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Decision making of the p53 network: Death by integration

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ABSTRACT

The tumor suppressor protein p53 plays a central role in the multiple response pathways activated by DNA damage. In particular, p53 is involved in both the pro-survival response of cell cycle arrest and DNA repair, and the pro-death response of apoptosis. How does the p53 network coordinate the different pathways that lead to the opposite cell fates and what is its strategy in making the life-death decisions? To address these questions, we develop an integrated mathematical model that embraces three key modules of the p53 network: p53 core regulation, p53-induced cell cycle arrest and p53-dependent apoptosis initiation. Our analyses reveal that different aspects of the nuclear p53 dynamic profile are being used to differentially regulate the pro-survival and the pro-death modules. While the activation of the pro-survival module is dependent on the current or recent status of the DNA damage, the activation of the pro-death module relies on the accumulation or integration of the damage level over time. Thus, the cell will take the death fate if it cannot recover from the damage within a time period that is inversely proportional to the damage level. This "adaptive timer" strategy is likely to be adopted in other stress response systems.

1. Introduction

The tumor suppressor protein p53 plays key regulatory roles in the cell's stress response pathways that can lead to the opposite cell fates (Braithwaite and Prives, 2006). In response to DNA damage, elevated p53 induces the transcription of a series of "pro-survival" proteins, such as p21, 14-3-3 and p53R2, to arrest the cell cycle and to repair the damaged DNA (Gatz and Wiesmuller, 2006; Kuerbitz et al., 1992). On the other hand, p53 also has transcriptional and non-transcriptional functions to trigger apoptosis, the cell's suicidal program (Chipuk and Green, 2006; Polyak et al., 1997). For the same cell type, the intensity of cellular stress is an important determinant of the cell fate, especially for radiation-caused DNA damage (Fei and El-Deiry, 2003). Cells with repairable damage usually prefers survival, while severe damage typically leads to cell death (Fei and El-Deiry, 2003; Speidel et al., 2006). Although various parts of the p53-mediated stress response pathways are extensively investigated experimentally and to some extent theoretically (Bagci et al., 2006; Geva-Zatorsky et al., 2006; Levine et al., 2006), one crucial question remains: when faced with different levels of DNA damage, how this network discriminatively regulates arrest, repair and apoptosis, and ultimately makes the best decision?

Another mystery associated with the p53 network is the functional significance of p53 oscillation under certain stress conditions. In 2000, Bar-Or et al. first observed periodic oscillation of nuclear p53 concentration after gamma radiation. Since then, oscillatory behavior of p53 after DNA damage has been found in several cell types, and in living mice (Hamstra et al., 2006; Ramalingam et al., 2007). A number of theoretical papers have been devoted to understand the mechanism of the oscillation (Ciliberto et al., 2005; Ma et al., 2005; Tiana et al., 2002; Wagner et al., 2005). It is speculated that this oscillation may have certain functional roles in cell fate decision (Tyson, 2006). However, despite these efforts it remains unclear whether and how the p53 oscillation plays any role in coordinating the stress response and/or in the cell-fate decision-making.

In this paper, we aim to address the following questions: (1) whether and how the p53 DNA damage response network uses different information to differentially regulate the pro-survival module and the pro-death module; (2) what is the strategy of the p53 network in the life-death decision making; and (3) what is the possible role of the p53 oscillation in this process. Based on the large amounts of literature on the p53 pathway, we first build

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a network of p53-mediated response to DNA damage, and then translate the network into ordinary differential equations. Analysis of this system suggests that distinct information of the nuclear p53 concentration is used to regulate the modules of cell cycle arrest and apoptosis: while the cell cycle arrest is determined by the *instantaneous* or peak values of the nuclear p53, the initiation of apoptosis depends on the *time integration* of the nuclear p53 level. This strategy gives the cell a time window – the length of which is roughly inversely proportional to the stress level – to recover from the stress before taking the death fate. With such a strategy, nuclear p53 oscillation can be beneficial in intermediate levels of damage—it expands the dynamic range of the differential response of the pro-survival and pro-death modules.

