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How Transcription Factors Understand Genomes – And How to Manipulate their Function

How regulatory information is genomically encoded and interpreted by transcription factor (TF) proteins holds the key for understanding evolution, embryonic development and disease progression. Yet, how a limited number TF copies in a typical nucleus discriminate between the millions of theoretical DNA binding sites at a remarkable speed remains unclear. Selective DNA recognition events facilitated by direct protein partnerships play a critical role and have been under scrutiny in our laboratory. We initially set out to study the DNA motif grammar within developmental enhancers by integrating computational genomics, structural biochemistry and stem cell biology. This way, we learned that for the Sox and Oct TF families, protein-protein interaction but not protein-DNA interaction interfaces encode selectivity determinants for the combinatorial recognition of distinctly configured enhancer DNA. By leveraging on those fundamental insights, we were able to rationally engineer synthetic TFs and swap their roles in lineage determination. For example, we could turn Sox17 into a highly potent pluripotency reprogramming factor and Sox2 into an inducer of endodermal development reversing the function of the wild-type proteins. The re-engineering of Sox2 and Sox17 was achieved by reciprocal point mutations at the Oct4 interaction interface swapping the co-selection of composite DNA motifs. In extension of this work, we are now beginning to understand how allosteric events, indirect readout mechanisms and secondary DNA binding sites contribute to the specificity, cooperativity and functional versatility of TFs.