Structural and binding studies of the Cav1.1 β1A subunit

Marco Casarotto
Australian National University

Yamuna Karunasekara
Australian National University

Shouvik Aditya
Australian National University

Jean Cappello
Australian National University

Angela Dulhunty
Australian National University

See next page for additional authors

Follow this and additional works at: https://ro.uow.edu.au/smhpapers

Part of the Medicine and Health Sciences Commons, and the Social and Behavioral Sciences Commons

Recommended Citation
Casarotto, Marco; Karunasekara, Yamuna; Aditya, Shouvik; Cappello, Jean; Dulhunty, Angela; Board, Philip; Oakley, Aaron; and Norris, Nicole C., "Structural and binding studies of the Cav1.1 β1A subunit" (2014). Faculty of Science, Medicine and Health - Papers: part A. 2241.
https://ro.uow.edu.au/smhpapers/2241

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library: research-pubs@uow.edu.au
Structural and binding studies of the Cav1.1 β1A subunit

Abstract
Abstract of poster presentation.

Disciplines
Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Authors
Marco Casarotto, Yamuna Karunasekara, Shouvik Aditya, Jean Cappello, Angela Dulhunty, Philip Board, Aaron Oakley, and Nicole C. Norris
Structural and Binding Studies of the Cav1.1 β1A Subunit

Marco G. Casarotto, Yamuna Karunasekara, Shouvik Aditya, Jean Cappello, Angela F. Dulhunty, Philip G. Board, Aaron J. Oakley, Nicole C. Norris.

1Australian National University, Canberra, Australia, 2University of Wollongong, Wollongong, Australia.

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.