2. Results

2.1. Modeling the p53 DNA damage response network

We focus on the DNA damage caused by radiation. The p53 DNA damage response network that we consider in this work is shown schematically in Fig. 1. It consists of three modules: p53 core regulation, p53-induced cell cycle arrest, and p53-dependent apoptosis. For each of these modules, we separately obtain its overall qualitative dynamic behavior by analyzing its bifurcation diagram, which is relatively independent of the model parameters.

The p53 core regulation module is shown in the upper box, which controls the p53 level and its dynamics. Nuclear p53 induces the transcription of Mdm2, while Mdm2 targets p53 for degradation through multistep ubiquitination (Marine et al., 2006). DNA damage induces the phosphorylation of p53 and Mdm2, leading to a lower binding affinity between the two and rapid degradation of Mdm2 (Chehab et al., 2000; Fei and El-Deiry, 2003). As a result, p53 level rises to a "response state" that can trigger downstream events including apoptosis and cell cycle arrest. Note that p53 also forms a negative feedback loop with its upstream kinases, which may influence the shape of its oscillatory dynamics (Batchelor et al., 2008). For simplicity we do not include this loop here, and refer the readers to Supporting Information for an analysis of its effect on our model. We assume that the DNA is damaged at time $t=0$ with a damage level l, and that the damage level is maintained at the constant level l until either the damage is repaired or the cell initiates apoptosis. It is straightforward to generalize to the case of a time-varying damage level, e.g. with the damage level l decreases gradually in time as the damaged DNA being repaired. DNA damage level positively affects two parameters: the phosphorylation rate of p53 and the degradation rate of Mdm2.

While poly-ubiquitinated p53 undergoes degradation, mono-ubiquitinated p53 is exported into the cytoplasm (Salmena and Pandolfi, 2007). We assume that non-nuclear p53 has a longer half-life than nuclear p53. As will be discussed later, this assumption is crucial to our proposed mechanism of life-death decision. Although there are no direct experimental measurements, a longer life-time of non-nuclear p53 is conceivable because: (1) Mdm2 localizes predominantly in the nucleus (Roth et al., 1998) and (2) mono-ubiquitination further targets p53 to the mitochondria where it undergoes de-ubiquitination by HAUSP (Marchenko et al., 2007). This non-ubiquitinated p53 will further evade the ubiquitin-mediated degradation, the major channel for its destruction (Marine et al., 2006). It has been shown that mutated p53 that cannot associate with Mdm2 has a half-life around 10 h (Blagosklonny, 2000; Tang et al., 2006). Thus it is reasonable to assume that the cytoplasmic and mitochondrial p53 (all named mitochondrial p53 thereafter for brevity) has a half-life no less than 5 h, the typical period for p53 oscillation (Lev Bar-Or et al., 2000; Ramalingam et al., 2007; Speidel et al., 2006).

At elevated levels, both the nuclear and mitochondrial p53 play key roles in initiating intrinsic apoptosis (Chipuk and Green, 2006) (see bottom-right box of Fig. 1). Nuclear p53 down-regulates the transcription of anti-apoptotic proteins such as Bcl2, up-regulates the pro-apoptotic proteins such as Puma and Noxa, and primes Bax and Bak (Cory and Adams, 2002). Meanwhile, when entering the

