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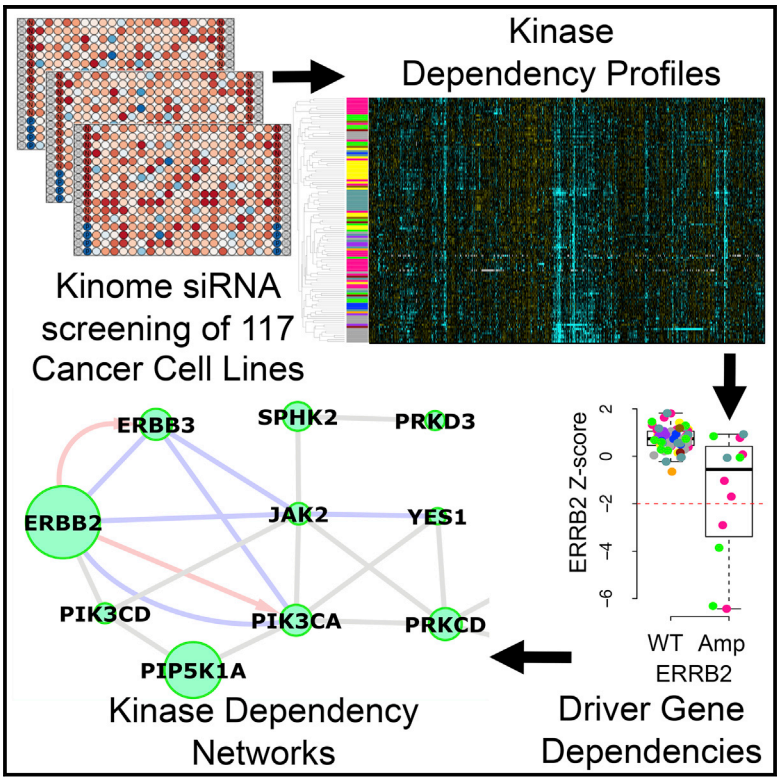
Cell Reports

Large-Scale Profiling of Kinase Dependencies in Cancer Cell Lines

Graphical Abstract



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In Brief

Campbell et al. use parallel siRNA screens to identify the kinase dependencies of 117 cancer cell lines from ten cancer types. They use this resource to identify kinase dependencies associated with specific cancer types or driver genes and show that the integration of protein interaction networks facilitates the interpretation of these dependencies.

Highlights

- Kinome-wide (714 gene) siRNA screens in 117 cell lines from ten cancer histotypes
- Integrating genotype data reveals cancer driver gene dependencies
- Integrating protein interaction data aids the interpretation of genetic dependencies
- Identified dependencies enable prediction of mutant cell line responses to drugs

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Large-Scale Profiling of Kinase Dependencies in Cancer Cell Lines

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SUMMARY

One approach to identifying cancer-specific vulnerabilities and therapeutic targets is to profile genetic dependencies in cancer cell lines. Here, we describe data from a series of siRNA screens that identify the kinase genetic dependencies in 117 cancer cell lines from ten cancer types. By integrating the siRNA screen data with molecular profiling data, including exome sequencing data, we show how vulnerabilities/genetic dependencies that are associated with mutations in specific cancer driver genes can be identified. By integrating additional data sets into this analysis, including protein-protein interaction data, we also demonstrate that the genetic dependencies associated with many cancer driver genes form dense connections on functional interaction networks. We demonstrate the utility of this resource by using it to predict the drug sensitivity of genetically or histologically defined subsets of tumor cell lines, including an increased sensitivity of osteosarcoma cell lines to FGFR inhibitors and SMAD4 mutant tumor cells to mitotic inhibitors.

INTRODUCTION

The phenotypic and genetic changes that occur during tumorigenesis alter the set of genes upon which cells are dependent. The best known example of this phenomenon of "genetic dependency" is oncogene addiction where tumor cells become dependent upon the activity of a single oncogene, which when inhibited leads to cancer cell death. Alternatively, tumor cells can become addicted to the activity of genes other than oncogenes, effects known as non-oncogene addictions (Luo et al., 2009), induced essential effects (Tischler et al., 2008), or synthetic lethal interactions (Kaelin, 2005). From a clinical perspective, identifying genetic dependencies in tumor cells could illuminate vulnerabilities that might be translated into therapeutic approaches to treat the disease. Examples of this approach include the development of drugs that target oncogene addiction effects, such as imatinib in the case of *ABL* addiction, and therapeutic approaches that exploit synthetic lethal effects, such as PARP inhibitors for *BRCA*-deficient cancers (Lord et al., 2015).

A number of groups have used high-throughput screening approaches such as RNAi or small molecule sensitivity screens to systematically identify genetic dependencies in tumor cell lines (Barretina et al., 2012; Brough et al., 2011; Cowley et al., 2014; Garnett et al., 2012; Koh et al., 2012). A particular focus has been in dissecting genetic dependencies that involve kinases (Brough et al., 2011; Grueneberg et al., 2008), as these enzymes play key roles in a number of oncogenic processes (Greenman et al., 2007) and are pharmacologically tractable (Sakharkar and Sakharkar, 2007; Workman and Al-Lazikani, 2013; Zhang et al., 2009). Previously, we used high-throughput short interfering (si)RNA screening to identify the kinase dependencies in a panel of 20 breast cancer derived cell lines (Brough et al., 2011). Here, we describe as a resource an expansion of this approach, namely parallel siRNA screens targeting 714 genes in 117 genetically and histologically diverse tumor cell lines. Building on our previous work (Brough et al., 2011), we extend our analytical approach to describe how this data set may be used as a hypothesis-generating tool for identifying candidate therapeutic targets associated with specific tumor histotypes or mutations in cancer driver genes. We also illustrate how, by integrating this functional data with orthogonal data sources such as protein-protein interaction data sets, these genetic dependencies might be dissected mechanistically.