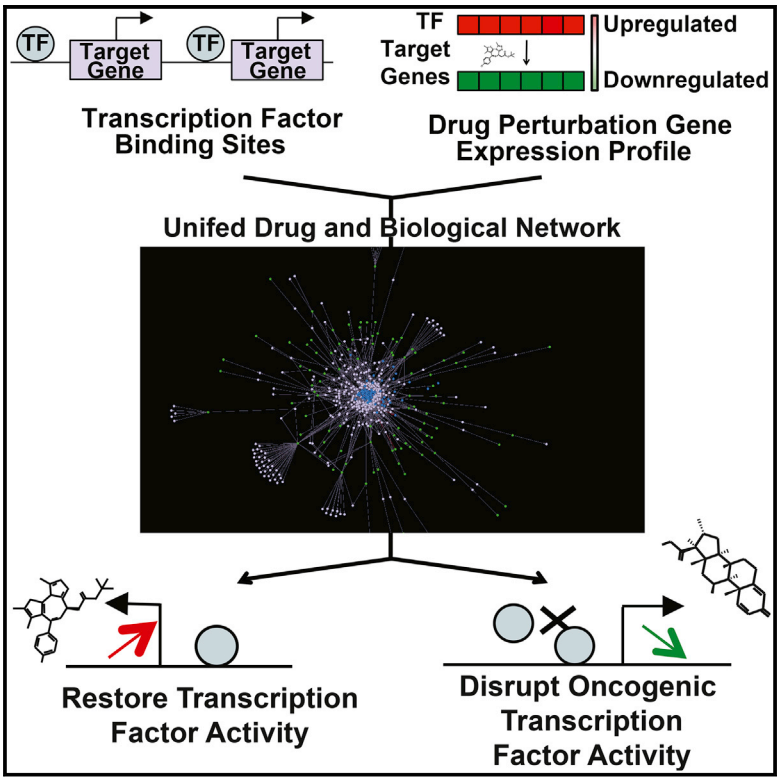
Report

Cell Reports

A Computational Drug Repositioning Approach for Targeting Oncogenic Transcription Factors

Graphical Abstract



Highlights

- A computational approach predicts drugs that modulate transcription factor activity
- Known drug-transcription factor interactions are recovered
- Dexamethasone is identified as a modulator of ERG activity
- Experimental data functionally validate dexamethasone-ERG interaction

Authors

Kaitlyn M. Gayvert, Etienne Dardenne, Cynthia Cheung, ..., Nicholas P. Tatonetti, David S. Rickman, Olivier Elemento

Correspondence

dsr2005@med.cornell.edu (D.S.R.), ole2001@med.cornell.edu (O.E.)

In Brief

Gayvert et al. present a broadly applicable systems biology method for identifying small molecules and drugs that modulate transcription factor activity. They identified dexamethasone as a candidate for the inhibition of the oncogenic transcription factor ERG and validate this prediction experimentally in several systems.

Gayvert et al., 2016, Cell Reports *15*, 2348–2356
June 14, 2016
http://dx.doi.org/10.1016/j.celrep.2016.05.037

OPEN ACCESS
CellPress

Cell Reports
Report

A Computational Drug Repositioning Approach for Targeting Oncogenic Transcription Factors

Kaitlyn M. Gayvert,[1,2,3] Etienne Dardenne,[4] Cynthia Cheung,[4] Mary Regina Boland,[5] Tal Lorberbaum,[5,6] Jackline Wanjala,[7] Yu Chen,[7] Mark A. Rubin,[2,4] Nicholas P. Tatonetti,[5] David S. Rickman,[2,4,*] and Olivier Elemento[1,2,*]