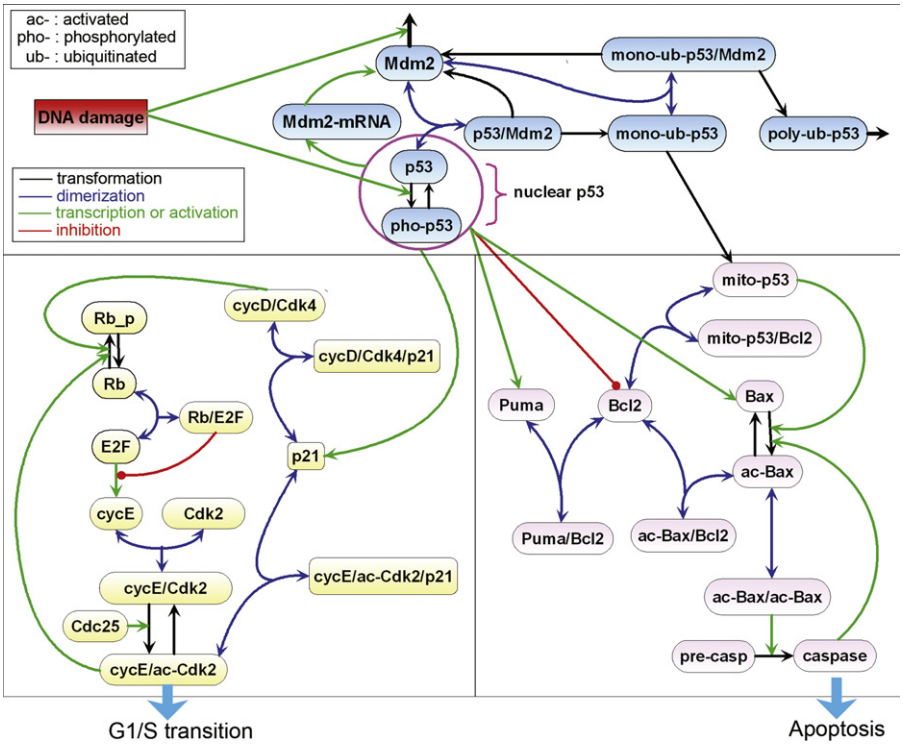

Fig. 1. The p53 DNA damage response network. Proteins with similar functions are grouped into one node denoted by their representative members.

cytoplasm and targeted the mitochondria, p53 directly activates the primed Bax and Bak for their oligomerization (Chipuk, 2004; Leu et al., 2004; Vaseva and Moll, 2008), inducing mitochondrial outer membrane permeabilization (MOMP). MOMP leads to the activation of the death executioner caspase (Cory and Adams, 2002). Caspase will further activate Bax besides its role in mass destruction, forming a positive feedback loop (Cory and Adams, 2002).

In contrast to its role in triggering cell death, p53 also plays important pro-recovery roles after DNA damage. p53 induces the transcription of DNA repair-related genes and may play a direct role in DNA repair and recombination (Gatz and Wiesmuller, 2006). Here we focus on the other pro-survival role of p53: arresting the cell cycle thus preventing the damage from aggravation and spreading, until the damaged DNA is repaired (Fei and El-Deiry, 2003). When the DNA is damaged, there are multiple pathways to arrest the cell cycle (Bartek and Lukas, 2001). There are p53-independent arresting mechanisms, which act quickly but transiently, and p53-dependent mechanisms, which involve transcription regulation and are responsible for the sustained cell cycle arrest (Bartek and Lukas, 2001). Furthermore, the cell cycle can be arrested in G1 or G2 phases. Toettcher et al. (2009) have investigated how the multiple arresting pathways can work together to achieve a fast and sustained cell cycle arrest that can re-enter the cell cycle at appropriate phase after the arrest. In our model, for simplicity, we only consider the p53-dependent G1 arrest (see the bottom-left box of Fig. 1). A sustained G1 arrest is achieved by nuclear p53 inducing the transcription of p21 (He et al., 2005), a short-lived protein that binds and inhibits both cycD/Cdk4 (the key complex in cell cycle entry (Massagué, 2004)) and cycE/ac-Cdk2 (the key complex in G1/S transition (Maki and Howley, 1997)). A p53-independent G1 arrest pathway, which involves DNA damage induced rapid destruction of Cdc25A (activator of cycE/Cdk2), can induce a fast cell cycle arrest that only last for several hours (Bartek and Lukas, 2001). The effect and influence of this pathway on our model is presented in the Supporting Information.

Some recent studies focused on the role of post-translational modifications of p53 for its target-gene selectivity in cell fate decision (Olsson et al., 2007; Zhang et al., 2009). Note that although our model does not explicitly include the target-gene selectivity of p53, to some extent the effect can be modeled by choosing different transcriptional parameters for different target genes.

Based on the description above (Fig. 1), ordinary differential equation (ODE) models of p53 regulation, apoptosis and G1 arrest modules were constructed. In these models, dimerization (blue line in Fig. 1) and transformation (black line) are modeled as elementary reactions; transcription/activation (green line) and inhibition (red line) are modeled using the Hill functions. Model parameters were chosen based on the literature whenever possible, and on the biochemical constraints (Aldridge et al., 2006). The details of the models are presented in the Supplementary Information. The three modules of the p53 network are first analyzed separately by treating the inter-module regulations as control parameters. A full dynamic simulation of the whole system is then followed to confirm the results and conclusions.

