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A Nonlinear Dynamical Model for Studying DNA Damage-induced p53-Mdm2 Interaction*

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Abstract: Exploring the nonlinear dynamics of the negative feedback loop composed of p53 and Mdm2 proteins, we propose a signal-response model to study the dynamical mechanism of the different oscillatory behaviors for the activities of p53 and Mdm2 proteins both in individual and population of cells. It is shown that the sustained and damped oscillatory dynamics could be described in a unified way when the dynamics of damage-derived signal is properly introduced.

Key words: p53-Mdm2 interaction; negative feedback loop; sustained and damped oscillatory dynamics; nonlinear dynamical model

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1 Introduction

Cells, as physiological regulatory systems, respond appropriately to various types and strengthens of external and internal stimuli by complex networks of interacting genes and proteins that process information. A common type of networks across organisms is the well-known negative feedback loop composed of one transcription arm and one protein-interaction arm[1－5]. In human cells, there exists a loop of the tumor suppressor protein p53 and its transcriptional target Mdm2.

The experiments on the signal-response relation between DNA damage and p53 expression have been carried out recently both at the population of cells[1] and in individual cells[2]. The former[1] has shown that under certain conditions, the activities of the average

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protein levels of p53 and Mdm2 behave damped oscillations due to DNA damage. The stronger the damage is, the higher and broader the amplitude of the average response. In contrast, the latter[2] sets out to address that in response to ionizing radiation, cells emit p53 in discrete pulses of fixed height and duration which do not depend on the strength of DNA damage, and with different number of pulses for the genetically identical cells. The mean number of pulses increases with the extent of DNA damage[5].

Several simple theoretical models[1, 6—8] based on the p53-Mdm2 autoregulatory feedback between the transcription of p53 and Mdm2 proteins have been proposed to qualitatively describe the dynamical behaviors of average protein levels in population of cells. However, what is the mechanism for the sustained oscillatory behaviors in individual level, what is the relation between the damped oscillatory behaviors in population of cells and undamped oscillatory behaviors in individual cells and whether one can describe these two kinds of dynamics in a unified way is still a challenging theoretical subject[2, 5].

In this paper, we propose a unified theoretical model of p53-Mdm2 negative feedback loop with the aim to describe the dynamical behaviors of protein levels both in individual and populations of cells in a self-consistent and unified way. It should be emphasized that the different from the previous models[1, 6—8], the dynamics of damage-derived signal is paid special attention in this paper in addition to take the knowledge of the biochemical mechanism of the system and to be simplified to the major components in the system, because the signal plays a crucial role in describing the different dynamical activities of the system. In the cellular level, the damage-derived signal is assumed as the form with abrupt transition ("on" ↔ "off") as signal strength passes forth and back across a threshold. For the case of population of cells, the signal should be an exponential function in time resulting from the ensemble average of the individual cells. Under above-mentioned considerations, the different oscillatory behaviors of experimental results[1, 2] will be satisfactorily reproduced in this paper.

In section 2, a phenomenological dynamical model will be introduced for the negative feedback network of p53-Mdm2 interaction. In section 3, the numerical results and the analysis will be shown for various conditions. Finally, the last section will be devoted for concluding remarks.

2 Model

We assume that the concentration of p53 protein $P(t)$ obeys the following kinetic equation:

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = S_{\mathrm{P}} - \alpha_{\mathrm{P}} M(t) P(t)[1 - \gamma_{\mathrm{P}} S(t)] - \mu_{\mathrm{P}} P(t) \quad . \tag{1}$$

On r. h. s. in Eq. (1), the first term describes the synthesis rate of the p53 protein, the second one represents Mdm2- and signal-dependent degradation of p53 and the last one reflects an Mdm2-independent mechanism for p53 degradation. The coefficient α_{P} represents the ability of Mdm2 to promote p53 degradation, and controls the basal level of p53. μ_{P} is the rate of Mdm2-independent degradation of p53. $S(t)$ is the damage-derived signal that is the key component as described above. The introduction of parameter γ_{P} is to take into account that to what extent the damage-derived signal $S(t)$ might inhibit the p53 degradation induced by the activation of Mdm2 protein.