[1]Institute for Computational Biomedicine, Department of Physiology and Biophysics, Weill Cornell Medical College, New York, NY 10021, USA
[2]Institute for Precision Medicine, Weill Cornell Medical College, New York, NY 10021, USA
[3]Tri-Institutional Training Program in Computational Biology and Medicine, New York, NY 10065, USA
[4]Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY 10021, USA
[5]Department of Biomedical Informatics, Columbia University, New York, NY 10027, USA
[6]Department of Physiology and Cellular Biophysics, Columbia University, New York, NY 10032, USA
[7]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
*Correspondence: dsr2005@med.cornell.edu (D.S.R.), ole2001@med.cornell.edu (O.E.)
http://dx.doi.org/10.1016/j.celrep.2016.05.037

SUMMARY

Mutations in transcription factor (TF) genes are frequently observed in tumors, often leading to aberrant transcriptional activity. Unfortunately, TFs are often considered undruggable due to the absence of targetable enzymatic activity. To address this problem, we developed CRAFTT, a computational drug-repositioning approach for targeting TF activity. CRAFTT combines ChIP-seq with drug-induced expression profiling to identify small molecules that can specifically perturb TF activity. Application to ENCODE ChIP-seq datasets revealed known drug-TF interactions, and a global drug-protein network analysis supported these predictions. Application of CRAFTT to ERG, a pro-invasive, frequently overexpressed oncogenic TF, predicted that dexamethasone would inhibit ERG activity. Dexamethasone significantly decreased cell invasion and migration in an ERG-dependent manner. Furthermore, analysis of electronic medical record data indicates a protective role for dexamethasone against prostate cancer. Altogether, our method provides a broadly applicable strategy for identifying drugs that specifically modulate TF activity.

INTRODUCTION

Transcription factors (TFs) are frequently mutated in cancer. These include factors that function in a variety of ways, including nuclear hormone receptors, resident nuclear proteins, and latent cytoplasmic factors (Darnell, 2002). One classic example of a recurrently altered TF is the tumor suppressor TF gene p53, which is mutated in up to 40% of human tumors (Libermann and Zerbini, 2006) yet has remained a highly elusive target for reactivation (Mees et al., 2009). Other examples include c-Myc, which is also among the most commonly altered genes in cancer (Ablain et al., 2011), ERG, and other ETS-family factors, which are fused to the androgen-controlled promoters in more than 50% of prostate cancer patients (Rickman et al., 2012).

Inhibition of oncogenes and reactivation of tumor suppressors have become well-established goals in anticancer drug development (Darnell, 2002). Yet TFs are generally considered difficult to drug (Mees et al., 2009). If a strategy could be developed for safely and effectively modulating the activity of specific TFs, it would affect the treatment of tumor types and subtypes driven by oncogenic TFs. In theory, a similar strategy could be applied to reactivate the lost activity of tumor-suppressive factors. Potential mechanisms for pharmacological activation or inhibition include disruption of direct DNA binding, perturbation or prevention of the interaction with cofactors and other interacting proteins (Libermann and Zerbini, 2006), and disruption or activation of upstream signaling mechanisms (Mees et al., 2009). Disrupting interactions with cofactors and other regulatory proteins is broadly viewed as one of the most promising approaches to altering the activity and function of TFs implicated in disease.

One of the first and best-understood successes in disrupting TFs was the identification of the combination of retinoic acid and arsenic trioxide for inhibition of the PML/RARA fusion oncogene in acute promyelocytic leukemia (APL). The PML/RARA fusion results in the repression of many genes, which in turn blocks the differentiation phenotype that is characteristic of APL (Ablain et al., 2011). The retinoic acid-arsenic combination induces PML/RARA degradation, which reactivates the silenced genes (Ablain et al., 2011). A small molecule, JQ1, has been discovered to inhibit c-Myc and n-Myc, both key regulators of cell proliferation, by inhibiting BET bromodomain proteins, which function as regulatory factors for c-Myc and n-Myc (Delmore et al., 2011; Puissant et al., 2013). While important, these studies are based on extremely detailed knowledge of the mechanisms and structures of the cofactors required for TF activity. Such knowledge is not always available, and as a result, there is no systematic way to identify small molecules that can specifically disrupt TF activity.