2.2. Nuclear p53 concentration oscillates at intermediate levels of DNA damage

Dynamic theory analysis of the p53 regulation module reveals a bifurcation diagram of nuclear p53 concentration as a function of the DNA damage level (Fig. 2A). It shows that the dynamic behavior of nuclear p53 undergoes transitions from low steady state to oscillation to high steady state, with increasing DNA damage level. Oscillations appear at the intermediate levels of DNA damage, with a period about 5 h; a high steady state appears at higher damage level. These results are consistent with existing experimental observations and theoretical modeling (Batchelor et al., 2008; Lev Bar-Or et al., 2000; Ramalingam et al., 2007; Speidel et al., 2006; Wagner et al., 2005).

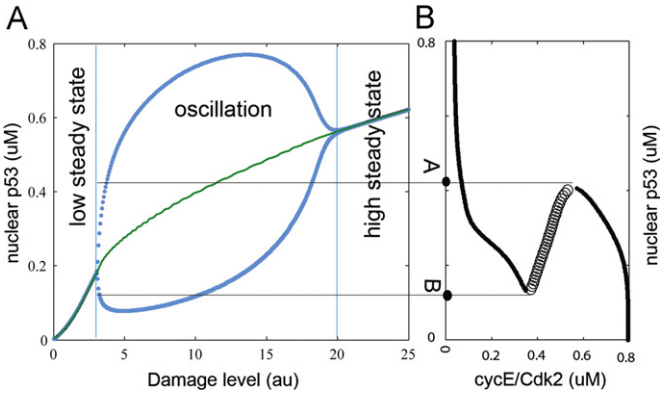

Fig. 2. (A) The phase diagram of the nuclear p53 as a function of the DNA damage level (dark blue). In the central region where nuclear p53 oscillates, the upper and lower branches denote the peak and valley values of the oscillation, respectively. The mean concentration of nuclear p53 is shown in green. (B) The bifurcation diagram of cycE/ac_Cdk2, with the nuclear p53 as the control parameter. Solid dots (seen as thick lines) indicate the stable fixed points; circles indicate the unstable fixed points. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

p53 also forms a negative feedback loop with its upstream kinases, which has been shown to influence the shape of p53 oscillation profile (Batchelor et al., 2008). To assess the impact of this additional loop on the bifurcation behavior of the p53 module, we carried out an analysis of a model with both the p53-Mdm2 loop and the p53-Wip1-Chk2 loop (Supporting Information, Section 3.1). We found that while this additional loop may change the bifurcation thresholds, it will not change qualitatively the overall structure of the bifurcation diagram.

Note that our analysis does not imply that with increasing DNA damage level the cell will always pass through the entire three phases of low-steady-state, oscillation, and high-steady-state because the damage level required for p53 to be in the high steady state region may be too severe to observe, or the signal might be transuded to the p53 regulation module in a non-linear fashion. The "observable" part of the entire phase diagram may depend on the damage type, cell type, and some other factors. We have performed a statistical study of the p53 module using a wide range of plausible model parameters (Supporting Information, Section 3.1). We found that while for most parameter sets the entire three phases can be observed with increasing damage level, a significant fraction of parameter sets allow only for partial phase diagram to be observed (Fig. S2). Nonetheless, according to our model, if both the oscillation and a high steady state level of p53 are observed in the same cell, the oscillation generally indicates a less severe damage.

