A cell-type-specific alternative splicing regulator shapes synapse properties in a trans-synaptic manner

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The specification of synaptic properties is fundamental for the function of neuronal circuits. ”Terminal selector” transcription factors coordinate terminal gene batteries that specify cell-type-specific properties. Moreover, pan-neuronal splicing regulators have been implicated in directing neuronal differentiation. However, the cellular logic of how splicing regulators instruct specific synaptic properties remains poorly understood. Here, we combine genome-wide mapping of mRNA targets and cell-type-specific loss-of-function studies to uncover the contribution of the RNA-binding protein SLM2 to hippocampal synapse specification. Focusing on pyramidal cells and somatostatin (SST)-positive GABAergic interneurons, we find that SLM2 preferentially binds and regulates alternative splicing of transcripts encoding synaptic proteins. In the absence of SLM2, neuronal populations exhibit normal intrinsic properties, but there are non-cell-autonomous synaptic phenotypes and associated defects in a hippocampus-dependent memory task. Thus, alternative splicing provides a critical layer of gene regulation that instructs specification of neuronal connectivity in a trans-synaptic manner.
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