Exploring the mechanism of the excitability of p53 pulse response

Aiqing Ma1, Xianhua Dai1,a

1School of Electronics and Information Technology, Sun Yat-Sen University, Guangzhou 51006, China

a Corresponding author: issdxh@mail.sysu.edu.cn

Abstract. DNA double-stranded breaks stimulate the digital pulse response of p53, which has the characteristic of excitability, and the mechanism of p53 pulse response has been extensively studied. However, the mechanism of the excitability of p53 pulse response remains to be elucidated. Here, we establish mathematical models of the p53 pulse response with different regulatory structures. Through simulation analysis and parameter space search, we find that the self-positive feedback of ATM can guarantee the excitability of p53 pulse response; We also analyze the effect of ATM-related parameters on the excitability of p53 pulse response. Our results are necessary for further exploring the mechanism of p53 pulse response and the cell fate decisions.

1. INTRODUCTION

As a central hub of cellular stress response, p53 plays an important role in maintaining the genomic integrity [1], it is reported that more than 50% of human cancers are caused by mutations in the p53 gene[2]. After DNA damage caused by γ-irradiation, p53 was shown that it exhibits repeated pulses with fixed amplitude and duration, whereas the number of pulses increases with higher damage[3, 4, 5]. Importantly it was proposed that the p53 pulse response has the characteristic of excitability[5, 6]. The mechanism of p53 pulse response has been extensively studied[4, 5, 7, 8]. However, the mechanism of excitability of p53 pulse response remains to be elucidated.

We first defined that the all-or-nothing response is characteristic for excitable systems[8, 9]. There is a stimulus threshold that can separate no response to a transient stimulation from full response [8-12]. Here, we establish mathematical models of p53 pulse response with different regulatory structures. Through simulation analysis and parameter space search, it is concluded that self-positive feedback regulation of ATM can guarantee the excitability of p53 pulse response; And we also discuss the effect of ATM-related parameters on excitability of p53 pulse response. This is necessary to further study the mechanism of p53 pulse response and the cell fate decisions.

2. RESULTS

2.1. Model

In the network of p53 responding to DNA double-stranded breaks, p53-mdm2 is the core negative feedback loops. As a transcription factor, p53 can induce Mdm2 expression[13], and then functional MDM2 serve as an E3-ubiquitin ligase and target p53 for proteasome-mediated degradation[14, 15]. Another feed-back loop is the p53-wip1, in which p53 activates Wip1 expression and Wip1 dephosphorylates p53, thus reducing its stability[16, 17]. This network contains third feed-back loop
between p53 and ATM mediated by wip1[18]. Upstream of p53 is the DNA damage sensor ATM, the activation process of ATM is very complicated and the molecular characterization of the early stages of DDR initiation remains incomplete, DNA double-strand breaks (DSBs) induce rapid autophosphorylation and activation of ataxia-telangiectasia mutated protein (ATM)[19], which then phosphorylates both p53[20, 21] and Mdm2 [22, 23] as well as other substrates. When the process of ATM activation is expressed only by a feed-forward loop, the network refers to Fig.1(a)[4, 5], and then translating the mechanism into ordinary equations refer to table1(a), and the parameter values refer to table2; When the process of activating ATM is expressed by a feed-forward loop and a self-positive feedback loop representing that the activated ATM can enhance ATM activation[8], the network refers to Fig.1(b), and then translating the mechanism into ordinary equations refer to table1(b), and the parameter values refers to table2. The parameter values were chosen by a trail-and-error method.

(a) Model I

(b) Model II

Figure 1 The network of p53 responding to DNA double-stranded breaks: (a) Model I; (b) Model II;
Table 1 The ordinary equations

(a) Model I
\[
\begin{align*}
\frac{d[A]{\text{ATM}}}{dt} &= \beta_1[D{\text{ATM}}(t)] - \alpha_1[W{\text{ip}}] + \alpha_2[W]{\text{ip}} \\
\frac{d[p{\text{S3}}]}{dt} &= \beta_3[p{\text{S3}}, M{\text{bin2}}] - \alpha_3[W]{\text{ip}} - \alpha_4[W]{\text{ip}} \\
\frac{d[M{\text{bin2}}]}{dt} &= \beta_4[p{\text{S3}}, \tau_m] - \alpha_5[A]{\text{TM}} + \alpha_6[M{\text{bin2}}] - \alpha_7[M]{\text{bin2}} \\
\frac{d[W]{\text{ip}}}{dt} &= \alpha_8[p{\text{S3}}, \tau_w] - \alpha_9[W]{\text{ip}}
\end{align*}
\]