2.3. Mitochondrial p53 is an integrator of nuclear p53 level

As discussed before, it is conceivable that the lifetime of the mitochondria p53 is considerably longer than the typical period of the p53 oscillations. Furthermore, there is no evidence showing that the mitochondria p53 can be actively imported back to the nucleus. If we assume that both the degradation rate and the nuclear reentry rate of the mitochondria p53 are quite small, the amount of the mitochondria p53 would be proportional to the time-integration of the nuclear p53 level. The rate equation for the mitochondria p53 is

$$\frac{d}{dt}[mito\_p53] = k[mono\_ub\_p53] - d_{mito}[mito\_p53], \quad (1)$$

where [*mono_ub_p53*] is the concentration of the nuclear mono-ubiquitinated p53 that is being exported to outside of the nucleus at a rate k, and d_{mito} is the sum of the degradation rate and the nuclear reentry rate of the mitochondria p53. In Supplementary Information, we show that $[mono\_ub\_p53] \propto [nu\_p53\_total]$, the total nuclear p53 concentration. Thus, under the assumption of small d_{mito},

$$\frac{d}{dt}[mito\_p53] \approx K[nu\_p53\_total]. \quad (2)$$

Integrating the above equation, we have:

$$[mito\_p53] \approx K \int_0^t [nu\_p53\_total] d\tau. \quad (3)$$

We therefore arrived at an important property of the system: the mitochondrial p53 level is approximately proportional to the time integral of the nuclear p53 level. This means that at a low steady-state level of the nuclear p53, the mitochondria p53 accumulates very slowly or does not accumulate at all. At a high steady-state level of the nuclear p53, the mitochondria p53 accumulates rapidly. In the case of an oscillatory nuclear p53, a fraction of the nuclear p53 is exported during each pulse, and the mitochondrial p53 accumulates in a staircase-like manner (Fig. 3A).

2.4. Accumulation of mitochondria p53 triggers apoptosis

As shown in Fig. 1, both the nuclear p53 and the mitochondria p53 can influence the apoptosis module. Treating the nuclear and the mitochondria p53 concentrations as control parameters and analyzing the ODE of the apoptosis module (Supplementary Information), we obtain the bifurcation diagram of the apoptosis executioner caspase (Fig. 3B). The switching-on of the caspase activity from low to high (via a saddle-node bifurcation) only happens when both the nuclear and the mitochondria p53 are above certain thresholds. However, the switch to the apoptotic state is mainly triggered by the accumulation of the mitochondrial p53.As shown in the figure, once the nuclear p53 exceeds certain threshold (between 0.2 and 0.4 μM), the switch from low caspase to high caspase activity is mainly driven by the increase of the mitochondrial p53 concentration. Also, the relatively slow time scale for the mitochondrial p53 accumulation makes it the time-limiting step for apoptosis initiation.

Although the majority of p53 localizes inside the nucleus, biological evidence supports the critical role of the mitochondrial p53 in apoptosis initiation. Speidel et al. (2006) observed that NIH3T3 cells go to cell cycle arrest and apoptosis under low and high doses of radiation, respectively. Comparing the cells with the two different fates, the expression of the pro-apoptotic proteins transcribed by the nuclear p53 does not have any obvious difference, while the mitochondrial p53 levels differ markedly (Speidel et al., 2006). Furthermore, inhibition of the mitochondrial p53 leads to the protection of mice from apoptosis, while the transcriptional function of p53 is not impaired (Strom et al., 2006).

As the accumulation of the mitochondria p53 is mainly responsible to trigger apoptosis and the mitochondrial p53 is an integrator of the nuclear p53 (Eq. (3)), we reach the conclusion that the nuclear p53 controls apoptosis through its time integration.

2.5. Peak values of nuclear p53 arrest cell cycle

The bistability nature of the cell-cycle arrest module has previously been suggested and observed (Yao et al., 2008). The p53-controlled bifurcations diagram of the cell cycle arrest module obtained from our model analysis is shown in Fig. 2B. With increased concentration of the nuclear p53, the level of cycE/ac-Cdk2 undergoes a transition from the high-value branch (cell cycle progression) to the low-value branch (cell cycle arrest) via a saddle

