

Reply to the Journal Club article by Sandra Peregrin Pedrique and Pietro Fazzari, reviewing Chen et al. (2010)

Yachi Chen

1 Department of Neurobiology and Behavior and Center for Nervous System Disorders, State University of New York at Stony Brook, Stony Brook, NY 11794; yachchen@ms.cc.sunysb.edu

In their Journal Club article, Sandra Peregrin Pedrique and Pietro Fazzari raised some excellent questions regarding our paper published in the Journal of Neuroscience. I thank them for critical review of our paper and would like to take this opportunity to respond. The first issue is that despite a reduction in dendritic growth and branching, the thickness of cortical plate, not cortical volume, is apparently normal in E19 Type III Nrg1 knockout mice. As we stated in our paper, this result is consistent with the finding in mice lacking ERBB4 (a candidate schizophrenia susceptibility gene) and ERBB2 showing no defects in cortical layered structure at P38 (Barros et al., 2009). Second, based on NRG1-ICD regulation of the postsynaptic density protein PSD-95, it would be interesting to study synaptogenesis and/or excitatory transmission between cortical pyramidal neurons in type III Nrg1 mutant animals as the reviewers suggest. Third, because NRG1-ICD has been previously shown to prevent apoptosis of sensory neurons in vitro (Bao et al., 2003), the question was asked as to whether the morphological defects of dendrites and axons of cortical neurons of the type III Nrg1 mutant mice might result from alterations in NRG1-ICD regulated apoptotic gene expression. It remains to be determined if NRG1-ICD similarly controls apoptotic gene expression in cortical neurons. In addition, as indicated in the “Methods” we only analyzed the growth and branching patterns of axons and dendrites of cortical neurons with intact nuclei showing no signs of nuclear fragmentation. We therefore believe that the axonal and dendritic defects of cortical neurons do not result from altered apoptotic gene expression. Fourth, the issue is raised on whether neuronal activity may trigger type III NRG1 proteolytic processing and signaling in our E18/E19 cortical cultures. In young cortical cultures prepared from E17 rat embryos, spontaneous neuronal activity appeared as early as 3 DIV (Kamioka et al., 1996). Neuronal activity therefore may play a potential role in type III NRG1 processing and function in cortical development. Another question is whether cells over-expressing the wild type version of type III NRG1 showed significantly higher level of transcriptional activation compared to that of control cells transfected with an empty vector in the absence of exogenous ERBB4. Our analysis did not indicate a statistical significance (Kruskal-Wallis One Way Analysis of Variance on Ranks).

Finally, the issue is raised as to whether normal growth and branching of cortical dendrites in ERBB4-deficient mice might result from functional redundancy of other members of...
the ERBB family. Among the 4 members of ERBB family, ERBB3 binds NRG1 but has an impaired tyrosine kinase domain. ERBB4 also binds to NRG1 and has a functional kinase domain. EGFR (or ERBB1) and ERBB2 do not bind NRG1. Therefore, EGFR can form functional dimers with ERBB4 whereas ERBB2 dimerizes with ERBB3 or ERBB4 to become catalytically active. As such, the catalytically active ERBB dimers that can be stimulated by NRG1 include: ERBB1/ERBB4, ERBB2/ERBB4, ERBB2/ERBB3 and ERBB4/ERBB4. In ERBB4-deficient mice, NRG1 binding activates only the ERBB2/ERBB3 heterodimer. However, ERBB2/ERBB3 heterodimers are most likely not present in E18/E19 cortical culture in our study because ERBB3 mRNA is not detected within the mouse brain during prenatal development and is only expressed in white matter tracts in adulthood (Fox and Kornblum, 2005). Furthermore, our results, showing normal dendritic morphology of cortical neurons in the presence of a pharmacological inhibitor that blocks the kinase activity of all ERBB members, provide additional support of our conclusion that type III NRG1 regulation of dendritic development does not require ERBB kinase activity.

References


