Identification and Characterization of a Novel, Isoform-Specific Phosphorylation Site of Collapsin Response Mediator Protein 1

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ABSTRACT

In vertebrates collapsin response mediator proteins (CRMPs) form a class of cytosolic phosphoproteins composed of five isoforms, CRMP1-5. This class of proteins has been most readily described with their involvement in Semaphorin 3A signaling, resulting in growth cone collapse of migratory neurons. Several threonine/ serine phosphorylation sites in the C-terminal regulatory domain of CRMPs have been previously described. Phosphorylation of these sites are thought to disrupt the protein's binding to tubulin heterodimers. Through a large-scale proteomic analysis of murine brain, we have identified a novel phosphorylation site, CRMP1 tyrosine 504 (Y504). We found this site is a primary target of the Src family of tyrosine kinases (SFKs), specifically Fyn. Site-directed mutagenesis, paired with functional experiments are being used to determine if this phosphorylation regulates CRMP binding to tubulin heterodimers. These experiments may help explain why CRMP1 deficient mice exhibit neuronal migration defects that cannot be compensated by CRMPs 2-5.