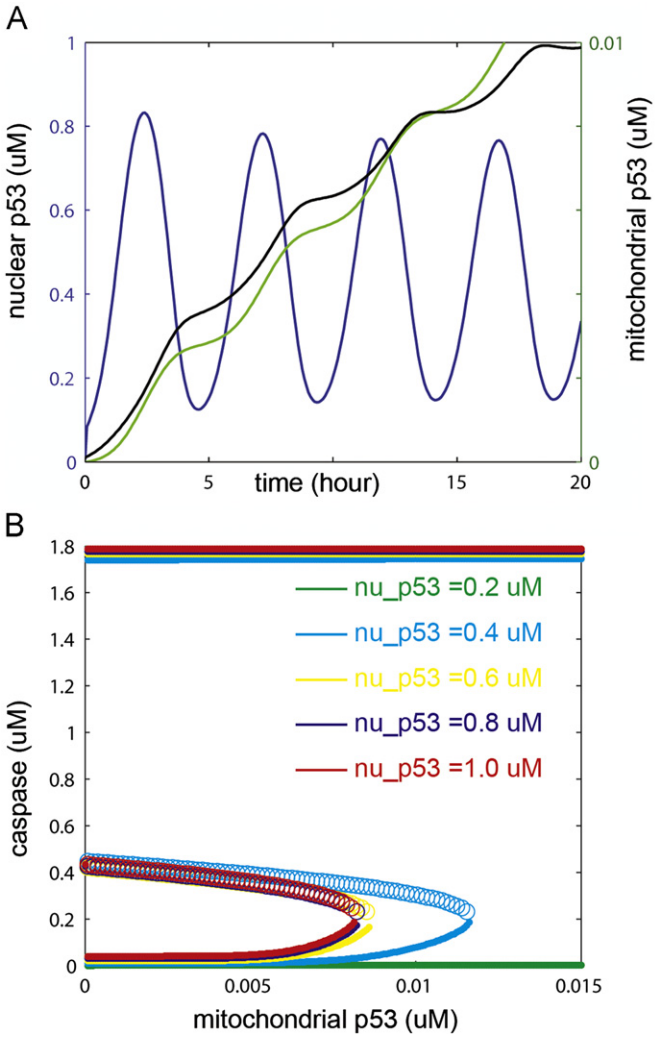

Fig. 3. (A) A time course of the nuclear p53 (blue), the total mitochondrial p53 (black) and the time integral of the nuclear p53 (green). The time integral has been normalized to the same scale of the mitochondrial p53. (B) The bifurcation diagram for the caspase, with the mitochondrial p53 as the control parameter. The diagram is shown with different nuclear p53 concentration, which changes the onset threshold of the mitochondrial p53 for apoptosis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

node bifurcation (Point A in Fig. 2B). Experimental observation indicates that the onset time for this p53-denpendent G1 arrest is about 4 h after the damage (Toettcher et al., 2009). However, nuclear p53 takes about the same time to accumulate (Toettcher et al., 2009). Thus, once the nuclear p53 reaches a nominal value, the arrest is relatively fast. There is a p53-independent pathway for G1 arrest upon DNA damage, via the DNA-damage-induced destruction of Cdc25A, which acts quickly but only transiently (Bartek and Lukas, 2001). We have investigated the effect of this mechanism on the bifurcation diagram of G1 arrest module and found that it shifts the position of the bifurcation points. Thus it can result in a faster arrest, but the overall structure of the bifurcation diagram is unchanged (Supporting Information Section 3.3; Figs. S5 and S6).

Due the bistability nature of the phase diagram, once the cell cycle is arrested, the nuclear p53 level has to decrease to a much lower value (Point B in Fig. 2B) for the cell cycle to resume. Thus, in the case of an oscillatory nuclear p53 level, it suffices to have the peak values exceeding the threshold (Point A in Fig. 2B) to arrest the cell cycle. Furthermore, the p53-assisted cell cycle arrest happens usually within an hour once the p53 rises to a high level (Bartek and

Lukas, 2001; He et al., 2005; Toettcher et al., 2009). On the contrary, the G1 progression has a longer time scale of the order of 10 h (Cooper, 1997). Thus, in the case of nuclear p53 oscillating between a high and a low level, even if the low level is below the point B in Fig. 2B, the cell cycle progression may not have time to resume before the next high value of p53 comes again. Results from our simulation of the full dynamic model confirmed this. Therefore, the peak values of the nuclear p53 determine the cell cycle arrest and its maintenance.

