Editorial

Artificial transcriptional modulators have for decades served as powerful tools for parsing the mechanistic details of the transcriptional process. In recent years, however, these tools have grown in importance as the connections between human disease and transcriptional misregulation have strengthened. Towards that end, much effort has been focused upon the discovery of molecules that directly interfere with the ability of a DNA-bound transcriptional activator to interact with its binding partners, thus serving to inhibit part or all of the activator's regulatory function.

There are two primary challenges that hamper the development of inhibitors of transcriptional activators. The first is commonly encountered in targeting a protein-protein interaction, that the interaction surface is often large with limited topology. An additional complication is that few of these interaction surfaces are well characterized, with little structural or binding detail available that would facilitate design efforts. A second roadblock is that for many transcriptional activators, the direct binding partners responsible for the relevant transcriptional activity are not known. Not surprisingly, this can cause considerable difficulties with regard to discovery of inhibitors and, further, in defining their precise mechanism.

In this issue of Biopolymers, we see several approaches aimed at overcoming the hurdles outlined above for the discovery of transcriptional inhibitors targeted to block the function of particular transcriptional activators. In the first paper, Paramjit Arora of New York University describes the state of the field of helix mimetics as applied to transcriptional inhibition. This includes, for example, the so-called hydrocarbon stapled and hydrogen bond surrogate helices that are able to target much larger binding surfaces than small molecules and are readily accessible synthetically. Bogdan Olenyuk of the University of Southern California has successfully developed natural product-derived small molecules called ETPs that interact with the CH1 domain of the coactivator CBP and in doing so, down-regulate genes controlled by the activator HIF1α, an activator that regulates the hypoxic response in tumors. In contrast to many activator-coactivator interactions, the interaction between HIF1α and the CH1 domain is well-characterized, facilitating these studies. Naoaki Fujii of St Jude Children's Research Hospital describes a structure-activity study of small molecules that selectively inhibit transcription regulated by the oncogenic transcription factor Gli1. Finally, Caleb Bates and William Pomerantz at the University of Michigan describe converting a group of small molecules originally characterized as transcriptional activators when targeted to DNA into inhibitors of the activators cJun and MLL. As these papers highlight, there has been great progress in the march towards effective transcriptional inhibitors and the next few years should bring even more exciting developments.

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