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Deciphering the Same Lifetimes of mRNA and the p53 Target Protein

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Deciphering the Same Lifetimes of mRNA and the p53 Target Protein

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Abstract- The tumour suppressor protein p53 is a transcription factor. After DNA damage, p53 concentrations exhibit pulsed or sustained dynamics that results in a number of target genes expression, triggering different cell fate. For p53 target genes, the mRNA decay rate constants of *PUMA*, *MDM2*, *p21*, and *BAX* are 73 h^{-1}, 0.27 h^{-1}, 0.265 h^{-1}, and 0.018 h^{-1}, respectively; the protein degradation rate constants are 0.056h^{-1}, 0.792 h^{-1}, 0.255 h^{-1}, and 0.0262 h^{-1}, respectively. What is the biological significance of the same lifetimes of mRNA and protein? For sustained p53 dynamics input, using a minimal model, I found that the same lifetimes of mRNA and protein can provide high sensitive target protein expression, drive protein expression to reach maximum at the shortest time. This result may be help for designing gene expression.

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I. Introduction

The tumour suppressor protein p53 is a transcription factor[1-4]. In response to DNA damage, p53 levels show pulsed or sustained dynamics[5, 6]. Different dynamics of p53 can activate different target genes expression, and trigger different cell fate [7-10]. How does p53 dynamics regulate target genes expression? The steady-state fold change $\overline{P}$ in target protein expression driven by p53 pulsing can be described by the Hill-type equation [11]

$$\overline{P} = 1 + \frac{\Delta}{T}\frac{\beta A^n}{K_A^n + A^n}, \qquad (1)$$

where Δ is the duration, T is the period, A is the amplitude, β is the maximal fold change in mRNA transcription, K_A is the dissociation constant.

And, the average steady-state fold changes in mRNA transcription and target protein expression are the same[11, 12], *i. e.*

$$\overline{m} = \overline{P}\ , \qquad (2)$$

where $\overline{m}$ represents the average steady-state fold change in mRNA transcription [12]. This equation reveals universal principles of central dogma of molecular biology.

According to the Hill-type equation, as shown in Fig. 1, the pulsed signalling nature is that fold change in p21 protein expression with high affinity is insensitive to amplitude modulation and easy to saturate (Fig. 1 A,B), duration and frequency rather than amplitude can fine-tune p21 protein expression with higher affinity beyond saturation (Fig. 1C,D). In addition, for $n > 1$, the cooperative binding can increase the sensitivity of amplitude modulation for lower-affinity expression[12]. By Equation 2, we can predict fold change in target protein expression from mRNA transcription.

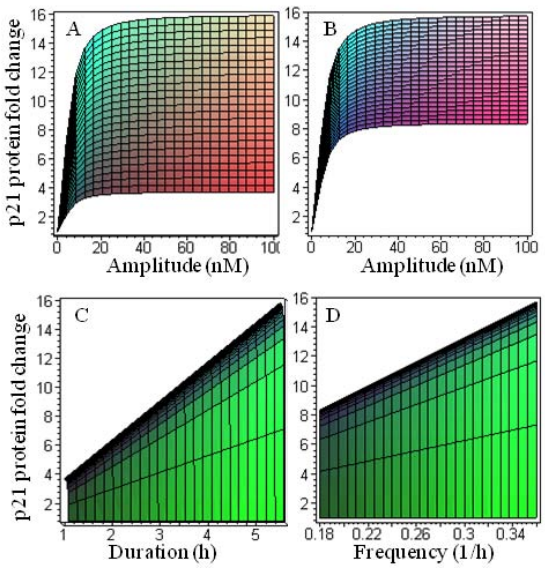

Fig. 1: Role of duration, frequency, and amplitude in p21 protein expression of p53 target with higher affinity. $K_A = 4.9$ nM, n=1.8. A. $T = 5.5$ h. B. $\Delta = 2.75$ h. $T = 5.5$ h. D. $\Delta = 2.75$ h.

The mean time to reach the average steady-state fold change $\overline{P}$ in target protein expression is mainly determined by the rate constants of mRNA decay and protein degradation. The short-lived p53 targets reached maximum transcript levels earlier than the long-lived p53 targets[9, 12, 13] The fold change in protein expression must spend a longer time to attain the average steady state for longer mRNA and protein half-

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lives. The mean number of p53 pulses required to reach average steady state is [11]:

$$\frac{\tau_{pulsed}}{T} \approx \frac{1}{\alpha T} + \frac{1}{\mu T} - \frac{1}{2}(1 - \frac{\Delta}{T}), \quad (3)$$

where τ_{pulsed} represents the mean time to attain average steady-state fold change in target protein expression under p53 pulsing, α and μ are the rate constants of mRNA decay and target protein degradation, respectively. Using Equation 3, for the p21 protein related to cell cycle arrest, the mean number of p53 pulses required to reach the steady state is:

$$\frac{\tau_{pulsed}}{T} \approx \frac{1}{0.265 \cdot 5.5} + \frac{1}{0.2546 \cdot 5.5} - \frac{1}{2}(1 - 0.37) = 1.085 \approx 1 \cdot$$

However, for the BAX protein related to apoptosis, the mean number of pulses is:

$$\frac{\tau_{pulsed}}{T} \approx \frac{1}{0.018 \cdot 5.5} + \frac{1}{0.0262 \cdot 5.5} - \frac{1}{2}(1 - 0.37) = 16.726 \approx 17 \cdot$$

Therefore, here, the p53 pulsing is a timer. Cells count the number of pulses to express the target gene. This counting mechanism not only provides sufficient time for DNA repair, but also leads to the accumulation of fold change in protein expression required for triggering apoptosis. Furthermore, the third term of Equation 3 shows that p53 pulses increase the sensitivity of gene expression.

