Selective Axonal Translation of Prenylated *Cdc42* mRNA Isoform Supports Axon Growth

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Abstract: The small Rho-family GTPase Cdc42 has long been known to have a role in cell motility and axon growth. The eukaryotic *cdc42* gene encodes for two different mRNAs with different C-termini and different 3'UTRs. These C-termini have motifs for the post-translational modifications, prenylation and palmitoylation. The palmitoylated-Cdc42 was shown to contribute to dendrite maturation while the prenylated-Cdc42 contributes to axon specification in hippocampal neurons. These two Cdc42 mRNA isoforms also have different 3'UTRs and we show that the mRNA encoding prenylated-Cdc42 isoform preferentially localizes into axons. The prenylated-Cdc42 and not the palmitoylated-Cdc42 supports axon growth in cultured sensory neurons, and this growth promotion requires axonal localization of the

encoding mRNA. Using siRNA rescue approaches, we show that targeting the palmitoylated Cdc42 mRNA into axons by 3'UTR swapping or mutating the prenylation site in the axonally localizing mRNA can only partial rescue when both Cdc42 isoforms are depleted, indicating that both localization and intra-axonal translation as well as the intact motif for prenylation are required for the full growth promoting effects of Cdc42.