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CTGF/CCN2 facilitates LRP4-mediated formation of the embryonic neuromuscular junction

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Abstract

At the neuromuscular junction (NMJ), lipoprotein-related receptor 4 (LRP4) mediates agrin-induced MuSK phosphorylation that leads to clustering of acetylcholine receptors (AChRs) in the postsynaptic region of the skeletal muscle. Additionally, the ectodomain of LRP4 is necessary for differentiation of the presynaptic nerve terminal. However, the molecules regulating LRP4 have not been fully elucidated yet. Here, we show that the CT domain of connective tissue growth factor (CTGF/CCN2) directly binds to the third beta-propeller domain of LRP4. CTGF/CCN2 enhances the binding of LRP4 to MuSK and facilitates the localization of LRP4 on the plasma membrane. CTGF/CCN2 enhances agrin-induced MuSK phosphorylation and AChR clustering in cultured myotubes. Ctgf-deficient mouse embryos ($Ctgf^{-/-}$) have small AChR clusters and abnormal dispersion of synaptic vesicles along the motor axon. Ultrastructurally, the presynaptic nerve terminals have reduced numbers of active zones and mitochondria. Functionally, $Ctgf^{-/-}$ embryos exhibit impaired NMJ signal transmission. These results indicate that CTGF/CCN2 interacts with LRP4 to facilitate clustering of AChRs at the motor endplate and the maturation of the nerve terminal.