GRP78 is essential for NMJ formation and maintenance

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The neuromuscular junction (NMJ) is a peripheral synapse between motor nerves and skeletal muscle fibers. It is critical to muscle contraction. NMJ formation is controlled by agrin, a factor released from motor neurons that binds to LRP4 (a LDLR family member) to activate the receptor tyrosine kinase MuSK in muscle cells and thus promotes the aggregation of acetylcholine receptors (AChRs). Recent data suggest that the agrin-LRP4-MuSK signaling is also important for NMJ maintenance. However, mechanisms controlling the signaling pathway are not well understood. To this end, we attempted to identified proteins that interact with LRP4 with an idea that they may regulates its stability or function. We purified the LRP4 complex from HSA-Flag-LRP4 transgenic mice where Flag-LRP4 is specifically expressed in skeletal muscles and identified GRP78 by mass spectrometry. GRP78 is a molecular chaperone critical for protein transport. We show that GRP78 was concentrated at the NMJ, and at postsynaptic sarcoplasmic reticulum. Muscle-specific knockout of GRP78 reduced LRP4 in muscles and leads NMJ deficits including excessive axon arborization and reduced AChR clusters. To characterize the roles of GRP78 in adult, we generated HSA-CreER;GRP78F/F mice, in which Cre could be induced by tamoxifen. We found that NMJs became fragmented and denervated in adult mice where GRP78 was inducibly knocked out. These results demonstrate a critical role of GRP78 in NMJ formation and maintenance, identify a novel play in regulating the agrin signaling pathway.