Transcriptional regulation by conditional co-operativity mediated by allosteric coupling between two disordered domains

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Regulation of the *phd/doc* toxin-antitoxin operon involves the toxin Doc as co- or de-repressor depending on the ratio between Phd and Doc. This unexplained transcriptional regulatory phenomenon is known as conditional cooperativity. Binding of Doc to the intrinsically disordered C-terminal domain of Phd structures the DNA binding domain of Phd, for the first time illustrating allostery between two distinct disordered protein domains. This coupling is disrupted in certain mutants of Phd that nevertheless retain wild type like binding of Doc. The Phd/Doc complex consists of a Doc monomer sandwiched between two Phd dimers. When bound to Doc, the Phd C-terminus adopts two different conformations that interact with distinct binding sites on the Doc surface. Both sites are required for Doc-mediated enhancement of the Phd-operator DNA affinity. Our combined structural and biochemical data allow us to put forward a model for the regulation of the phd/doc operon that explains conditional co-operativity. We propose that a monomeric Doc molecule, capable of interacting with two Phd dimers simultaneously, acts as a bridge between two Phd dimers, increasing the avidity of Phd for DNA and thus enhancing the repression of the operon. Moreover our studies on Phd provide for the first time direct experimental evidence demonstrating allosteric coupling between two disordered domains. The N-terminal domain of Phd exists in solution as an equilibrium between a DNA binding-competent ordered state and a DNA binding-incompetent disordered state. The equilibrium between both states is influenced not only by its direct ligand, the operator site, but also by binding of the Doc co-repressor to the intrinsically disordered C-terminal segment of Phd.

Reference: A. Garcia-Pino, S. Balasubramanian, L. Wyns, E. Gazit, H. De Greve, R.D. Magnuson, D. Charlier, N.A.J. Van Nuland, R. Loris, *Cell* **142**, 101-110 (2010)