels seen in $Plaur^{-/-}$ mice is responsible for the observed interneuron deficits.

Behavioral Consequences of Altered HGF-Met Signaling

While cellular and physiological changes in mice with altered HGF-Met signaling are informative, they would not make for convincing animal models without accompanying behavioral alterations reflective of ASD symptoms. While not all of the mouse lines which have been examined have been extensively characterized, several show behavioral phenotypes which suggest that altered HGF signaling could contribute to autistic-like behavior.

$Plaur^{-/-}$ mice show a number of behavioral alterations when compared to WT littermates. Among these, $Plaur^{-/-}$ mice have been shown to display increased anxiety-like behaviors in the light-dark avoidance test and the elevated plus maze [25,28]. In addition to increased anxiety, $Plaur^{-/-}$ mice have impaired cognitive flexibility as measured by reversal learning a process which has been shown to be dependent on the OFC [92-94]. $Plaur^{-/-}$ and WT animals both learn the rules similarly, but once the rules are reversed, the $Plaur^{-/-}$ mice require more trials to master the task [92]. The $Plaur^{-/-}$ mice exhibit abnormal electroencephalogram (EEG) activity and have spontaneous seizures, as well as an increased sensitivity to chemically induced seizures [28]. HGF supplementation rescues the seizures and anxiety behaviors seen in $Plaur^{-/-}$ mice [25]. Our recent findings indicate impaired social interactions and attentional processing in $Plaur^{-/-}$ mice (unpublished observations) and current studies are focused on assessing communication responses in the WT and $Plaur^{-/-}$ groups.

$Met^{fx/fx}/Dlx^{Cre}$ mice show no alterations in locomotor activity in the open field or in tests of anxiety-like behavior such as light-dark avoidance or the elevated plus maze [19]. $Met^{fx/fx}/Dlx^{Cre}$ mice were also tested in the Morris water maze, which can be used to test both spatial learning (mediated by the hippocampus) and procedural learning (mediated by the striatum) [95,96]. In the water maze, $Met^{fx/fx}/Dlx^{Cre}$ mice performed similarly to controls during a probe test, as well as during a reversal probe test where the hidden platform was moved to the opposite quadrant from where it was during training. Both tests are used to measure hippocampal-dependent spatial learning [95,97]. However, in a cued platform task, which is dependent on striatal function [95,97], $Met^{fx/fx}/Dlx^{Cre}$ mice were slower to reach the platform than control mice. This suggests that despite abnormalities in the population of interneurons in both the hippocampus and striatum of $Met^{fx/fx}/Dlx^{Cre}$ mice, hippocampal function remains relatively normal, while striatal function, mainly habit learning, is disrupted.

Reversal learning was also affected in $Met^{fx/fx}/Dlx^{Cre}$ mice [19], similarly to $Plaur^{-/-}$ mice. $Met^{fx/fx}/Dlx^{Cre}$ mice performed similarly to controls in learning the initial discrimination task, but required significantly longer to reach criterion during the reversal portion [19]. That the mice acquire the initial discrimination normally suggests that they have no problem learning the task or discriminating between the cues, while their deficit in the reversal portion of the task suggests a lack of behavioral flexibility or a problem inhibiting the previously rewarded response. A similar loss of behavioral flexibility may be involved in the restricted or repetitive behavior which is frequently observed in autistic children [98].

Conclusions

Mice with altered HGF-Met signaling show alterations in the interneuron populations of the frontal cortex, striatum, and hippocampus. While spatial learning (dependent on the hippocampus) appears normal in $Met^{fx/fx}/Dlx^{Cre}$ and $Plaur^{-/-}$ mice, $Met^{fx/fx}/Dlx^{Cre}$ mice show deficits in procedural learning, and both strains are impaired on a reversal learning task. In $Plaur^{-/-}$ mice, restoration of normal HGF levels via genetic intervention restores both interneuron numbers and normal behavior. Repetitive behaviors are frequently observed in ASD [98], and have been associated with diminished inhibitory control of prior responses [99], which depends on frontal-striatal circuits [100,101].

Inhibition of previously-rewarded responses is a critical component of reversal learning, and this may be inhibited in $Met^{fx/fx}/Dlx^{Cre}$ and $Plaur^{-/-}$ mice [19,92]. It would therefore appear as though the loss of GABAergic (and in particular PV⁺) interneurons in the frontal cortex and striatum could contribute to the behavioral alterations observed in $Plaur^{-/-}$ mice, and possibly in $Met^{fx/fx}/Dlx^{Cre}$ mice as well. For example, the OFC has been shown to be required for normal reversal learning [93], and both $Plaur^{-/-}$ and $Met^{fx/fx}/Dlx^{Cre}$ mice show both reduced numbers of PV^+ interneurons in the OFC and impaired reversal learning. Furthermore, supplementation of HGF levels in $Plaur^{-/-}$ mice restores both PV cell number and reversal learning to normal [92]. While other causes cannot be ruled out, it would appear that the changes in interneuron numbers in the striatum and frontal cortex could lead to the behavioral changes seen in $Plaur^{-/-}$ and $Met^{fx/fx}/Dlx^{Cre}$ mice by altering cortical and striatal signaling. While cortico-striatal signaling has been shown to be altered in $Met^{fx/fx}/Emx1^{Cre}$ mice [82]. Further studies are needed to elucidate the effects of loss of Met signaling in excitatory neurons on behavior.

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This article was originally published in a special issue, **Animal Models in Autism** handled by Editor(s). Dr. Craig M. Powell, The University of Texas Southwestern Medical Center Dallas, USA