

# A neuron specific alternative STIM1 splice variant recruits new signaling complexes to affect presynaptic release

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Store-operated Ca<sup>2+</sup> entry is a ubiquitous mechanism that contributes to the regulation of basal and receptor-triggered Ca<sup>2+</sup> concentrations thereby governing signaling and cell homeostasis. The two known isoforms STIM1 and STIM2 sense the ER Ca<sup>2+</sup> content and oligomerize to trigger Ca<sup>2+</sup> entry by gating Orai channels. We have characterized a novel STIM1 splice variant, STIM1B, where neuronal-specific insertion of an additional short exon (11B) results in a C-terminally truncated STIM1 lacking 145 amino acids including part of the C-terminal inhibitory domain (CTID), microtubule associated EB binding sites, the S/P rich region and the polybasic domain. STIM1B shows slower kinetics of cluster formation and I<sub>CRAC</sub> activated by STIM1B shows reduced slow calcium-dependent inactivation (SCID). STIM1B is the predominant STIM1 isoform in cerebellar Purkinje neurons but also displays prominent expression in hippocampal as well as other neurons where it preferentially localizes to neurites in contrast to a more somatic STIM1wt localization. Specifically, in autaptic hippocampal neurons, STIM1B, but not STIM1 causes synaptic facilitation upon high frequency stimulation, demonstrating that cell-type specific splicing may adapt neuronal SOCE to support synaptic function [1]. Current work aims at delineating the targeting of SOCE components in neurons using CRISPR/Cas9-mediated epitope tagging of endogenous proteins, understanding frequency dependent regulation of transmitter release by intracellular Ca<sup>2+</sup> stores, identifying the specific sequence and the mechanisms responsible for exon specific function as well as investigating the role of recruited additional channels and regulators.

[1] Ramesh G, Jarzembowski L, Schwarz Y, Konrad M, Poth V, Schwär G, Lauer AA, Grimm MOW, Alansary D, Bruns D, Niemeyer BA: Short novel STIM1B uncovers a mechanism of synaptic enhancement, Cell Reports, 2021, 34, 108844.

