Amino acid coevolution reveals novel monomer conformations in DNA-binding response regulators

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DNA-binding response regulators (DBRRs) function in tandem with their partner kinase proteins to form two-component signal transduction systems in bacteria. DBRR proteins are generally composed of an N-terminal receiver domain, which interacts directly with its kinase partner, and a C-terminal DNA-binding effector domain. Effector domains in comparison to receiver domains are more evolutionarily diverse, allowing for DBRR proteins to be further subdivided into multiple classes including the two most dominant classes: OmpR and NarL. However, interdomain residue interactions between the receiver and effector domains have not yet been extensively investigated. Here, we study the protein sequences of DBRR proteins belonging to these two main classes, analyzing amino acid coevolution to thoroughly investigate the evolutionary signatures of interdomain residue interactions. Coevolutionary analysis uncovered known interdomain and dimeric interactions as well as novel monomeric interdomain interactions. These novel monomeric conformations guided by residue interactions exhibited two conserved contact patches that inhibit the activation and DNA-binding functionality of DBRR proteins. These coevolutionary contacts suggest that the same functional mechanisms of DNA-binding regulation and interdomain cooperation are encoded in the two different DBRR classes. This work not only uncovers a missing piece of the DBRR life cycles, but also will contribute to developing response regulator-based biosensors by providing deeper understanding of functional cooperation between receiver and effector domains.