$M(t)$ represents the concentration of Mdm2 protein whose kinetic equation is given as:

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = S_{\mathrm{M}} + \alpha_{\mathrm{M}} \Gamma(t) - \mu_{\mathrm{M}} M(t) \quad . \tag{2}$$

Here the coefficient S_{M} denotes the rate of p53-independent Mdm2 transcription and translation, whereas the last term describes Mdm2 degradation. The coefficient α_{M} denotes the maximal initia-

tion rate of Mdm2 transcript initiation upregulated by p53[6]. μ_M is the rate of Mdm2 degradation. $\Gamma(t)$ in the second term, a mathematical representation of an unknown mechanism leading to the regulation of transcription of Mdm2 by p53 protein, is a Hill-type function and reads

$$\Gamma(t)=\frac{\{P(t-\tau)\}^N}{K^N+\{P(t-\tau)\}^N} \quad , \qquad (3)$$

where time τ takes into account the transcriptional and/or translational time delay, between the activation of p53 and the induction of Mdm2. The parameter K corresponds to some sort of threshold-for-activation for p53-protein concentration, and N is a Hill coefficient that determines the steepness of $\Gamma(t)$.

It should be mentioned that it is not so easy to define the values of all the parameters incorporated in the model. Most of the parameters cannot be defined since the lack of reliable experimental data. Some of them can be roughly estimated phenomenologically, for example, μ_P is taken to be small with respect to the Mdm2-dependent rate of p53 elimination, reflects the fact that although other mechanisms for the degradation of p53 may exist, a large body of data points to Mdm2 as the key regulator of p53 stability[1]. Typical transcriptional elongation and processing rates would result in a time delay of around 20—60 min[1]. The first order degradation rate of Mdm2 μ_M could be chosen as 0.05/min, which corresponds to Mdm2 half-lives approximately 20—25 min under basal condition. The Hill coefficient N is set to be 20 with reference to Ref [1].

The numerical simulation has shown that when the parameters used in this paper change in a reasonable range, the oscillatory behaviors of the solutions of Eqs. (1) and (2) are robust, and the eigenvalues of the dynamical matrix of Eqs. (1) and (2) are always negative. Thus the solutions are expected to be always stable.

3 Numerical Results and Discussions

3.1 The case of individual cells

When cells are exposed to the damaging agents, such as UV or ionizing radiation, the signal $S(t)$ will be derived which eventually activates an initial pulse of p53 concentration. From the biological point of view, in cellular level, $S(t)$ can be considered as switch "on" and will be with abrupt transition from "on" to "off" when signal is resolved, as the behavior of the p53-Mdm2 system evolves to give reasonably defined quanta of repair enzymes in response to stress[2]. $S(t)$ might be defined as:

$$S(t)=\Theta(t-n\tau_{th})=\begin{cases}1, & t\leqslant n\tau_{th}\\ 0, & t>n\tau_{th}\end{cases} \quad . \qquad (4)$$

Where n is a non-negative integer. τ_{th} is the characteristic duration within which the signal stress is in the region of oscillatory response and a pulse is activated. $n\tau_{th}$ accounts for the total time scale of $S(t)$. The value of τ_{th} used in this paper is $\tau_{th}\approx 125$ min, which is obtained from the characteristic frequency of the solutions of Eqs. (1) and (2).