For p53 target genes, the mRNA decay rate constants of *PUMA*, *MDM2*, *p21*, and the *BAX* are 73 h^{-1}, 0.27 h^{-1}, 0.265 h^{-1}, and 0.018 h^{-1},[8, 14] respectively, and the protein degradation rate constants are 0.056 h^{-1}, 0.792 h^{-1}, 0.255 h^{-1}, and 0.0262 h^{-1},[15]respectively. For *p21* and *BAX*, why are the lifetimes of mRNA and protein so close? Here, I will investigate the biological significance of a phenomenon.

II. Mathematical Model and its Solution

To calculate the response time and mean time to attain the steady-state fold change, for sustained p53 signalling, we have the model of target gene expression dynamics [11]

$$\frac{dm(t)}{dt} = \alpha\left(1 + \beta\frac{A^n}{K_A^n + A^n} - m(t)\right), \quad m(0) = 1, \quad (4)$$

$$\frac{dP(t)}{dt} = \mu(m(t) - P(t)), \qquad P(0) = 1 \quad . \quad (5)$$

Here $m(t)$ and $P(t)$ represent the fold changes in mRNA and target protein in response to sustained p53 dynamics, respectively, β is the maximal mRNA fold change, A is the sustained p53 concentration, K_A is the dissociation constant, α, μ are the rate constants of mRNA decay and protein degradation, respectively.

If $\alpha \neq \mu$, we have

$$P_1(t) = 1 + m_d - \frac{m_d}{\mu - \alpha}(\mu e^{-\alpha t} - \alpha e^{-\mu t}). \quad (6)$$

If $\alpha = \mu$, we have

$$P_2(t) = 1 + m_d - m_d(\mu t + 1)e^{-\mu t}. \quad (7)$$

Here, $m_d = \frac{\beta A^n}{K_A^n + A^n}$.

III. Results

a) *The response time for the different rate constants* $\alpha \neq \mu$

The response time is defined as the time needed to reach halfway between basal and activated steady state in target protein[16]. The steady state for Equation 6 is

$$P_{1,st} = 1 + m_d,$$

thus, the response time $t_{1,r}$ satisfies the equation

$$1 + m_d - \frac{m_d}{\mu - \alpha}(\mu e^{-\alpha t_{1,r}} - \alpha e^{-\mu t_{1,r}}) = 1 + \frac{m_d}{2}. \quad (8)$$

When $\alpha t_{1,r} \ll 1$, $\mu t_{1,r} \ll 1$, we have

$$t_{1,r} = \frac{1}{\sqrt{\alpha\mu}}. \quad (9)$$

b) *The response time for the same rate constants* $\alpha = \mu$

The steady state for Equation 7 is

$$P_{2,st} = 1 + m_d,$$

thus, the response time $t_{2,r}$ satisfies the equation:

$$1+m_d-m_d(\mu t_{2,r}+1)e^{-\mu t_{2,r}}=1+\frac{m_d}{2}. \quad (10)$$

When $\mu t_{2,r} \ll 1$, we have the solution

$$t_{2,r}=\frac{1}{\sqrt{2}\mu} \quad (11)$$

c) The condition for $t_{2,r} < t_{1,r}$

For $t_{2,r} < t_{1,r}$, from Equations 9 and 11, we have

$$\frac{1}{\sqrt{2}\mu}<\frac{1}{\sqrt{\alpha\mu}}, \text{ i. e. } \mu>\frac{\alpha}{2}. \quad (12)$$

Therefore, for $\mu>\frac{\alpha}{2}$, the fold changes in target protein expression with the different rate constants of mRNA decay and protein degradation can provide high sensitivity by regulating the mRNA decay rate constant to be the same as the rate constant of protein degradation. As shown in Fig 2, let $\alpha=\mu=0.7916\ \mathrm{h}^{-1}$, the MDM2 protein expression dynamics (green) exhibits more sensitivity than that (red) with $\alpha=0.27\ \mathrm{h}^{-1}$ and $\mu=0.7916\ \mathrm{h}^{-1}$.

