

A rapid and sensitive high-throughput screening method to identify compounds targeting protein-nucleic acids interactions

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Abstract Details

DNA-binding and RNA-binding proteins are usually considered 'undruggable' partly due to the lack of an efficient method to identify inhibitors from existing small molecule repositories. Here we report a rapid and sensitive high-throughput screening approach to identify compounds targeting protein-nucleic acids interactions based on protein-DNA or protein-RNA interaction enzyme-linked immunosorbent assays (PDI-ELISA or PRI-ELISA). We validated the PDI-ELISA method using the mammalian high-mobility-group protein AT-hook 2 (HMGA2) as the protein of interest and netropsin as the inhibitor of HMGA2-DNA interactions. With this method we successfully identified several inhibitors and an activator for HMGA2-DNA interactions from a collection of 29 DNA-binding compounds. Guided by this screening excise, we showed that netropsin, the specific inhibitor of HMGA2-DNA interactions, strongly inhibited the differentiation of the mouse pre-adipocyte 3T3-L1 cells into adipocytes, most likely through a mechanism by which the inhibition is through preventing the binding of HMGA2 to the target DNA sequences. This method should be broadly applicable to identify compounds or proteins modulating many DNA-binding or RNA-binding proteins.

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