Avidity-driven polarity axis establishment via multivalent lipid-GTPase module interactions.

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While Rho GTPases are indispensible regulators of cellular polarity, the mechanisms underlying their anisotropic activation at membranes have been elusive. Using the budding yeast Cdc42 GTPase module, which includes a Guanine nucleotide Exchange Factor (GEF) Cdc24 and the scaffold Bem1, we recently reported that avidity generated via multivalent anionic lipid interactions is a critical mechanistic constituent of polarity establishment. We identified basic cluster (BC) motifs in Bem1 that drive the interaction of the scaffold-GEF complex with anionic lipids at the cell pole. This interaction appears to influence lipid acyl chain ordering, thus regulating membrane rigidity and feedback between Cdc42 and the membrane environment. Sequential mutation of the Bem1 BC motifs, PX domain and the PH domain of Cdc24 led to a progressive loss of cellular polarity stemming from defective Cdc42 nanoclustering on the plasma membrane and perturbed signaling [1]. Our work demonstrates the importance of avidity via multivalent anionic lipid interactions in the spatial control of GTPase activation [2].

[1] Sartorel E, Ünlü C, Jose M, Massoni-Laporte A, Meca J, Sibarita JB and McCusker D. (2018). Phosphatidylserine and GTPase activation control Cdc42 nanoclustering to counter dissipative diffusion. *Molecular Biology of the Cell.* 29: 1299-1310.

[2] Meca J, Massoni-Laporte A, Sartorel E, Martinez D, Loquet A, Habenstein B and McCusker D. (2018). Avidity-driven polarity axis establishment via multivalent lipid-GTPase module interactions. *The EMBO Journal.* e99652.