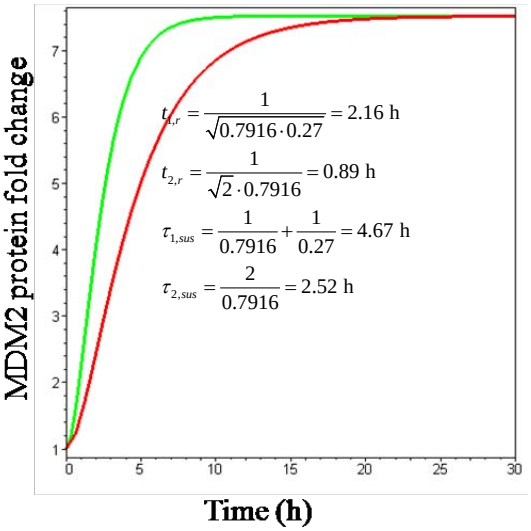

Fig. 2: MDM2 protein expression dynamics with $\alpha=0.27\ \mathrm{h}^{-1}$ and $\mu=0.7916\ \mathrm{h}^{-1}$ (red). MDM2 protein expression dynamics with $\alpha=\mu=0.7916\ \mathrm{h}^{-1}$ (green).

d) The mean time to reach steady-state fold change in the target protein expression

In Equation 3, τ_{pulsed} represents the mean time to attain the average steady-state fold change driven by p53 pulsing. Let $\Delta=T$, from Equation 3, we have

$$\tau_{sus}=\frac{1}{\alpha}+\frac{1}{\beta}, \quad (13)$$

which describes the mean time to reach steady-state fold change in protein driven by sustained p53 dynamics. In order to deepen the understanding of such mean time, similar to Salazar, C., *et al* [17], I try to derive the Equation 13 again by a different way. τ_{sus} can be defined as

$$\tau_{sus}=\frac{\int_0^{+\infty}(P_{1,st}-P_1(t))dt}{P_{1,st}-1}. \quad (14)$$

Thus, if $\alpha \neq \mu$,

$$\tau_{sus}=\frac{1}{\mu-\alpha}\int_0^{+\infty}(\mu e^{-\alpha t}-\alpha e^{-\mu t})dt=\frac{1}{\alpha}+\frac{1}{\mu} \quad (15)$$

Similarly, if $\alpha=\mu$, we have

$$\tau_{sus}=\frac{\int_0^{+\infty}(P_{2,st}-P_2(t))dt}{P_{2,st}-1}=\int_0^{+\infty}(1+\mu t)e^{-\mu t}dt=\frac{2}{\mu}. \quad (16)$$

e) The optimising principle for target protein expression dynamics upon sustained p53 input

From equation 15, we have

$$\tau_{sus}=\frac{1}{\alpha}+\frac{1}{\mu}=\left(\frac{1}{\sqrt{\alpha}}-\frac{1}{\sqrt{\mu}}\right)^2+\frac{2}{\sqrt{\alpha\mu}}\geq\frac{2}{\sqrt{\alpha\mu}}. \quad (17)$$

Therefore, τ_{sus} reaches a minimum if and only if $\alpha=\mu$.

For p53 target genes *p21* and *BAX*, the rate constants of mRNA decay and protein degradation are very close, which satisfies this simple optimizing principle, so that cells can reach rapidly the state of cell cycle arrest or apoptosis. However, for *MDM2*, the different lifetimes may produce sufficient time needed for feedback inhibition.

IV. Discussion

Let us investigate a fundamental property that is independent of the lifetimes of mRNA and p53 target protein. From Equations 4-5, we can easily obtain the

steady-state fold changes in mRNA transcription and target protein expression under sustained p53 dynamics:

$$\bar{m} = \bar{P} = 1 + \beta \frac{A^n}{K_A^n + A^n}. \quad (18)$$

Thus, we obtained again a fundamental property of gene expression pathway that the steady-state fold changes in mRNA and target protein expression are the same. This is the classical Hill equation that reveals the regulatory principle of target protein expression. For a higher binding affinity, $K_A \ll A$, we have

$$\bar{m} = \bar{P} = 1 + \beta. \quad (19)$$

Thus, the steady-state fold change in target protein expression with higher affinity reaches the maximal mRNA fold change. The target protein expression with lower affinity is sensitive to the change in amplitude. Compared with Equations 1 and 18, the fold change in target protein expression under sustained p53 dynamics is greater than that under pulsed p53 dynamics. Therefore, sustained p53 dynamics can easily trigger cell apoptosis.

V. Conclusion

p53 target protein expression dynamics is determined by the rate constants of mRNA decay and protein degradation. The mathematical time needed to attain the steady-state fold change in protein goes to infinite, thus, the response time and mean time are defined as two flexible indicators that characterize the sensitivity of target protein expression.

If the rate constant of protein degradation is greater than half of the rate constant of mRNA decay, increasing the mRNA decay rate constant to be the same as the protein degradation rate constant can provide higher sensitivity. Similarly, if the mRNA decay rate constant is greater than half of the protein degradation rate constant, increasing the protein degradation rate constant to be the same as the mRNA decay rate constant can also provide higher sensitivity.

The mean time needed to attain the steady-state fold change in target protein expression reaches a minimum if and only if the lifetimes of mRNA and target protein are the same.

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