

Faculty of Biology Paper of the Month: December 2013

Awarded to Graduate Student Iris Dror



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Covariation between homeodomain transcription factors and the shape of their DNA binding sites

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ABSTRACT

Protein–DNA recognition is a critical component of gene regulatory processes but the underlying molecular mechanisms are not yet completely understood. Whereas the DNA binding preferences of transcription factors (TFs) are commonly described using nucleotide sequences, the 3D DNA structure is recognized by proteins and is crucial for achieving binding specificity. However, the ability to analyze DNA shape in a high-throughput manner made it only recently feasible to integrate structural information into studies of protein–DNA binding. Here we focused on the homeodomain family of TFs and analyzed the DNA shape of thousands of their DNA binding sites, investigating the covariation between the protein sequence and the sequence and shape of their DNA targets. We found distinct homeodomain regions that were more correlated with either the nucleotide sequence or the DNA shape of their preferred binding sites, demonstrating different readout mechanisms through which homeodomains attain DNA binding specificity. We identified specific homeodomain residues that likely play key roles in DNA recognition via shape readout. Finally, we showed that adding DNA shape information when characterizing binding sites improved the prediction accuracy of homeodomain binding specificities. Taken together, our findings indicate that DNA shape information can generally provide new mechanistic insights into TF binding.