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Relationship between cancer mutations and parameter sensitivity in Rb pathway

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HIGHLIGHTS

- Nonlinear dynamical analysis of the Rb-E2F pathway model is conducted.
- Two saddle-node bifurcations are involved in G1/S transition.
- Parameter sensitivity analysis on the first bifurcation point was carried out.
- Sensitive parameters highly correspond to high-frequency oncogenic mutations.

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ABSTRACT

It has long been known that formation of all sorts of tumors is largely owing to the genomic variations. Oncogenic mutations are often found focused on one or more important pathways which indicate that it is meaningful to investigate oncogenic mutations and oncogenic mechanisms from the point of view of biological network. Recently, we found that in apoptosis pathway of mammalian cell, mutations that cause large variations on the bifurcation point are more probably oncogenic mutations. Here, we used the Rb-E2F pathway in mammalian cell in response to growth factor as another example to verify this correlation. To conduct this study, nonlinear dynamics equations that describe the behavior of the Rb-E2F pathway was first constructed. Then we identified sensitive parameters which have a great influence on the system's bifurcation point. And we found that the sensitive parameters are highly related to high-frequency oncogenic mutations after comparing the results of parameter sensitivity analysis with profile of known cancer mutations. Moreover, the position of bifurcation point rather than concentration of a certain protein is a better measurement to determine biological network's function. Our results further confirm that nonlinear dynamics analysis of biological networks is an important way to understand oncogenesis. And the analysis method can become a powerful tool to understand and analyze the function of biological network.

1. Introduction

Cancer has been considered as a genetic disease (Vogelstein and Kinzler, 2004) which is a very grave threat to mankind's health and normal life. Since the war on cancer started almost half century ago, enormous effort has been spent on identifying oncogenic mutations. However, although tens of thousands oncogenic mutations have been identified so far, the discovery that specific genomic alterations varied from tumor to tumor even within the same cancer type has been a puzzle to most of researchers. In the last decade, results of high-throughput cancer genomic researches indicate that oncogenic mutations are often focused on one or more important pathways (Ding et al., 2008; Kimura et al., 2008), including p53-DNA damage signaling pathway, apoptosis pathway, G1/S transition pathway, etc. (Jones et al., 2008). This discovery suggested that oncogenic mechanisms should be understood from a network perspective. Biological networks which can capture the basic characteristics of biological systems are usually helpful to solve the complicated biological problems and their computational models can obtain insight into the systems behaviors (Alon, 2003). Studying oncogenesis from a systemic and dynamic standpoint is needed in order to understand its mechanisms. At present, there are many network-based

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approaches being applied on oncogenesis research. Torkamani and Schork used a network reconstruction approach with analysis of gene co-expression module to identify rare oncogenic mutations (Torkamani and Schork, 2009). Cerami et al. utilized a method of automated network analysis for finding novel cancer-causing progress and driver mutant genes (Cerami et al., 2010). Stites et al. developed a mathematic model to analyze oncogenic Ras activation (Stites et al., 2007). A more recent approach to investigate important genetic mutations in cancer is to study how the mutations in the p53 apoptosis pathway response to DNA damage and change the dynamics of the regulatory network (Chen et al., 2014). By conducting a parameter sensitivity analysis of the Ordinary Differential Equation (ODE), it was found that parameters which have a great influence on the system's bifurcation points are highly related to the high-frequency oncogenic mutations identified by cancer genomic projects. Therefore, it is tempting to explore whether other core functions of biological networks exist such as close correlations.

Based on these considerations, we constructed a computational model of RB-E2F pathway in mammalian cells, which is the core part of G1/S transition (Bertoli et al., 2013), to examine the connection between the parameter sensitivity of the Rb-E2F network and the oncogenic mutations. It was well established that one of the hallmarks of cancer is enabling replicative immortality, and Rb mutations is one of the most fundamental events in oncogenesis (Dick and Rubin, 2013). Using the tool of parameter sensitivity analysis, we ranked parameters' sensitivity by the percent change of bifurcation point's position. Comparing the identified sensitive parameters with known cancer cell mutation profile, we found that the sensitive parameters which can cause large variation on the bifurcation point's position are positively correlated to the high-frequency mutations of oncogene. These studies may provide a helpful theoretical tool for doing research on mutations of oncogene.