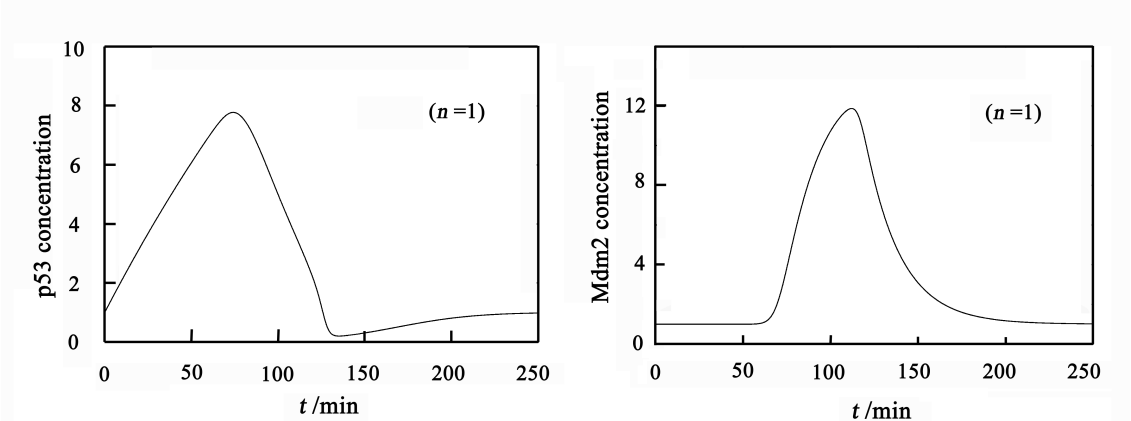

Fig. 1　Concentration of p53 tumor suppressor protein and its transcriptional target Mdm2 relative to their basal levels with the parameters: $S_P=0.5$, $\alpha_P=2.5$, $\gamma_P=0.968$, $\mu_P=2.5\times10^{-4}$, $S_M=2.35\times10^{-3}$, $\alpha_M=0.03$, $\mu_M=0.05$, $K=25$, $N=20$. The initial conditions of $P(t)$ and $M(t)$ are defined by their basal values as $P(0)=4.25$ and $M(0)=0.047$. The dynamics of signal $S(t)$ is described by Eq. (4). The transcriptional time delay $\tau=25$ min.

Fig. 1 shows the dynamical evolution of the concentration of p53 and Mdm2 proteins for the case in individual cells with $S(t)$ defined in Eq. (4), which are scaled with their basal values $P(0)=4.25$ and $M(0)=0.047$. Under the normal environment, the amount of p53 protein in the cell is kept low and tightly regulated by a genetic network built of Mdm2 and p53 itself. p53 is produced at an essentially constant rate and promotes the expression of the *Mdm2* gene[9]. On the other hand, the Mdm2 protein binds to p53 and promotes its degradation[10], decreasing its concentration. When DNA molecule is damaged, a cascade of events causes phosphorylation of several serines in the p53 protein, which modifies its binding properties to Mdm2[11]. As a consequence, the cell experiences a sudden increase in the concentration of p53, which activates a group of genes responsible for cell growth arrest and apoptosis. The increase in p53 protein levels and the transcription activity of p53 lead, in turn, to increase the production of Mdm2. Mdm2 protein again promotes the rapid degradation of the p53 protein, so as the sustained oscillations occur. Note that, as displayed in Fig. 1, the characteristic feature is that the minima of p53 level roughly coincide with the maxima of Mdm2 level and vice versa[2]. When the signal is completely resolved, the p53-Mdm2 loop returns to the normal case and the levels of p53 and Mdm2 to their basal values.

3.2　The case at the population of cells

When we turn to the case at population of cells, the p53-activating signal might be average over the different strength of damage stress in individual cells due to the stochastic mechanism in the gene expression[12—14] as mentioned in Sec. 1. The resulting $S(t)$ is assumed as $S(t)=S(0)\exp(-t/\tau_s)$. It can be easily proven that the parameter τ_s is the average of τ_{th} over the Poisson ensemble of individual cells when τ_{th} is supposed to be a constant since we ignored the difference of various types of damage and the p53-dependent DNA repair processes. Generally speaking, τ_s is much larger than the characteristic period of oscillation τ_{th}.

