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Dynamic evolution of forkhead transcription factors and changes in their DNA-binding sites

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Forkhead box (Fox) proteins are transcription factors (TFs) related with various diseases. The Fox family, defined by a highly conserved winged helix DNA-binding domain (DBD), has diverged into dozens of subfamilies in animals, fungi, and related protists. We have used a combination of maximum likelihood phylogenetic inference and unbiased functional assays of DNA binding capacity to explore the evolution of DNA binding specificity within the Fox family. We present converging evidence that similar alternative sequence preferences have arisen repeatedly and independently in the course of Fox evolution. The vast majority of DNA binding specificity changes we observed are not explained by alterations in the known DNA-contacting amino acid residues conferring specificity for canonical Fox binding sites. Intriguingly, we have found Fox DBDs that retain the ability to bind very specifically to two completely distinct DNA sequence motifs. We propose an alternate specificity-determining mechanism whereby conformational rearrangements of the DBD broaden the spectrum of sequence motifs that a TF can recognize. DNA binding bispecificity suggests a new source of modularity and flexibility in gene regulation and may play an important role in the evolution of transcriptional regulatory networks [1]. In this conference, we will also discuss changes in Fox domain sequences and their binding sites by estimating ancestral sequences of several Fox subfamilies.

[1] Nakagawa S, Gisselbrecht SS, Rogers JM, Hartl DL, Bulyk ML., DNA-binding specificity changes in the evolution of forkhead transcription factors, *Proceedings of the National Academy of Sciences of the United States of America*,110(30):12349-12354, 2013.