(b) Model II
\[
\begin{align*}
\frac{d[A]{\text{ATM}}}{dt} &= \beta_1[D{\text{ATM}}(t)] + \beta_2[A]{\text{TM}} + \alpha_1[W]{\text{ip}} - \alpha_2[W]{\text{ip}} \\
\frac{d[p{\text{S3}}]}{dt} &= \beta_3[p{\text{S3}}, M{\text{bin2}}] - \alpha_3[W]{\text{ip}} - \alpha_4[W]{\text{ip}} \\
\frac{d[M{\text{bin2}}]}{dt} &= \beta_4[p{\text{S3}}, \tau_m] - \alpha_5[A]{\text{TM}} + \alpha_6[M{\text{bin2}}] - \alpha_7[M]{\text{bin2}} \\
\frac{d[W]{\text{ip}}}{dt} &= \alpha_8[p{\text{S3}}, \tau_w] - \alpha_9[W]{\text{ip}}
\end{align*}
\]

Table 2 Parameter values

| \(\beta_1\) | 0.81(0.11) | \(\beta_{11}\) | 0.6 | \(\alpha_{11}\) | 2.7 | \(\beta_2\) | 0.8 | \(\alpha_{21}\) | 1.4 | \(\alpha_{22}\) | 0.14 | \(\beta_3\) | 0.9 | \(\alpha_{31}\) | 0.5 | \(\alpha_3\) | 1 | \(\beta_4\) | 0.5 | \(\alpha_4\) | 0.7 | \(m_1\) | 4 | \(T_1\) | 0.5 | \(m_2\) | 4 | \(T_2\) | 1 | \(\tau_m\) | 0.7 | \(\tau_w\) | 1.25 |
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2.2. Simulation

Model I

We set DAM(t) as a step signal. The simulation result of Model I is shown in Fig. 2(a). We can see that the output of p53 is sustained pulse response, and the amplitude and the width of pulse are stable, which is consistent with the experimental results. The system with this structure can produce pulse response of p53. Then, DAM(t) is set to a signal with different dose of stimulation, the pulse response of p53 is linear output, the system with this structure doesn't have the characteristic of excitability Fig2(b); Next, we search the parameter space of all parameters, and only one parameter is changed at a time, the other parameters are unchanged. And the system with this regulation structure doesn't have the excitable characteristic in the parameter space Fig.3. The color value indicates the difference between amplitudes of two largest pulses. It can be seen that the minimum value of the difference is 0.32, so the system with this regulation structure does not have excitable characteristic in all parameter spaces.
Figure 2 Simulation of p53 pulse response and excitability: (a) p53 pulse response simulation; (b) Excitability simulation;

Figure 3 Exploring the excitable characteristic by searching the parameter space of all parameters

**Model II**

We set DAM(t) as a step signal, and the simulation result of Model II is shown in Fig.4(a). We can see that the output of p53 is sustained pulse response, the amplitude and the width of pulse are stable, which is consistent with the experimental results. This regulatory structure can also generate pulse
response of p53; Then, DAM(t) is set to a signal with different dose of stimulation, and the output of pulse response is saturated. That is, there is a stimulus threshold that can separate no response to a transient stimulation from full response, it is the hallmark of the excitable system Fig.4(b).

![Simulation of p53 pulse response and excitability](image)

Figure 4 Simulation of p53 pulse response and excitability: (a) p53 pulse response simulation; (2) Excitability simulation;

2.3. Analysis the effect of ATM-related parameters on excitability of p53 pulse response

Beta1 is the damage-dependent activation rate of ATM. Beta11 is the self-dependent activation rate of ATM. We want to know how does the excitability characteristic of p53 alter when the two parameters have different values. The color value indicates the difference between amplitude values of two largest pulses. In fig. 5, it can be seen that when the beta1 is the smallest value, beta11 satisfying the excitable characteristic has larger parameter ranges. And with the increase of beta1, the parameter range of beta11 satisfying the excitable characteristic becomes smaller, and the excitable characteristic of the p53 pulse response can be guaranteed only when beta11 takes a larger value. And the ranges of the two parameters that are capable of achieving excitability of p53 pulse response are presented.
3. CONCLUSION AND DISCUSSION

We used the mathematical model and numerical methods to explore the mechanism of excitable characteristic of p53 pulse response. We presented that the self-positive feedback of ATM can achieve the excitable characteristic of p53 pulse response, the system without the self-positive feedback of ATM doesn’t have the excitable characteristic in full-parameter space. And the ranges of two parameters beta1 and beta11 that are capable of achieving excitability of p53 pulse response have also been discussed. According to the theory of dynamical system, we know that the positive feedback is necessary for the excitable system[8]. Our results are important for further exploring the mechanisms of p53 pulse response and the cell fate decisions.

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