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Pharmacological manipulation of transcription factor protein-protein interactions: opportunities and obstacles

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Abstract

Much research on transcription factor biology and their genetic pathways has been undertaken over the last 30 years, especially in the field of developmental biology and cancer. Yet, very little is known about the molecular modalities of highly dynamic interactions between transcription factors, genomic DNA, and protein partners. Methodological breakthroughs such as RNA-seq (RNA-sequencing), ChIP-seq (chromatin immunoprecipitation sequencing), RIME (rapid immunoprecipitation mass spectrometry of endogenous proteins), and single-molecule imaging will dramatically accelerate the discovery rate of their molecular mode of action in the next few years.
From a pharmacological viewpoint, conventional methods used to target transcription factor activity with molecules mimicking endogenous ligands fail to achieve high specificity and are limited by a lack of identification of new molecular targets. Protein-protein interactions are likely to represent one of the next major classes of therapeutic targets. Transcription factors, known to act mostly via protein-protein interaction, may well be at the forefront of this type of drug development. One hurdle in this field remains the difficulty to collate structural data into meaningful information for rational drug design. Another hurdle is the lack of chemical libraries meeting the structural requirements of protein-protein interaction disruption.
As more attempts at modulating transcription factor activity are undertaken, valuable knowledge will be accumulated on the modality of action required to modulate transcription and how these findings can be applied to developing transcription factor drugs. Key discoveries will spawn into new therapeutic approaches not only as anticancer targets but also for other indications, such as those with an inflammatory component including neurodegenerative disorders, diabetes, and chronic liver and kidney diseases.

Keywords: Transcription, Screening, Proteomics, Interactome, Pharmacology, Specificity, Cancer, Genomics

Introduction

The concept of pharmacological manipulation of protein-protein interaction (PPI) was clearly demonstrated with taxane anticancer drugs, paclitaxel and docetaxel, identified half a century ago. These compounds of natural and semisynthetic origins block microtubule depolymerization and mitosis in tumor cells via a mechanism of stabilization of tubulin heterodimers, eventually leading to apoptosis [1]. In 2014, the market for taxane anticancer drugs was valued at around US$6 billion for United States, Japan, and Europe [2]. It is now widely admitted that a large majority of the estimated 3,000 druggable proteins [3] function as complexes within a network of interactions [4-6], rather than acting as single effectors. As a result, the modulation of protein-protein interactions by small organic molecules, so-called "protein-protein interaction disruptors" or PPIDs, offers innovative therapeutic avenues [7,8].

Within the field of PPIDs' discovery, particular types of protein-protein interactions are easier to target than others, such as transmembrane, cytoskeleton, and mitotic proteins, as well as nuclear receptors, with exciting anticancer and anti-infective indications. Nuclear proteins such as transcription factors (TFs) still remain a challenge to manipulate using chemical-based strategies. Pharmacological management of transcription factors is usually

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achieved in more classical ways, including inhibition of upstream phosphokinase (lack of specificity) [9,10] or via mimicking endogenous ligands (nuclear receptors) [11,12]. Despite major hurdles in specifically targeting transcription factor activity, their central role in controlling cell signaling and their mode of action as dynamic complexes position them at the forefront as targets of choice for PPIDs (Figure 1).

In this review, we aim to reposition the study of transcription factor biology in its historical context and from there to weigh the impact of recent methodological and conceptual breakthroughs on future developments. We will briefly discuss strategies to develop pharmacological manipulation of transcription factors, focusing on protein-protein interactions and small compounds.

