Toward a Therapeutic Application of Artificial Transcription Factors

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We have developed novel methods for generating sequence-specific DNA-binding proteins that recognize predetermined DNA sequence elements. These DNA-binding proteins were then fused to domains that rendered the proteins capable of either up- or down-regulating the expression of genes whose promoter regions contain the target DNA sequences. To generate these artificial transcription factors, we first isolated diverse zinc fingers with distinct DNA-binding specificities. We used these zinc fingers as modular building blocks in the construct of novel, sequence-specific DNA-binding proteins. Fusion of these novel zinc finger proteins with either a transcriptional activation or repression domain yielded potent transcriptional activators or repressors, respectively. We were able to selectively activate or repress the expression of Vascular Endothelial Growth Factor (VEGF), a critical protein factor involved in tumor growth and metastasis, in human cells, using these artificial transcription activators or repressors, respectively. Taken together, these results indicate that the human genome encodes novel zinc fingers that have diverse DNA-binding specificities and that these domains can be used as modular building blocks to design new sequence-specific DNA-binding proteins and artificial transcription factors. Our approach, termed GeneGrip technology, should facilitate the construction of customized DNA-binding proteins for use in research, medicine, and biotechnology.