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Mathematical modeling of p53 pulses in G2 phase with DNA damage

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ABSTRACT

A mathematical model of p53 pulses involved in G2/M phase transition is proposed to study the response of p53-centered signaling network and checkpoint mechanisms of G2 phase to DNA damages. The oscillation by p53-Mdm2 feedback loop as the response to DNA damage is first simulated. This follows by modeling the signaling network in G2 phase and realizing its importance in cell cycle progression. The signaling network is used to assess effects of different intensities of DNA damage on G2 phase transition. An examination of the dynamics of cell fate decision module shows that p53 arrester and Wip1 play key roles in DNA repair and may be an important target of cancer therapy. The present numerical analysis based on the proposed model may be useful for the inference of p53-mediated mechanisms in response to DNA damage in G2 phase under different damage conditions.

1. Introduction

Cellular exposure to IR radiation can lead to DNA damage, such as single-strand or double-strand DNA breaks, and delay the normal cell cycle progression [1]. When DNA damage occurs, cells can trigger the self-defensive mechanisms to induce apoptosis, which provides an efficient way to eliminate cells that are potentially dangerous. As a tumor suppressor, p53 gene plays an essential role in mediating apoptosis progress as evidenced by frequent mutations of p53 in tumors [2]. In normal cells, the expression of p53 is inhibited by Mdm2 [3]. Upon DNA damage, p53 is activated to regulate the transcription and translation of downstream target genes, mediating cell fate decision [4]. Different from apoptosis, the cell cycle arrest facilitates DNA repair and promotes cell survival.

The G2 phase, which is a second growth phase in the cell cycle, is a temporal gap between the end of DNA synthesis and the beginning of mitosis [5,6]. The subsequent replication of DNA molecules are separated into two daughter cells during mitosis phase (M phase), which represents the completion of a cell cycle progression [7]. The transition state from G2 phase to M phase is important in regulating cell division and maintaining genomic stability. If DNA damage occurs, the cell progression in G2 phase is ceased to verify state of the cell and, if needed, to repair it before damaged DNA is transmitted to progeny cells [8]. The G2 phase transition has checkpoint mechanism that controls the cell cycle progression in response to DNA damage. If the DNA damage cannot be recognized by these checkpoints, the cell division will be unrestricted.

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In order to investigate the response of p53-centered signaling network and checkpoint mechanisms of G2 phase to DNA damages, several models have been reported [9–15]. Especially, Iwamoto et al. [9] constructed a mathematical model which simulates the cell cycle transition involving the DNA-damage signal transduction pathway. This model focuses on the chemical interactions among the biochemical species of the G1/S transition, their dynamic behavior, and the DNA signal transduction mechanism including the damped oscillation of p53. Ma et al. [10] proposed a model to identify the p53 pulses can be generated by p53-Mdm2 feedback loop with a long time delay. Zhang et al. [11] proposed a model of the p53 signal network and associated the network dynamics with the cell cycle arrest/apoptosis in the DNA damage checkpoint response. Sun et al. [12] presented an integrated model, in which ATM activation and p53 oscillation in the cell cycle were incorporated with downstream apoptotic events. Batchelor et al. [13] reported a recurrent mechanism for the generation of p53 pulses. Computational analyses were also implemented to indicate the high levels of basal DNA damage are responsible for generating sustained pulses of p53 in the cell cycle. Zhang et al. [14,15] performed a mathematical analysis of G2 cell cycle arrest by integrating G2 checkpoint model with p53-Mdm2 oscillation system and DNA damage signaling pathway.

Because p53 plays a transcription-independent role in the DNA repair, mechanisms of the p53-mediated cellular response to DNA damage in G2 phase need to be further addressed. Here, we propose a mathematical model to examine the dynamics of the p53-centered network involved in G2 phase based on the previous models [9,11] and the latest experimental observations. Three modules are included in the proposed model, i.e. a p53-centered feedback control module, a DNA damage induced G2 phase module and a cell fate decision module. In this study, the numerical simulations serve to investigate the dynamics of active $p53^*$ and $p53^*$-Mdm2 feedback loop involved in the G2 phase correspondence to the intensity of DNA damage. We evaluate the effects of DNA damage on the G2 phase transition, including dynamic behaviors of important checkpoints in G2 cell cycle such as MPF, aCdc25, and Wee1, and Wip1. Moreover, we also investigate the dynamics of p53 arrest and Wip1 which is identified to has a key role in the cell fate decision and may be an important target of cancer therapy. Our numerical analysis based on the proposed model may be useful for the inference of p53-mediated mechanisms in response to DNA damage in G2 phase under different damage conditions.

2. Mathematical model

The response of G2 phase to DNA damage signal can be envisioned as a signal transduction process. We construct an integrated model composed of three modules: (i) a p53-centered feedback control module, (ii) a DNA damage induced G2 phase module and (iii) a cell fate decision module. Based on the previous models [9,10,14,15], our proposed model has integrated the vital signal pathways in G2 phase with the cell fate decision. The cell cycle model structured by Zhang et al. [11] has been incorporated into our G2 phase model. Our proposed model consists of 27 dependent variables and 95 kinetic parameters.

2.1. Model overview

Our model is able to characterize the p53 signaling network which is involved in the G2 phase in response to the DNA damage, as shown in Fig. 1. The response of the G2 phase to DNA damage can be envisioned as a signal transduction process, which was represented by integrating the p53-Mdm2 feedback loop with the interaction between the primary phosphorylation of p53 on Ser-15 and Wip1.

When cells exposed to DNA damage (such as IR), a certain number of double strand breaks (DSBs) are produced and DNA repair proteins are quickly recruited to break sites, forming DSB-protein complexes (DSBCs). Subsequently, ATM/ATR is activated by DSBCs. Meanwhile, under a continuous DNA damage signal, the oncogenes are prompted and the over-expression of oncogenes further trigger the activation of ARF [16]. Then the P53-Mdm2 feedback loop is activated by the cooperation of activated ATM and activated ARF. Finally, the activated p53 regulates the downstream genes and controls the cell fate decision in response to genome stresses [15]. Nevertheless, when DNA damage occurs, the MPF activation is retarded to repair the DNA damages. The transcriptional activity of p53 is recovered to transcript p21 which inhibits and binds to MPF to form p21/MPF complex, further inducing a cell to initiate mitosis.

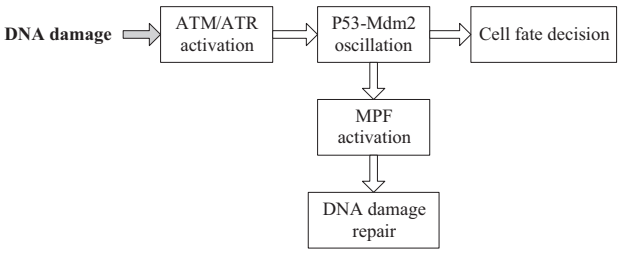

Fig. 1. An integrated model of p53 signaling network in response to DNA damage.