Mathematical Modeling of G1/S Phase in the Cell Cycle with Involving the p53/Mdm2 Network

Kazunari Iwamoto¹, Yoshihiko Tashima¹, Hiroyuki Hamada¹, Yukihiro Eguchi², Masahiro Okamoto¹

¹ Laboratory for bioinformatics, Graduate School of Systems Life Sciences, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan
² Bioarchitecture center, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

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1 Introduction

In the cell cycle, G1-phase progression is induced by the transduction of cell proliferation signal, which is regulated by the checkpoint mechanism for the purpose of monitoring the transition from G1-phase to S-phase (G1/S transition). Simultaneously, the checkpoint mechanism receives the DNA damage signal by p53/Mdm2 network and prevents G1/S transition with occurring DNA damage. Since the disruption of this mechanism results in the transformation of normal cells, the elucidation of the interaction between the transduction of DNA damage signal and the checkpoint mechanism is indispensable to suppress the occurrence of tumors. However, complex network of the checkpoint makes it difficult to clarify this mechanism by employing in vivo and in vitro experiments.

In this study, we designed a novel mathematical model of G1/S phase with the transduction of DNA damage signal and verified the dynamics for which the DNA damage signals influence the checkpoint in G1/S phase.

2 Mathematical Model and Method

In G1-phase, E2F contributing to G1/S transition binds to Rb protein (Rb/E2F complex), which inhibits the activity of E2F. The transduction of cell proliferation signal promotes the synthesis of cyclin (cyc) D. The cycD binds to the cyclin dependent kinase (CDK) 4, which forms the cycD/CDK4 complex of an active form. This complex phosphorylates Rb protein and phosphorylated Rb protein dissociates from E2F. The activated E2F promotes the synthesis of cycE. The free cycE binds to the CDK2, which forms cycE/CDK2 complex. The cycE/CDK2 also phosphorylates...
Rb protein. In addition, after the following the synthesis of the cycE, E2F promotes the synthesis of cycA. The free cycA binds to CDK2, which forms cycA/CDK2 complex. The cycA/CDK2 promotes the degradation of E2F. The decrease in the protein level of E2F results in the suppression of the synthesis of both cycE and cycA. As for p16, p21 and p27, the regulatory mode of p16 inhibits cycD/CDK4, p21 and p27 inhibits both cycE/CDK2 and cycA/CDK2. The DNA damage signal inhibits Mdm2-dependent degradation of p53. Since the p53 activates the synthesis of p21, both cycE/CDK2 and cycA/CDK2 are inhibited by DNA damage signal. This is the mechanism of p53-dependent cell cycle arrest in G1-phase, and DNA damage is repaired during the arrest. In order to evaluate the effect of the DNA damage signal on the dynamics in G1/S phase, we designed a novel mathematical model (proposed model), which integrated Tashima’s G1/S phase model with Lev Bar-Or’s p53/Mdm2 network model [1, 2]. The proposed model is showed in Fig.1, which is represented by 28 ordinary simultaneous differential equations on chemical species including 76 kinetic parameters.

3 Results and Discussion

The time courses of some chemical species in G1/S phase with or without occurring DNA damage are showed in Fig.2.

Without occurring DNA damage, the protein level of both cycE and cycE/CDK2 increased with that of E2F. Thereafter, as the protein levels of cycA and cycA/CDK2 increased, the protein level of E2F decreased and those of cycE and cycE/CDK2 also decreased. On the other hand, with occurring DNA damage, the peak levels of E2F, cycE and cycE/CDK2 decreased and their peak times delayed. Furthermore, the peak level of cycA/CDK2 decreased. The dynamics of cycE/CDK2 in the proposed model with occurring DNA damage qualitatively agreed with the biological findings reported by D’Anna et al. [3].

Both of with and without occurring DNA damage, since the proposed model realized qualitatively biological findings, the proposed model is available for the system analysis of the dynamics with the transduction of DNA damage signal in G1/S phase. It is not clear, however, for the effect of the intensity of DNA damage signal on the dynamics of E2F. In future, we will verify the relation between the intensity of DNA damage signal and the dynamics of p16, p21 and p27, and investigate some dominant factors in G1/S phase with occurring DNA damage.

References

