Evolution of Novel Response Element Specificity in the Glucocorticoid Receptor

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Abstract

Specific recognition of DNA response elements by transcription factors is a key step in the regulation of gene expression. Some transcription factors recognize multiple, distinct response elements to mediate transrepression of transactivation of target genes. However, the mechanism by which a single transcription factor can evolve to recognize multiple response elements is unclear. Here, we study the evolution of the glucocorticoid receptor, which recognizes distinct response elements to mediate activation or repression its target genes. The glucocorticoid receptor binds to activating glucocorticoid response elements, or (+)GREs, as a dimer to activate transcription. Alternatively, GR binds to negative glucocorticoid response elements (nGREs) in a monomeric fashion to repress transcription. We demonstrate that, of the extant 3-keto steroid receptors, only the glucocorticoid receptor can bind to and repress transcription in a nGRE-dependent manner, despite the ability of all 3-keto steroid receptors to bind to and activate gene transcription from (+)GREs. Surprisingly, using ancestral gene reconstruction, we find that nGRE binding and gene repression was a feature of the ancestor of all extant 3-keto steroid receptors. nGRE binding and repression originated as a subfunction of the ancestral 3-keto steroid receptor coincident with (+)GRE binding, and this subfunction was optimized in the evolutionary lineage of the glucocorticoid receptor but lost in the ancestors of the mineralocorticoid, progesterone, and androgen receptors. Further, using x-ray crystallography and other structural biology approaches, we define the structural mechanisms by which the modern-day DNA binding specificity evolved in the glucocorticoid receptor.