Analysis for the Conflict between G2/M Phase Arrest in the Cell Cycle and Apoptosis Induction

Yoshihiko Tashima
yoshihiko@brs.kyushu-u.ac.jp

Yu Kisaka
kisaka@brs.kyushu-u.ac.jp

Hiroyuki Hamada
hamada@brs.kyushu-u.ac.jp

Taizo Hanaï
taizo@brs.kyushu-u.ac.jp

Yukihiro Eguchi
eguchi-y@mki.co.jp

Masahiro Okamoto
okahon@brs.kyushu-u.ac.jp

1 Laboratory for bioinformatics, Graduate School of Systems Life Sciences, Kyushu University, 6-10-1 Hakozaki, Higashiku, Fukuoka 812-8581, Japan

2 Bioarchitecture center, Kyushu University, 6-10-1 Hakozaki, Higashiku, Fukuoka 812-8581, Japan

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1 Introduction

When DNA is damaged by the irradiation or chemical agents in vitro, the damage signal activates the tumor suppressor protein p53 followed by the stimulation of the transcriptions of many related genes such as p21, 14-3-3, Bax, Bcl-2 and so forth. These genes may determine the destination of the cell whether the cell cycle arrest or apoptosis induction. Thus, p53 is responsible for the conflict between the cell cycle arrest and apoptosis induction. Recently, it was reported that the protein levels of the p53/Mdm2 shows the oscillation under the condition of occurring some DNA damages [1, 2]. However, the physiological role of the oscillation in p53 level for the controlling the conflict between the cell cycle arrest and apoptosis induction is still unclear [2]. In this study, we proposed a novel mathematical model which can realize the qualitative temporal dynamics of both G2/M phase and apoptosis events involving the p53/Mdm2 oscillation. Then, we elucidated the influence that p53 plays an important role on the controlling the conflict between G2/M phase arrest and apoptosis with or without occurring low/high DNA damages.

2 Mathematical Model and Method

The central reactions for G2/M phase and apoptosis are the activation/inactivation of M phase promoting factor (MPF) and Caspase3, respectively. In these reactions steps, p53 protein is one of the major regulators. When the irradiation or chemical agents damaged DNA in vitro, the damage signal activated the p53, and then the activated p53 determines the destination of the cell whether cell cycle arrest or apoptosis induction. With occurring low DNA damage, p53 is released from Mdm2-mediated repression. Activated p53 preferably stimulated the transcription of CDK inhibitor p21 and CDK phosphatase inhibitor 14-3-3 to arrest cell cycle progression. On the other hand, with occurring high DNA damage, activated p53 preferably stimulated the transcription of Bax [3]. Then, an increase in the level of Bax leads to the activation of Caspase3 to induce the apoptosis events through the mitochondria/cytochrome c-mediated apoptotic pathway.

Up to now, based on the interactions between these proteins, many mathematical models such as G2/M phase, p53/Mdm2 network and apoptosis induction were designed. Aguda proposed the mathematical model of G2/M phase (Aguda’s model) [4]. In Aguda’s model, the
dynamics of MPF, the inhibiton factor p21 and the activation factor Cdc25 were qualitatively simulated the experimentally observed dynamics with and without occurring some DNA damages. Bagci et al. proposed the mathematical model of apoptosis through the mitochondria/cytochrome c-mediated pathway (Bagci’s model) [5]. In Bagci’s model, the increase of caspase3 on the response to apoptotic stimuli in mitochondria-dependent apoptosis was qualitatively simulated experimentally facts. However, the both models are not able to simulate the oscillation in p53 level under the condition of high-dose DNA damage. In contrast to the both models, Lev Bar-Or et al. proposed the mathematical model (Lev Bar-Or’s model) for the p53/Mdm2 network [1]. In Lev Bar-Or’s model, a negative feedback loop between p53 and Mdm2 generated the p53 oscillation. So, we proposed a novel mathematical model (Proposed model: Figure. 1) by integrating both Aguda’s model and Bagci’s model with Lev Bar-Or’s model in order to elucidate the role of p53 oscillation on controlling the conflict between cell cycle arrest and apoptosis induction.

The proposed model consisted of 51 chemical species and 101 kinetic parameters in the simultaneous ordinary differential equations.

3 Results and Discussion

The numerical solutions of the dynamics were qualitatively consistent with biological findings. As shown in Fig 2(a), at the small initial value of DNA damage signal (=0.002), p53 showed the saturable temporal profile without oscillation and caspase3 decreased to almost zero level. In contrast, as shown in Figure 2(b), the slight increase in the initial concentration of DNA damage signal (0.002 → 0.003) caused the significant change in dynamics of p53 and caspase3; p53 showed damped oscillation and caspase3 drastically increased with long time lag. It was suggested that the p53 oscillation preferably relates to the apoptosis induction rather than cell cycle arrest. We will further analyze the physiological function of p53/Mdm2 oscillation for the conflict between cell cycle arrest and apoptosis induction hereafter by using the numerical simulation and system analysis techniques in detail.

References


