ErbB4 Can Promote Inhibitory Synapse Formation by Cell Adhesion, Independent of Its Kinase Activity

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ErbB4 plays a critical role in neurodevelopment and has been suggested as susceptibility gene of schizophrenia. Although it is well-known as a tyrosine kinase, ErbB4's function independent of its kinase activity remains unknown. To address this question, we first transfected a kinase-deficient ErbB4 gene into HEK293T cells and found induction of postsynaptic clustering in co-cultured neurons. To further confirm whether kinase activity is important for the functioning of ErbB4, we generated ErbB4-K751M mice, which loss their kinase activity from germ cells. Surprisingly, we found that ErbB4-K751M mice showed normal interneuron migration, inhibitory synapse formation and neurotransmission. Behavioral tests including open field test, contextual fear-conditioning and pre-pulse inhibition showed no deficits either. Notably, co-IP suggests an interaction between ErbB4 and SLIT And NTRK Like Family Member 3 (Slitrk3) which locates at the inhibitory postsynaptic site and is critical for synapse formation. After blocking this interaction, the synaptic transmission decreased in a non-cell autonomous manner. These observations indicate that in contrast to its known kinase activity, ErbB4's more important role, therefore, might be as a cell adhesion molecule interacting with Slitrk3 at the synapse. Together, ErbB4 might function as a cell adhesion molecule that is important in both neurodevelopment and neurotransmission.