From Figs. 2 and 3, it is seen that the scaled concentrations undergo damped oscillations with respect to their basal levels. The characteristic damp scale of oscillation is around 20 hours. The damage signal is resolved after about 5 days and the levels will then decrease to a certain value that represents the stationary levels of p53 and Mdm2 proteins. In terms of Eqs. (1)—(3), the stationary values can be estimated with

$$M(0)=M(t\to\infty)=\frac{S_M}{\mu_M}\quad . \tag{5}$$

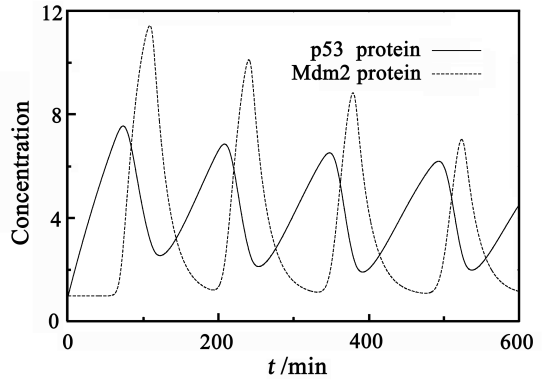

Fig. 2　Concentration of p53 and Mdm2 relative to their basal levels. A signal stress $S(t)=S(0)\exp(-t/\tau_s)$ is introduced in initial stage with $S(0)=1.0$ and $\tau_s=10\,000$ min. Reference of the coordinates and the parameter values are the same as in Fig. 1.

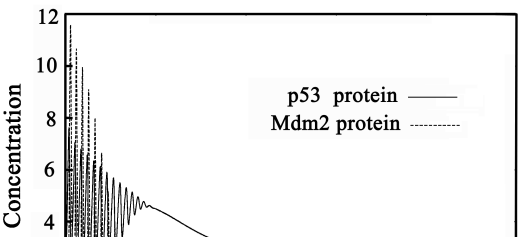

Fig. 3 Concentration of p53 and Mdm2 relative to their basal levels for large time scale. A signal stress $S(t)$, reference of the coordinates and the parameter values are the same as in Fig. 2.

$$P(0)=P(t\to\infty)=\frac{S_P\mu_M}{\alpha_P S_M+\mu_P\mu_M}\quad .\qquad (6)$$

With the used parameters, it is easily to obtain $M(t\to\infty)\approx 0.047$ and $P(t\to\infty)\approx 4.25$.

Origin of oscillation and damping Here it is worthwhile to clarify the origins of oscillation and damping mechanisms. The oscillatory dynamical behaviors could be ascribed to the autoregulatory feedback loop in which p53 positively regulates Mdm2 expression while Mdm2 negatively regulates p53 levels and activity. And the time delay in p53-dependent induction of Mdm2 should also be crucial for the oscillatory behavior. In order to clarify these points more clearly, let us consider the case without time delay, i.e., $\tau=0$, which means that the production of Mdm2 is regarded as instantaneously regulated by p53. As shown in Fig. 4, it is clearly seen that levels of p53 and Mdm2 proteins smoothly evolve and tend to the stationary values. There is no oscillation except the initial stage, which could be considered as resulting from the threshold of the parameter K. Effect of time delay also can be seen from Fig. 5 for various values of τ. Within this model, the significant oscillation only can be obtained from appropriate time delay, i.e., $\tau\approx 20$—60 min. Comparing Fig. 2, 3 with Fig. 4, we might conclude that the negative feedback mechanism and time delays could be considered as drive of the oscillations.