2. Models and simulation

2.1. Model construction

The network of Rb-E2F pathway is built based on the related literature known so far. The schematic draft of the network is shown in Fig. 1. The essential of the network is based on interactions among several key regulators: E2F1 transcription factor, cyclin–Cdk complexes, retinoblastoma (Rb) protein, cMyc, and Cdk inhibitors (CKIs) (Kohn, 1998; Qu et al., 2003; Novak and Tyson, 2004). The check point of the G1/S transition can be represented by the concentration of activated CycE–Cdk2 complex which exceed a certain threshold will start the transition. The family of E2F transcription factor are important regulators in the progress of cell cycle and DNA replication (Sears and Nevins, 2002; Frolov and Dyson, 2004; Yao et al., 2008; Wu et al., 2001). In quiescent cells, E2F's transcriptional activation function of downstream genes is suppressed because of bounding with Rb protein. The Cdk inhibitors, which include p27, p21 and p15 (Sherr and Roberts, 1999), bind cell cycle protein and Cdk complex that form CdkI/Cyclin/Cdk terpolymer. The terpolymer can inhibit cell cycle progress including repressing of cell cycle entry and G1/S transition. When cell receives sufficient signal of cell proliferation, Rb protein will be phosphorylated by cMyc-induced CycD/Cdk4 and release from the E2F–Rb complex. The E2F which is also released will activate transcription of downstream genes including cycE which can bind Cdk2. The bound cycE/Cdk2 complex further phosphorylate Rb promoting cell cycle progression.

Computational models of Rb-E2F pathway have been constructed before (Yao et al., 2008; Csikasz-Nagy et al., 2006; Barberis et al., 2007; Pfeuty et al., 2008; Barik et al., 2010), and based on those models we proposed our model as shown in Fig. 1. The main difference of our model to other models is that the growth stimulation is not the signal directly received by the cell surface receptor. This process actually involves complicated signal transduction actions, such as PI3K/mTOR, Ras/Raf and their interactive pathway, which are activated by mitogenic factors (Gille and Downward, 1999). Because this part of signal transduction pathways was not the focus of our current study, in this work we neglected these processes and concentrated our study on Rb-E2F pathway. The nodes and their interactions in Fig. 1 can be translated into corresponding ODEs using well established biochemical reaction kinetics (see Supporting Information). We chose the growth factor as control variable for studying the dynamic and quantitative information.

2.2. Simulation calculation

We next conducted the nonlinear dynamic analysis to investigate the system's dynamic changes. Since ac-CycE/Cdk2 level

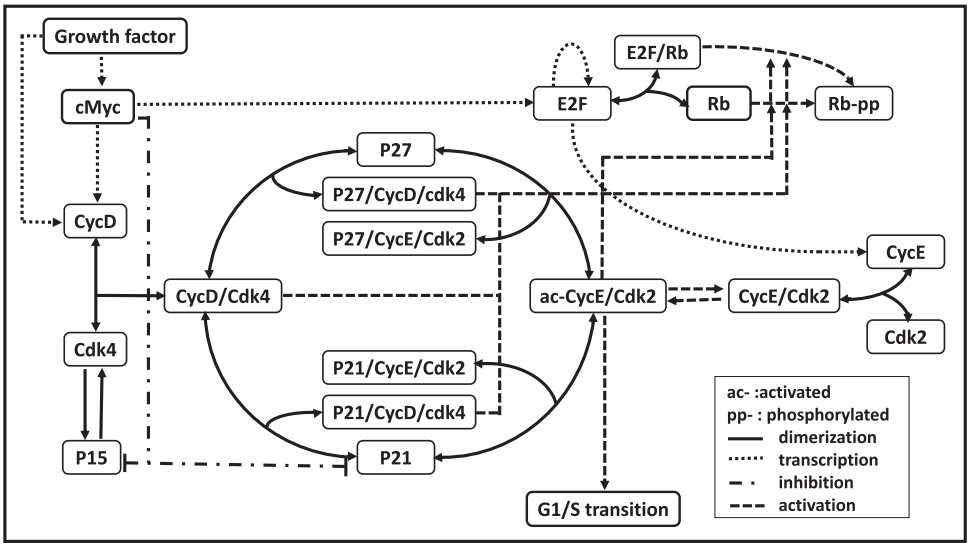

Fig. 1. The Rb-E2F pathway in response to growth factor. "ac-", activated; "pp", phosphorylated; and "/" stands for a complex. The components' production and degradation terms do not show in Fig. 1 but are considered into ordinary differential equations. Several proteins with similar function are grouped into one node.