

Structural Characterization of the ACCH Domain of Angiomotin Family Members

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The Angiomotin (Amot) family of adaptor proteins directly coordinates signaling events during cellular and neural differentiation and proliferation. A critical feature of all Amot proteins is a novel lipid binding domain, the Amot coiled-coil homology (ACCH) domain, which confers its association with membranes and affects membrane curvature and deformation. Specifically, this domain has the unique ability to selectively bind monophosphorylated phosphatidylinositols (PIs) and cholesterol. Furthermore, Amot family members bind core polarity proteins that control the organization of the apical domain of epithelial cells as well as Yap, a transcriptional co-activator that appears to be the key regulator of cell growth.

Amots have been shown to have a critical role in endothelial and epithelial cell migration, invasion, and tubule formation, and they are believed to regulate angiogenesis, which promotes tumor growth and metastasis. Amot overexpression and mutations have been linked to neuroepithelial tumors, such as glioblastomas, brain hemangioendotheliomas, neurofibromatosis, and many other cancers, such as breast cancer. The role of Amots in epithelial and endothelial cancer growth and metastasis have been linked to poor prognosis and unfavorable clinical outcomes.

Understanding the structure-function relationship of the ACCH domain may provide pathways to modulate protein sorting and downstream signaling events inducing cellular differentiation, cancer cell proliferation, and cell migration. The goal of this project is to generate a solution structure of the Amot80/130 and AmotL2 (Mascot) ACCH domains using SAXS and WAXS data as well as various protein modeling software, thereby suggesting possible routes to modulate their activity associated with various tumors. Additionally, this structure will be compared against theoretical models to determine the statistical accuracy of the theoretical models. Furthermore, we hypothesize that generating these models will allow us to determine the structure of another analogue of A80/130, the Angiomotin-like 1 (JEAP) ACCH domain.