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# Structural and binding studies of the Cav1.1 β1A subunit

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**Abstract**
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**Structural and Binding Studies of the Cav1.1 β1A Subunit**

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Excitation-contraction (EC) coupling in skeletal muscle requires a physical coupling between the voltage-gated calcium channel (Cav1.1) in the surface membrane and the skeletal ryanodine receptor (RyR1) $Ca^{2+}$ release channel in the membrane of the sarcoplasmic reticulum $Ca^{2+}$ store. Although the exact molecular mechanism of EC coupling is unresolved, both the α1s and β1a subunits of Cav1.1 are essential for this process. The β1a subunit has a modular structure consisting of SH3/guanylate kinase (GK) domains separated by a variable hook region. The GK domain binds with high affinity to the I-II loop of the α1 subunit, but the functional significance of the SH3 domain remains undefined.

Until now the structure of the Cav1.1 β1a subunit has not been experimentally determined, but other Cav β-isoform structures have suggested that the SH3 binding site is occluded, preventing binding to polyproline-rich partners. This prediction is at odds with our findings that show the Cav1.1 β1a subunit and the α1s subunit II-III loop interact (Kd = ~3 μM). We demonstrate that this interaction takes place through the SH3 domain of the β1a subunit and a proline-rich region of the α1s II-III loop, which has previously been shown to be critical for skeletal-type EC-coupling (1). Through mutational studies we demonstrate that isoform-specific differences in the SH3 RT loop enable the interaction of the β1a SH3 domain with proline-rich binding motifs.

Our determination of the crystal structure of Cav1.1 β1a provides the first opportunity to examine differences between this isoform and other published structures. In light of this novel structure and binding data, we discuss the specific role of the β1a subunit in EC coupling and its relationship with the Cav1.1 α1 subunit and RyR1.

1. Kugler, G. et al (2004). J Biol Chem 279(6): 4721-4728.