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by

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Designing C2H2 Zinc Finger Proteins to Target Specific DNA Sequences

ABSTRACT

Zinc fingers, the most abundant DNA binding motifs in eukaryotes, provide one of the simplest and best understood protein-DNA binding mechanisms. They promise to become valuable tools for genome modification and clinical intervention in disease because they can be used to target proteins, including nucleases and transcription factors, to virtually any desired location in any genome. Consisting of multiple modular and interchangeable nucleic acid binding domains, C2H2 zinc finger proteins provide an excellent framework for engineering new sequence-specific DNA binding proteins. Using known C2H2 zinc finger binding specificities, we have developed a program to locate candidate sequences for zinc finger binding within a given DNA sequence. In ongoing work, we are designing and experimentally testing additional zinc finger binding modules by exploiting knowledge-based approaches that incorporate information such as binding affinities, module position dependence, and DNA sequence/structural characteristics. Our short-term goal is to develop tools that can be used both to identify optimal DNA sites for targeting any desired genomic region and to predict optimal zinc finger protein sequences that recognize these sites with high affinity and specificity. Insight gained from these studies should be valuable in deciphering the "protein-DNA recognition code" that mediates gene regulation in cells.