On the surface, it sounds strange to suggest that oncogenes, genes associated with cancer, could also be linked to the etiology of autism, but the action of these gene products, as well as gene variants, found associated with a significant number of autistic children, suggest otherwise. This editorial presents:

1. a summary of the actions of two oncogene related receptors, epidermal growth factor receptor (EGFR) and c-Met, as well as the primary ligands of these receptors, epidermal growth factor (EGF) and hepatocyte growth factor (HGF), respectively;
2. the research that supports the association of these products with cancer; and
3. evidence suggesting that these oncogene related proteins are also associated with diseases of the nervous system, specifically autism.

EGFR and c-Met are cell-surface tyrosine kinase receptors that have been implicated in diverse cellular processes and as regulators of several microRNAs (miRNAs), which contribute to tumor progression.1–6

EGF stimulates cell growth, proliferation, and differentiation by binding to its receptor, EGFR.7 HGF regulates cell growth, cell motility, and morphogenesis by activating a tyrosine kinase signaling cascade after binding to the proto-oncogenic c-Met receptor. Its ability to stimulate mitogenesis, motility, and matrix invasion gives it a central role in angiogenesis, tumorigenesis, and tissue regeneration.8

In cells, the tyrosine kinase activity of c-Met and EGFR initiates a signal transduction cascade. This results in changes in intracellular calcium levels, increased glycolysis and protein synthesis, which ultimately leads to DNA synthesis and cell proliferation.9 There is much evidence that there is crosstalk between EGFR and c-Met kinase pathways. For example, c-Met associates with EGFR in tumor cells, and this association facilitates the phosphorylation of c-Met in the absence of HGF.10,11 There is also evidence suggesting a synergistic effect of EGF and HGF tyrosine kinase inhibitors on cancer.
proliferation, and downstream activation of signal transduction resulting in an additive effect on motility. Therefore, c-Met is best known as an oncogene, but MET signaling also participates in the immune system regulation, embryogenesis, and in peripheral organ development and gastrointestinal repair.

These tyrosine kinase receptors are also associated with the nervous system structure, function, and pathology. MET and HGF, both expressed in the developing nervous system, have been implicated in neuronal development, specifically in the cerebral cortex and cerebellum. Impaired MET/HGF signaling interferes with interneuron migration and disrupts neuronal growth in the cortex and also leads to a decreased proliferation of granule cells, causing a parallel reduction in the size of the cerebellum.

These features have also been observed in the brains of autistic individuals. The role of aberrant MET signaling in interneuron development could be related to GABAergic pathophysiological changes in autism. A functional polymorphism in the MET gene promoter, which leads to decreased transcription of MET, significantly increases the risk for developing ASD, and disruption of MET and related gene expression in animal models results in altered GABA expression, as well as, epileptic and autistic-like behavior. Also, MET transcript and MET protein expression are decreased in the temporal cortex of individuals with autism.

EGFR, also mostly known most as a prominent oncogene product, is absent in mature astrocytes, but has been reported as sporadically present in astrocytes in various disorders of the CNS, ranging from tumor development to neurodegenerative diseases. Rapid upregulation of EGFR and its ligands occurs in astrocytes after ischemia, axotomy, electrolytic lesion, and entorhinal ablation. Upregulation is also observed in the damaged regions of brains in patients after stroke or with Alzheimer’s disease and in astrocytes of the optic nerves in patients with glaucoma. Owing to the known synergism and crosstalk between the c-Met and EGFR pathways, particularly the effect of EGF and HGF on proliferation, downstream activation of signal transduction and cell motility, our lab recently investigated EGFR in autistic children and found increased plasma levels of EGFR (unpublished, submitted data). However, to our knowledge, there have been no other reports of a relationship between EGFR and autism in the literature.

There is genetic evidence implicating involvement of multiple genes in the MET and possibly other receptor tyrosine kinase pathways such as EGFR, in autism spectrum disorders. The signaling ligands for these receptors, EGF and HGF have been found in abnormal concentration in autistic children. Our lab has reported decreased plasma HGF in autistic children with GI disease and decreased EGF in a general population of autistic children. Our research supports the work of others. Sugihara et al. found decreased HGF in an older (adult) autism group and Onore et al. found decreased EGF in autistic children.

It is unclear why plasma EGF and HGF levels are low in autistic children. However, decreased levels of both of these growth factors are more strongly associated with autistic children with GI disease, suggesting that altered intestinal physiology such as changed absorption or flora, may be involved. EGF and HGF both exhibit anti-inflammatory action, so decreased levels may be associated with increased inflammation seen in many individuals with autism.

There is mounting evidence to suggest that environmental and epigenetic factors play a stronger role in the etiology of autism. DNA methylation alterations have been found in multiple regions of the brains of individuals with autism and there may be an association between DNA methylation and regulation of c-Met and HGF levels. This suggests that epigenetic factors may be playing a role in EGF and HGF concentrations.

Receptor tyrosine kinases (RTKs), c-Met, and EGFR, when signaled, stimulate a cascade of reactions forming intermediate products such as ERK and PI3K. These intermediates and related products influence cell division, motility, and morphology changes. Supporting the notion that RTK pathways are associated with autism is the fact that certain neuro-syndromes, with high penetrance of ASD, have aberrant ERK and PI3K intracellular signaling pathways. Decreased PI3K activation may contribute in some instances to ASD, and disruption of PI3K signaling also has been implicated in other psychiatric disorders of neurodevelopmental origin, such as schizophrenia.

In summary, variants of the oncogene receptors, MET and EGFR, and decreased levels of their ligands HGF and EGF, respectively, are associated with autism. The tyrosine kinase activity of these receptors initiates a signal transduction cascade, which ultimately stimulates many cell processes, including cell growth, division, and repair mechanisms. We strongly suggest that it is important to continue to investigate the inheritance and epigenetics of these tyrosine kinase pathways as they might relate to the etiology of autism.

Author Contributions
Conceived the concept: AJR. Analyzed the data: AJR. Wrote the first draft of the manuscript: AJR. Made critical revisions: AJR. The author reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS
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REFERENCES


