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InaD PDZs 4-5 Act as an Allosterically-Regulated Dynamic Scaffold STEPHEN HELMS, UT Southwestern, PRASHANT MISHRA, Caltech, MICHAEL SOCOLICH, RAMA RANGANATHAN, UT Southwestern — The *Drosophila* scaffolding protein InaD is required for proper visual signaling. We previously identified that the fifth PDZ domain of InaD undergoes light-dependent PKC-mediated formation of a disulfide bond which disrupts the binding site. We investigated the interaction of this switch with the adjacent PDZ4 of InaD. We showed that PDZ4 destabilizes the disulfide bond and promotes binding of PDZ5 to its ligand, indicating a previously unidentified allosteric interaction between the two domains. We solved the structure of PDZ45 to 2.4Å, which revealed that PDZ4 forms an extensive interface with PDZ5 but does not alter its conformation. NMR HSQC spectra, however, indicated that nearly all of PDZ5 is in a different chemical environment in PDZ45. Finally, we identified that PDZ45 is phosphorylated by PKC in vitro at a site located near the domain interface. Intriguingly, the disulfide bond in PDZ5 is an evolutionary adaptation of just fast-flying flies, revealing the remarkable ability of evolution to rapidly build novel regulatory features into scaffolding proteins.

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