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TRANSCRIPTION FACTORS: A NEW FRONTIER IN PHARMACEUTICAL DEVELOPMENT?

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Recent advances in the understanding of transcription factor biology have led to the development of new strategies to aid in the search for human therapeutics. While natural products and synthetic compounds remain the primary source of potential therapeutics, the biological and pharmacological assays employing whole animals or isolated tissues are no longer the sole recourse for selection of efficacious small molecule pharmaceuticals. Within the last decade, characterization of the molecular pathways that regulate eukaryotic gene expression has given rise to the rational design of assays which target disease processes at the level of gene function. Compounds that inhibit or stimulate transcription factors associated with specific gene expression can now be developed into powerful new drugs.

The regulation of protein encoding genes involved in normal metabolic processes or correlated with disease progression occurs primarily at the level of transcription. Gene transcription, or the synthesis of mRNA from template DNA, is principally accomplished by RNA polymerase II (pol II). Pol II is unable to efficiently or accurately synthesize RNA without the close collaboration of a variety of associated proteins, termed transcription factors. General transcription factors (ubiquitous cellular proteins required for the transcription of all protein-encoding genes) aid pol II in aligning itself to the core promoter region of the gene [1, 2], which encompasses the transcription initiation site. Other transcription factors, which are specific to a subset of genes, bind to a second region of the promoter composed of many short (6–12 bp) sequence elements that regulate spatial and temporal expression of the gene. These regulatory elements may be a few hundred base pairs upstream (or downstream) from the transcription initiation site, or located many kilobases away. Collectively, these regions may bind several different gene-specific transcription factors, each of which may effect transcription initiation and rate [3, 4]. Cross-talk between DNA-bound, gene-specific transcription factors may also contribute positively or negatively to the process.

Transcription factors are well-qualified targets for pharmaceutical development on three counts: diversity, specificity and central role in human disease. It has been estimated that the human genome encodes as many as 3000 different gene-specific transcription factors [5], 300 of which have already been described. When considering systemic administration of therapeutics, gene-specific factors are advantageous in their promoter-specificity and regulation of expression of only a limited number of genes. Additionally, no two gene-specific factors are identical, providing unique biological surfaces for drug targeting. Gene-specific factors are commonplace in human disease, and count among their ranks one third of all known proto-oncogenes. Anti-oncogenic factors, including p53 [6] and WT-1 (Wilms' tumor gene) [7], are also members of this group. The life cycles of many viral pathogens are dependent upon virally-encoded transcription factors as well. For example, the virally encoded protein VP16 of the herpes simplex virus (HSV) initiates the cascade of viral gene expression that arises following viral infection [8]. The advantage of target specificity in this last case is especially evident, as disrupting the function of virally-produced VP16 would have no detrimental effect on human cellular function.

Gene-specific transcription factors are composed of functionally distinct domains which predispose them to the effects of small-molecule pharmaceuticals. One domain recognizes a specific DNA sequence and binds it, and another interacts with the general transcriptional machinery and either facilitates or inhibits transcription initiation. If the factor binds DNA as a multimer (most often a dimer), a domain for multimerization will also be present. Targeting any one of these three domains would result in a loss of function, along with the associative loss of transcriptional regulation. Interaction with either the DNA binding region or the multimerization region would prevent the factor from adhering to its target sequence, whereas binding to the transcriptional activation domain could interfere with transcription initiation alone and still permit sequence-specific DNA binding. Some multi-component systems may present even more surfaces for drug interaction: VP16, the aforementioned virion protein of HSV, forms a heteromeric complex with the accessory cellular protein host cell factor (HCF), before both can assemble with the octamer motif binding protein (Oct-1) to recognize a specific sequence to which the complex can bind. Inhibiting the interaction of VP16 with HCF, Oct-1 or DNA will render it non-functional [9, 10], again increasing the possibilities for intervention by the binding action of a small molecule drug.

Traditional drug development has long relied upon screening libraries of synthetic compounds and natural products (including plant, fungal and

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bacterial extracts). While this should prove to be an excellent source of transcription based drugs as well, elucidation of the structure and function of gene-specific transcription factors will greatly streamline this process of discovery. In the area of high throughput screening, cell-based assays can test the function of a particular transcription factor in an engineered cell line by linking the action of the factor to the expression of an easily detected reporter protein. This allows for the detection of compounds that either perturb the function of a transcription factor or alter signal transduction pathways required for its activity. With greater characterization of a factor's structure–function relationship, the implementation of *in vitro* assays utilizing recombinant proteins is possible. These focus on discrete properties of the factor, including protein oligomerization and DNA binding, and provide a focused and more specific screening strategy. In both of the above screening methods, it is important to control for the response to non-specific inhibitors. This is most easily accomplished by utilizing similar assays which employ different transcription factors; compounds which interfere in both cases are likely to lack the specificity needed in a potent therapeutic. Ultimately, the 3-dimensional atomic conformation of transcription factors can be utilized for rational drug design, as molecules are "custom-built" to complex with the reactive surfaces of these factors and render them inert. With the application of these strategies, transcription factor based therapeutics will surely expand the frontier of new pharmaceutical development.

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