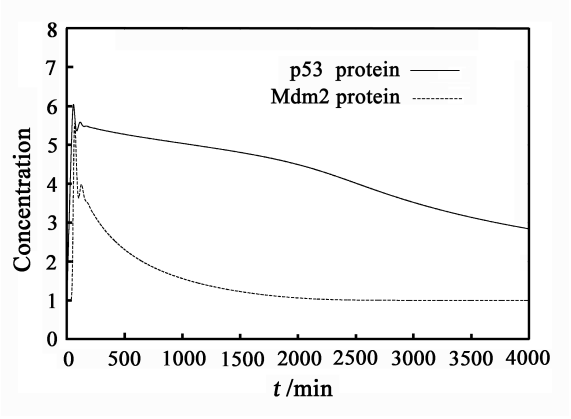

Fig. 4　Concentration of p53 and Mdm2 proteins for $\tau=0$. Reference of the coordinates and remaining parameter values are the same as in Fig. 2.

Let us further suppose that the irradiation damage of DNA keeps unresolved (this case might occur in the most severe cases of strong damage), which means that $S(t)$ keeps constant $S(0)$ or the parameter $\tau_s\sim\infty$. In such case, the amplitude of oscillations is sustained and the levels oscillate stationarily. When τ_s changes from large through small, as shown in Fig. 6, the damping mechanism starts to play a role and the damping of the oscillations might become strong. The meaningful oscillation could be obtained when the signal emanating from the damage persist long enough afterwards (say, $\tau_s>>\tau_{th}$).

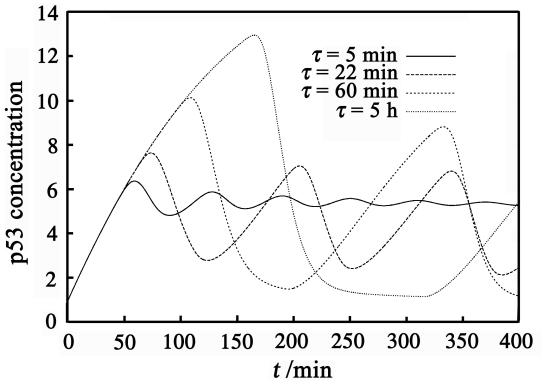

Fig. 5　Effect of time delay in p53-dependent induction of Mdm2 on the protein levels. Reference of the coordinates and remaining parameter values are the same as in Fig. 2.

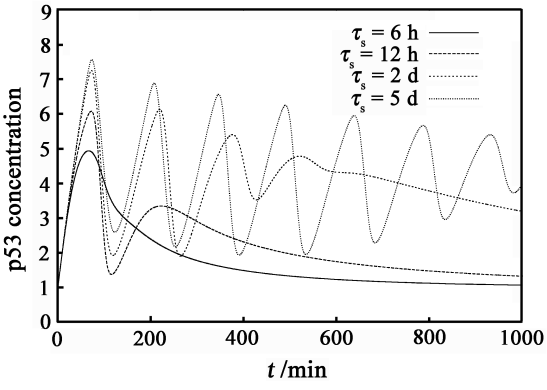

Fig. 6　Dependence of the oscillations on the damage repair rate τ_s. Reference of the coordinates and remaining parameter values are the same as in Fig. 2.

Effect of irradiation strength The experimental results[1, 5] have shown that the oscillation

only occur for a high damage. At weak damage level, the activation of damage-induced signaling pathways is likely to be relatively insufficient[1, 5]. In order to understand this point more clearly, the effects of damage strength $S(0)$ on p53 protein concentration are shown in Fig. 7. For higher values of signal ($S(0)=1.0$), the oscillations could be expected, on the contrary, for lower one (say, $S(0)=0.8$), the concentration of p53 protein increases to higher value with a longer time consuming, and reach a threshold for sparing p53 protein from destabilizing effects on Mdm2 protein.