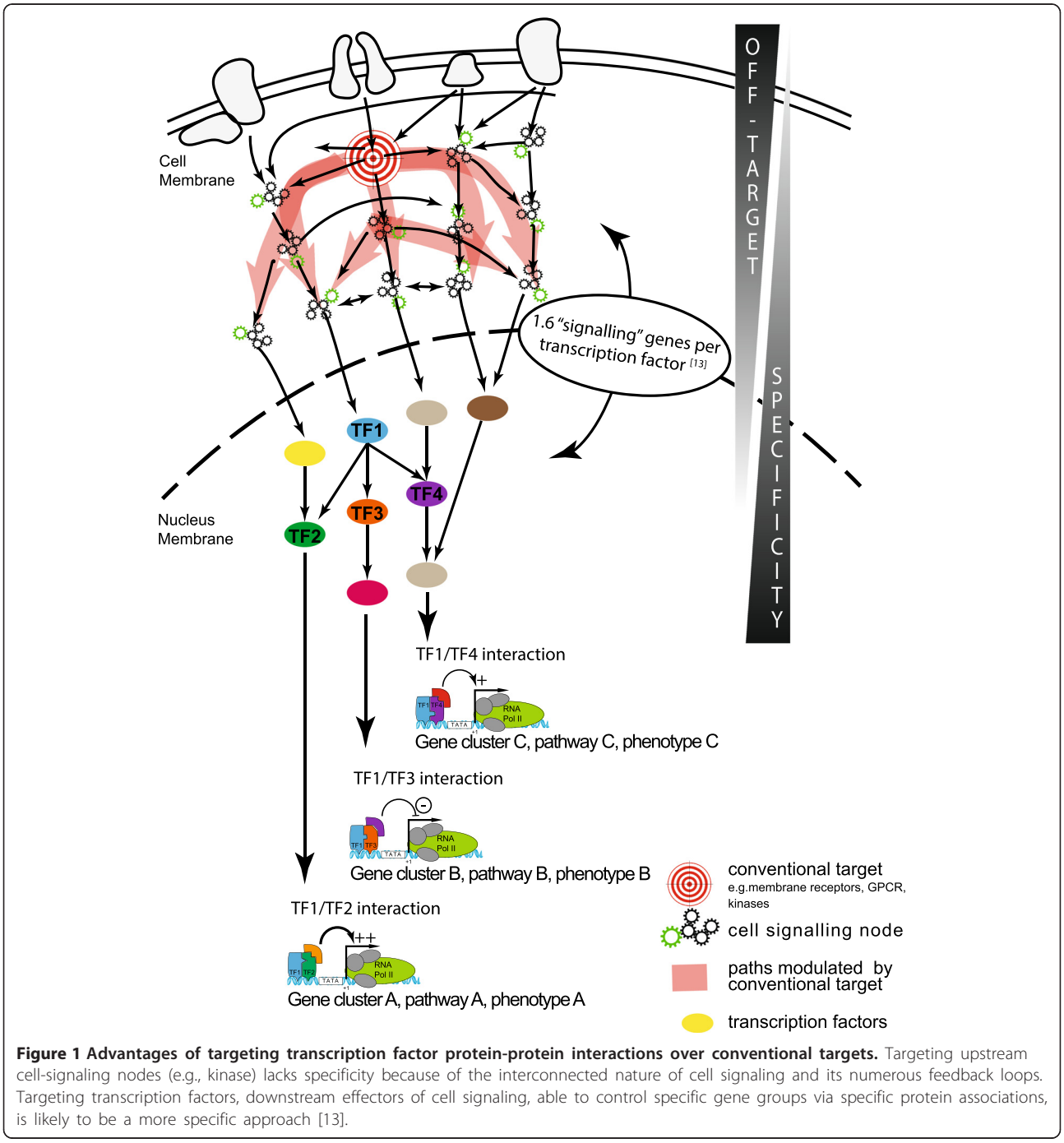

Figure 1 Advantages of targeting transcription factor protein-protein interactions over conventional targets. Targeting upstream cell-signaling nodes (e.g., kinase) lacks specificity because of the interconnected nature of cell signaling and its numerous feedback loops. Targeting transcription factors, downstream effectors of cell signaling, able to control specific gene groups via specific protein associations, is likely to be a more specific approach [13].