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Structural insights into the organization of the cavin membrane coat

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Caveola membrane invaginations are a striking feature of many vertebrate cell types, and are critical for cell signaling, endocytosis and mechanotransduction. Their formation depends on the caveolins and the cavin peripheral membrane proteins (cavin1, cavin2, cavin3 and cavin4), although there is currently no atomic level information addressing the mechanisms that underpin caveola assembly. Here we show that a minimal N-terminal domain of the cavin proteins (the HR1 fragment) is required and sufficient for their homo and hetero-oligomerisation. The crystal structures of mouse cavin1 and zebrafish cavin4 HR1 domains reveal highly conserved trimeric coiled-coil architectures, with unique intra-subunit interactions that determine the specificity of coiled-coil formation. A conspicuous feature of the HR1 domain is a basic surface patch, conserved among all cavins and across all species, which we show can mediate interaction with negatively-charged membrane lipids including phosphoinositides. Mutations in this domain prevent membrane association and perturb caveolae formation in vivo. Interestingly the cavin proteins possess intrinsic membrane remodeling properties in vitro, that we propose is important for the formation of caveolae. Finally, we show that full-length cavin proteins possess characteristic rod-shape structures that reflect the coiled-coil architecture of the HR1 assembly domain and have dimensions corresponding closely to the striations observed on the surface of caveolae in vivo. We therefore propose the striations forming the common coat of caveola are composed of polymerised cavin trimers.

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Summary

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