Fine mapping titin's C-zone: Matching cardiac myosin-binding protein C stripes with titin's super-repeats.

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Abstract

Titin is largely comprised of serially-linked immunoglobulin (Ig) and fibronectin type-III (Fn3) domains. Many of these domains are arranged in an 11 domain super-repeat pattern that is repeated 11 times, forming the so-named titin C-zone in the A-band region of the sarcomere. Each super-repeat is thought to provide binding sites for thick filament proteins, such as cMyBP-C (cardiac myosin-binding protein C). However, it remains to be established which of titin's 11C-zone super-repeats anchor cMyBP-C as titin contains 11 super-repeats and cMyBP-C is found in 9 stripes only. To study the layout of titin's C-zone in relation to MyBP-C, immunolabeling studies were performed on mouse skinned myocardium with antibodies to titin and cMyBP-C, using both immunoelectron microscopy and super-resolution optical microscopy. Results indicate that cMyBP-C locates near the interface between titin's C-zone super-repeats. Studies on a mouse model in which two of titin's C-zone repeats have been genetically deleted support that the first Ig domain of a super-repeat is important for anchoring cMyBP-C but also Fn3 domains located at the end of the preceding repeat. Furthermore, not all super-repeat interfaces are equal as the interface between super-repeat 1 and 2 (close to titin's D-zone) does not contain cMyBP-C. Finally, titin's C-zone does not extend all the way to the bare zone but instead terminates at the level of the second myosin crown. This study enhances insights in the molecular layout of the C-zone of titin, its relation to cMyBP-C, and its possible roles in cardiomyopathies.

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