Chapter 45
Dynamical Analysis of Drug Efficacy and Mechanism of Action Using GFP Reporters

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ABSTRACT

To the development of effective cancer drug, it is necessary to, first, identify drugs and their possible combinations that could exert desired control over the type of cancer being considered; second, have a drug testing method that allows one to assess the variety of responses that can be provoked by drugs. To facilitate such an experiment-modeling-experiment cycle for drug development, a method based on the dynamical systems of pathways is presented. It involves a three-state experimental design: (1) formulate an oncologic pathway model of relevant cancer; (2) perturb the pathways with the drugs of known effects on components of the pathways of interest; and (3) measure process activity indicators at various points on cell populations. To evaluate the drug response in a high-throughput manner, a green fluorescent protein reporter-based technology has been developed. The authors apply the dynamical approach to several issues in the context of colon cancer cell lines.

INTRODUCTION

Target identification and validation are critical components of the targeted drug discovery (Bleicher2003, Hoelder 2012, Dahlin 2015). Predicting drug effectiveness through potential target is typically via a bottom-up conceptualization of tumor function. It assumes that sufficient knowledge regarding cellular processes can be gathered through genomic, proteomic, and metabolic profiling projects. Such knowl-

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edge can then be used to recognize tumor vulnerabilities, screen potential drugs and construct effective targeted therapies (Lee 2009, T.C.G.A. Network 2008). For this constructivist approach to succeed, the vulnerabilities must be based on simple linear relationships, in which inactivating a particular target will be sufficient to control the tumor.

To illustrate the kind of special situation that contributes to a direct correlation between therapy and disease control, we consider two cancer types, chronic myelogenous leukemia (CML) and acute promyelocytic leukemia (APML), in which substantial improvements in patient outcomes have been achieved by targeted therapy. In these cancers, a single type of translocation fusing parts of two genes is a pathognomonic indicator of the disease and an excellent biochemical target for therapeutic targeting (Chen 1991, Druker 2001, Nowell 1960, Rowley 1977). These cases seem to be fairly extreme outliers from the bulk of cancer types in two ways.

The first is the striking uniformity of CML and APML tumors. Significant homogeneity of particular, discriminating patterns of gene expression in a particular subtype of tumor is rare, yet both of these tumors show exactly this characteristic (Dong 2010, Nowiki 2003). It appears that such tumors arise from a specific partially differentiated precursor cell that exhibits most of the characteristics of a cancer and that those missing cancer characteristics occur as a consequence of a single genomic alteration (Pear 1998). This behavior is in stark contrast to the considerable heterogeneity of molecular pathologies that appear to arise from various differentiated precursors in many cancers, such as breast cancer (Perou 2000). Also consider melanoma, which originates from a single, highly-differentiated cell, the melanocyte, and has yet to be sub-classified into clinically useful groups on the basis of molecular pathology. The second way in which CML and APML differ from most cancers is that, as opposed to CML and APML, tumors arising from highly differentiated cell types appear to have to breach more types of controls opposing oncogenesis. Even when starting from a single differentiated type, they appear to break these controls in a wider variety of ways.

These differences in tumor-type homogeneity and underlying molecular pathology are inversely correlated to the efficacy of the drugs available for the differing tumor types, i.e., high efficacy with low tumor complexity and low efficacy with high tumor complexity. Due to the manifold regulatory structures in complex systems, multiple inputs affect each output and the control structure includes parallel, redundant, and feedback loop processes. Thus if the tumor itself is not actively responding to the drug, it is very likely that many operations susceptible to a drug will not even be operating. Even for the cases the drug does work, like the hits found through drug screening, the effect could be due to mechanism other than what is originally designed. So it's very important to identify the exact response the drug induces.

Traditionally, this is done by protein assays, like western blot (Brough 2009, Geisler 2015). The assay should examine the downstream of the desired targets, like the phosphorylation status of certain proteins. More recently, high-throughput technique like microarray and RNA-Seq are also available, which measure the transcriptional activity (Smith 2006, Sirota 2011). However, these methods are often time consuming and costly. Furthermore, it takes time for any drug to drive out desired effects, and the response time varies for different drugs. Yet the traditional approaches often only take one time point for examination, and often miss critical information (Orth 2008).

In this chapter we discuss a model-based dynamical experimental method to facilitate better pathology identification and better matching of tumors with targeted drugs. The method could potentially address many central questions relevant to the mechanics of drug function: Are the responses consistent with the intended targeting? Is a single intervention at a given point successful in stopping the altered function? Do combinations directed at a particular pair of proliferation and survival generators produce synergy

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