

University of Maryland Baltimore Graduate School

Announcement of Doctoral Dissertation Defense*

Candidate: Maegen A. Borzok

Date, Time, and Place: Dec. 19, 2007, 11 AM, HSFII room S600 (the room is still tentative)

Dissertation Title: Identifying the roles of sAnk1 through its interaction with Obscurin

Dissertation Abstract**:

The myoplasm of adult muscle fibers contains two highly ordered components that are necessary for contraction, myofibrils and their associated membranes, but the mechanisms that assemble these structures and align them so precisely during development are still poorly understood. Striated muscle has two systems of internal membranes, the sarcoplasmic reticulum (SR) and the transverse tubules (t-tubules) that, in coordination with the sarcolemma, modulate cytosolic Ca^{2+} release, through the Ca^{2+} release channel (ryanodine receptor, or RyR), and reuptake, through the Ca^{2+} -ATPase of the SR (SERCA), during cycles of contraction and relaxation, respectively. Close and spatially precise association of the compartments of the SR with the contractile apparatus is necessary for proper contraction and relaxation of striated muscle. To date, little is known about the interactions that maintain this association.

Here I propose a mechanism in which two proteins, small ankyrin 1 (sAnk1, Ank1.5), a transmembrane protein of the network SR, and obscurin, a giant protein that wraps around the sarcomere at the level of M-bands and Z-disks, where the network SR concentrates, bind to each other to form a scaffold that organizes the network SR around the the contractile apparatus. I have used two methods to address this hypothesis. First, I have assessed the biochemical nature of the interaction between sAnk1 and obscurin. I have shown that the binding between sAnk1 and obscurin is mediated primarily by electrostatic interactions that involve patches of positively charged residues localized to the surface of the sAnk1 molecule and that are present in ankyrin repeats. Second, I have used RNAi technology to reduce the expression of sAnk1 in adult muscle fibers and then assessed the changes in the subcellular architecture of the myofibers. In fibers with reduced levels of sAnk1, other proteins of the network SR, specifically SERCA and sarcolipin, a SERCA-regulatory protein, are also disrupted. These effects were specific however, as RNAi targeting sAnk1 caused no change in the expression or organization of obscurin or other proteins associated with sarcomeres. Markers of the terminal cisternae of the SR, including ryanodine receptor, calsequestrin, and junctophilin, as well as Ca^{2+} channels (DHPR) in the transverse tubules, were not significantly affected, although their localization around the A-I junctions of myofibers were not as precise when sAnk1 expression was reduced. These results suggest a novel function for sAnk1 in the organization of the network SR, which is likely to be mediated by its interaction with obscurin.

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The Open Presentation is open to the university community and invitees of the candidate. Any member of the Graduate Faculty may observe the Final Examination. Only committee members may vote. For more information, see **Procedures for Examination of the Doctoral Dissertation.*

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Updated: February 24, 2006