Toward understanding the structure of Amot's ACCH Domain

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Amots are a family of adaptor proteins widely involved in cell signaling and lipid binding. Amot80 has been linked to cellular proliferation in breast cancer via the VEGF and MAPK signaling pathways, while Amot130 and AmotL1 have been linked to cellular inhibition via the HIPPO signaling pathway. Amot family members also have a characteristic lipid-binding domain – named the ACCH Domain for its predicted coil-coil structure – that has the ability to selectively target phosphoinositols followed by deformation of the membrane. Understanding the structure-function relationship of this domain may provide options to modulate these signaling pathways, directly affecting cellular differentiation, proliferation, and migration. Extensive crystallization attempts for this domain have failed, leading to a bioinformatics and biophysics-combined approach. Using SAXS, data for the globular structure of Amot80 has been generated and analyzed. Additionally, the threading programs ITASSER and LOMETS were used to develop 20 computational theoretical models. By fitting the computational models to the SAXS data, potential ACCH domain models were generated, and then scored based on accuracy of fit via C-score, TM-Score, and RMSD values. This 3D model can then be used to discover how Amot interacts with lipids and further the understanding of Amot's role in the cancer-signaling cascade.