Quick guide

Diaphanous-related Formin homology proteins

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What are Diaphanous-related Formin homology (DRF) proteins? DRF proteins constitute a subfamily of Rho GTPase-binding Formin homology (FH) proteins, first defined after the discovery of conserved FH1 and FH2 domains shared between Diaphanous and Bni1p, required for cytokinesis in flies and yeast, respectively, and Formins, limb deformity genes in mice. As effectors for activated, GTP-bound Rho, DRFs are involved in remodeling actin and microtubule networks, intracellular mRNA trafficking, serum response factor-regulated gene expression, and cytokinesis. DRFs are distinct from other FH proteins in possessing conserved amino-terminal GTPase-binding and carboxy-terminal Dia-autoregulatory domains (called GBD and DAD, respectively). Human DRF defects are associated with deafness and infertility.

How are they regulated? Rho activates DRFs by binding to the GBD and disrupting the GBD–DAD interaction (see Figure 1). Autoinhibition can be relieved experimentally by GBD truncation or by overexpression of the DAD domain, which mimics Rho binding. Both cause microfilament and microtubule rearrangements similar to the effects of activated Rho proteins. It is not known how activation affects DRF biological activities; the only known Rho-regulated event is the release of DAD from its intramolecular association.

How do DRFs manipulate microfilaments? Truncated Bni1p, consisting of its FH1-FH2 domains and a portion of its carboxy-terminal coiled coil, is sufficient to cause barbed-end nucleation of actin microfilaments *in vitro*. Similar observations have been made for the mammalian DRFs (H. Higgs, personal communication). Although there is no evidence that this minimal region is sufficient to increase cellular F-actin content, its expression promotes the formation of what seem to be tightly bundled actin cables in budding yeast.

How do DRF proteins signal to microtubules? Rho activation of DRFs in animal cells promotes microfilament-microtubule alignment and microtubule stabilization. Genetic evidence suggests that DRFs may act as conduits between Rho GTPases and microtubule end-binding proteins that modulate microtubule dynamics.

Do DRFs collaborate with other cytoskeletal remodeling proteins? Yes, and some of these, such as profilin, Src non-receptor kinases and other scaffold proteins, IRSp53, and WISH/DIP/SPIN90, also associate with the WASP family of autoregulated/GTPase-activated scaffold proteins. DRFs also form complexes with two other F-actin binding proteins, Bud6p and peptide elongation factor 1α (eEF1A). Genetic and biochemical experiments in yeast and animal cells illustrate an important role for DRFs in mRNA targeting, a critical process in the dynamic regulation of cell morphology.

Where can I find out more?

Chang, F. and Peter, M. (2002). Cell biology. Formins set the record straight. Science *297*, 531–532.
Gundersen, G.G. (2002). Evolutionary conservation of microtubule-capture mechanisms. Nat. Rev. Mol. Cell Biol. *3*, 296–304.
Hollenbeck, P. (2001). Cytoskeleton: Microtubules get the signal. Curr. Biol. *11*, R820–R823.

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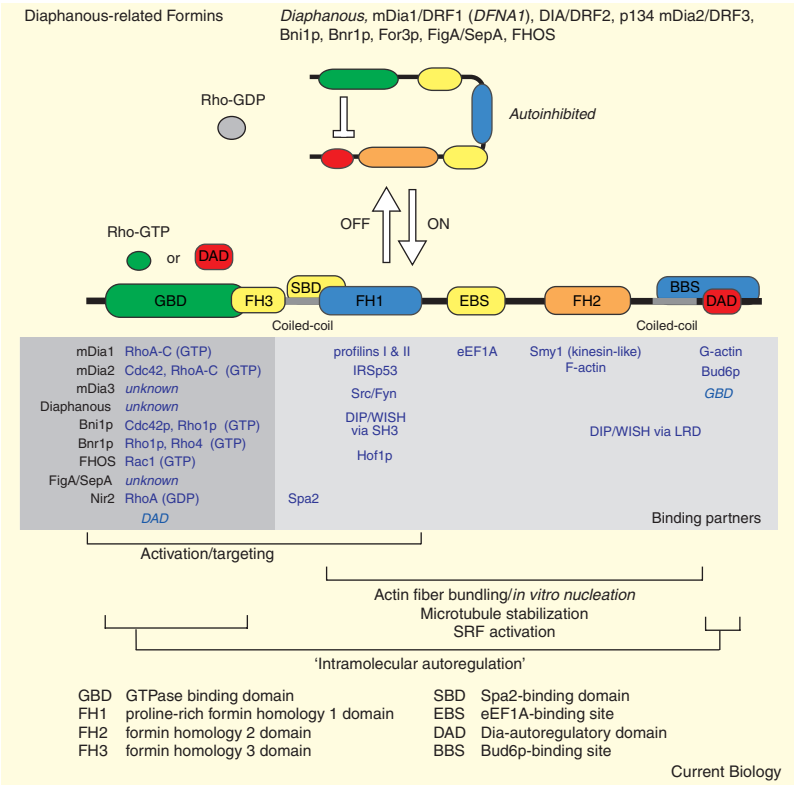

Figure 1. Molecular regulation of the Diaphanous-related Formins.
In addition to the FH domains, DRFs share a loosely conserved GBD and the highly conserved DAD; DAD is similar to WASP/Scar WH2 domains and likewise binds G-actin (A.S.A. and B. Wallar, unpublished observation). Known binding partners for the indicated domains are indicated in the grey box. Functional attributes for the various regions are indicated by the brackets.