

Chapter 61

Evaluation of Coupled Nuclear and Cytoplasmic p53 Dynamics

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ABSTRACT

The tumor suppressor protein p53 predominantly serves as a sequence specific transcription factor that may be activated upon exposure to diverse stimuli. One potent death inducer, p53-upregulated mediator of apoptosis (PUMA), is transcriptionally induced by p53. Once released into the cytoplasm, PUMA can lead to the activation of Bcl-2 apoptotic network. The cytoplasmic proapoptotic roles of p53 have recently been discovered, and these findings have placed p53 into the chemical interaction network with Bcl-2 family members. PUMA can also relieve p53 from the sequestration of antiapoptotic members. Released p53 further enters the nucleus and induces PUMA expression. We proposed that this positive feedback loop could lead to bistability. Further sensitivity analysis suggested that the system which covers the interactions between p53 and BCL-2 family members is considerably sensitive to p53 production rate. Meanwhile, downstream network components are much more affected by certain parameters than upstream effectors. Therefore, this newly discovered positive feedback loop might play critical roles in apoptotic network.

INTRODUCTION

The p53 tumor suppressor protein is a sequence specific transcription factor and its biological roles are closely mediated by modulating the expression of numerous target genes (Whibley et al., 2009). In particular, p53 can trigger apoptosis in response to diverse stimuli, among which irradiation induced damage has caught much attention.

Intricate regulation and manipulation of p53 and its related pathways are considerably important for consistent development and cancer evasion in harsh environment (Evan et al., 2008). Therefore, the dynamic patterns of p53 have become an active area of research. Many recent studies have established well-defined oscillation patterns in p53 dynamics and these observations motivated

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the constructions of many mathematical models (Lahav et al., 2004; Geva-Zatorsky et al., 2006).

Differential equation based models included either delays or combined feedback loops to reproduce p53 oscillations (damped, undamped or digital), although some of the feedback loops seem ambiguous (Bar-Or et al., 2000; Monk, 2003; Ma et al., 2005; Ciliberto et al., 2005; Chickarmane et al., 2007; Zhang et al., 2007; Batchelor et al., 2008; Proctor et al., 2008; Puszynski et al., 2008). Some other theoretical analyses focused on bistability or temporal patterns and intended to elucidate physiological roles of p53 in biological systems (Wee et al., 2006; Wee et al., 2009). Generally speaking, feedback strengths play important roles in dynamic pattern determination. The system in which positive feedback dominates confers bistability, and oscillations occur when negative feedback becomes dominant (Tyson et al., 2003). Thus, investigation of individual feedback loops could help further our understanding of network performance and provide powerful insights.

A recently discovered bcl-2 homology domain only (BH3-only) protein, p53-upregulated mediator of apoptosis (PUMA), which couples nuclear and cytoplasmic functions of p53 under stress conditions, is a potent death inducer (Chipuk et al., 2005). PUMA is a B-cell lymphoma 2 (BCL-2) family member and is able to dissociate p53 from the sequestration of anti-apoptotic members B-cell lymphoma x long (BclxL)/Bcl-2. Then, free p53 proteins enter the nucleus and induce a plethora of downstream targets including PUMA (Schuler et al., 2005). The synthesized PUMA further releases p53 from BclxL/Bcl-2 into the cytoplasm thus establishes a positive feedback loop and bistability may occur. An eruption of p53 is devastating because p53 can directly activate Bax/Bak (proapoptotic Bcl-2 family proteins) besides its role as a transcription factor (Schuler et al., 2005). Thus, this positive feedback loop is physiologically important in apoptosis progression.

Diverse feedback loops are imbedded in p53 network and an integrated model that covers

entire feedback loops is unfeasible and probably masks individual roles of feedback loops. Therefore, we took a different approach in which only one positive feedback loop is scrutinized. In this study, we investigated a positive feedback loop in p53 signaling transduction pathways and found inherent bistability which connects both nuclear (transcriptional induction) and cytoplasmic (a BH3-like function) functions of p53. Furthermore, we employed different kinds of sensitivity analyses to elucidate feedback performance as sensitivity analysis can also indicate biological effects of mutations or artificial manipulation by altering system parameters.

BACKGROUND

During early years, several p53 models have been constructed. Bar-Or et al. (2000) presented a simplified model in an attempt to explain the mechanism of damped oscillation, and similar dynamics were also presented by Monk (2003) when a time delay was introduced. In a field-breaking study of p53-MDM2 in individual cells, Lahav et al. (2004) found the expression of p53 followed a series of pulses and the mean period of the oscillations were relatively fixed and the mean number of pulses increased with irradiation dose. Ma et al. (2005) introduced a stochastic process in damage repair process and best reproduced the digital pulses. Ciliberto et al. (2005) and Chickarmane et al. (2007) moved the p53 system from steady state into a region of stable limit cycle in response to damage, which is then drawn back when damage is eliminated. Tyson's group compared these models and delineated several new scenarios although the speculated mechanisms seemed to be cell type specific (Zhang et al., 2007). All these above models concentrate on the digital pulses of p53 in single cells. Geva-Zatorsky et al. (2006) found that p53 performs sustained oscillation with γ -irradiation when observations last longer. However, some other theoretical analyses also focus on bistabil-

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