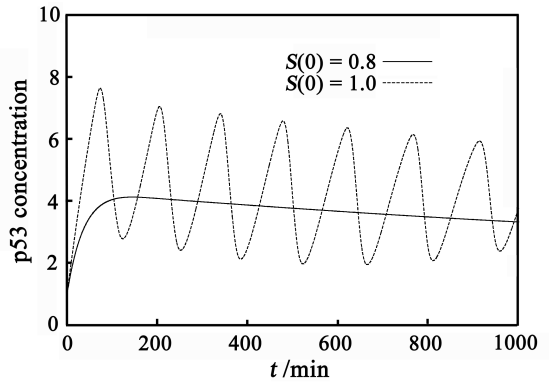

Fig. 7 Effects of the strength of irradiation signal on p53 levels. Reference of the coordinates and remaining parameter values are the same as in Fig. 2. The curve for higher signal ($S(0)=1.0$) is identical to the p53 curve in Fig. 2.

The above numerical results can be understood from Eq. (1). As is easily verified, the maximal value of p53 concentration $P^{\max}(t)$ at time $t_{\max}$ can be estimated by

$$P^{\max}(t_{\max})=\frac{S_P}{\alpha_P M(t_{\max})(1-\gamma_P S(t_{\max})-\mu_P} \quad . \quad (7)$$

For stronger irradiation damage (larger value of $S(0)$), a larger values of $P^{\max}(t_{\max})$ could be expected, which might be larger than the threshold parameter K in Eq. (3) and thus to stimulate the transcription and to increase the level of Mdm2 protein (note that in general, N in Eq. (3) is with a large value 20). Consequently, the level of p53 protein will be reduced. This negative feedback mechanism will cause the oscillations of concentrations of both p53 and Mdm2 pro-

teins.

However, for lower level of irradiation damage, $S(t)$ is not strong enough to keep p53 degradation weak, $P^{\max}(t_{\max})$ will possibly be not larger enough to surpass the threshold. When $P^{\max}(t_{\max}) < K$, the Mdm2 will remain transcriptional inactive. The concentration level of p53 protein will smoothly vary without oscillation and tend to its stationary value.

With the aid of Fourier analysis, it has been shown that the power spectrum of the oscillation part of the p53 concentration as shown in Figs. 2 and 3 could be divided into two parts $\omega = \omega_r + i\omega_i$. the imaginary part of frequency ω_i, which represents the damping of oscillation, coincides with the time scale of signal resolution $\sim 1/\tau_s$, in meantime, the real one ω_r corresponds to the time period of the pulses $\omega_r = 2\pi/\tau_{th}$. This result verifies our analysis of the origin of the oscillation and the damping mechanism.

4 Concluding Remarks

We proposed a unified model of p53-Mdm2 negative feedback loop and studied the dynamical mechanism of the activities of p53 and Mdm2 proteins in the cases of individual and population of cells.

It has been shown that both the sustained oscillatory dynamics in individual cells and the damped ones in the population of cells could be understood in a unified way when the dynamics of damage-derived signal is properly introduced. It has been clarified that the origin of the oscillation mechanism could be ascribed to the nonlinear dynamics of the autoregulatory negative feedback loop and the time delay in p53-dependent induction Mdm2. Meanwhile, the damping on oscillation might be related to the resolution DNA damage.

This study may provide us with a general understanding of the oscillatory dynamics found in various physical, chemical and biological systems. This study has the significance in gene therapy application.

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DNA 损伤致 p53-Mdm2 相互作用的非线性动力学模型*

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摘 要: p53-Mdm2 相互作用在 DNA 损伤的细胞响应方面起着非常重要的作用。最新实验结果表明, 在受到各种辐射损伤而引起 DNA 损伤后, 细胞中的 p53 蛋白浓度在单体细胞和群体细胞情况下, 表现为非衰减振荡和衰减振荡两种不同的动力学行为。通过研究 p53-Mdm2 负反馈回路的非线性动力学, 分析了各种(特别是 DNA 损伤, p53 和 Mdm2 浓度三者之间的)动力学关系, 提出了一个能同时描述这两种不同动力学行为的非线性模型。

关 键 词: p53-Mdm2 相互作用; 负反馈回路; 非衰减振荡和衰减振荡; 非线性动力学模型

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