3. Discussion

3.1. The information processing strategy of the DNA damage response network

Our analyses of the p53 network suggest that the cell uses different aspects of the information from the nuclear p53 profile to differentially regulate pro-survival and pro-death modules. Cell cycle arrest depends on the present status of the nuclear p53 level—once the nuclear p53 level is above certain threshold the cell cycle is arrested. On the other hand, the initiation of apoptosis depends on the accumulation of the mitochondria p53, which is roughly proportional to the time-integration of the nuclear p53 level (Eq. (3)). The integration-dependent apoptosis initiation can be beneficial, as in this case the cell fate is determined not only by the degree of the DNA damage but also by the perceived ability for the cell to repair it. Corresponding to each damage level, the cell sets up a timer for apoptosis initiation. If the cell repairs the damaged DNA within the time window, the concentration of p53 drops and the timer is stopped—the cell survives. Otherwise, the timer sets off and the cell starts irreversibly the apoptosis program.

Since the average nuclear p53 level correlates positively with the damage level (see Fig. 2A), the time for the mitochondria p53 to reach a threshold (to trigger apoptosis) is roughly inversely proportional to the damage level. That is, the higher the damage level is, the faster the cell will commit to apoptosis and thus leaving a smaller time window for the cell to repair its damaged DNA. In Fig. 4, we show the dynamic behavior of key proteins for three different levels of DNA damage. At a very small damage level (Fig. 4A), the nuclear p53 level is very low and the mitochondria p53 never accumulates to a substantial level. The cell continues to divide and no apoptosis will be initiated, no matter how long the damage lasts. At an intermediate damage level (Fig. 4B), the nuclear p53 oscillates, the cell cycle is arrested, and the mitochondria p53 accumulates with time. If the cell does not repair its damaged DNA (thus reducing the p53 level) in about 35 h, the caspase is activated and the cell enters the irreversible process of apoptosis. At a high level of damage (Fig. 4C), the nuclear p53 is maintained at a high level and the mitochondria p53 accumulates fast. In this case, if the cell does not repair its damaged DNA in about 10 h, the apoptosis will take place.

This behavior of a decreasing survival rate with increasing damage level is summarized in Fig. 5, in which the dependence of cell fates on damage level and damage duration is shown. The red line separating life from death indicates the time window at a given damage level, beyond which the cell will die if the damaged DNA is not repaired. The inverse dependence of time window on the damage level is a smart strategy. The more severe the damage is, the smaller the chance to completely repair it, and potentially the more dangerous it is to the organism. Thus, to maximize the probability of the survival of the whole organism, it is reasonable to give the less damaged cells more chance (time) to recover and to be more "intolerable" to the more damaged cells.

In our model analysis, the DNA damage level is kept as a constant. One can, based on further assumptions about the repair rate, let the damage level decrease with time, reflecting the fact that the damage is being repaired. We have investigated such a model and a similar cell-fate phase diagram as functions of the initial damage level and the repair rate can be obtained (Supporting Information Section 4; Fig. S7).

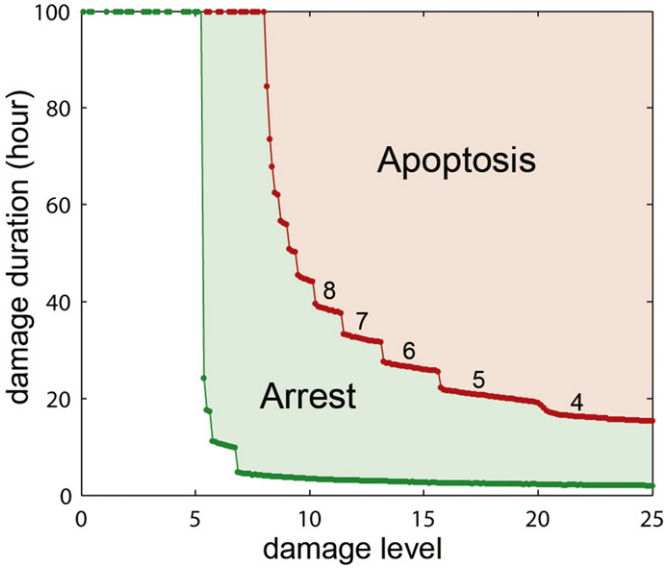

Fig. 5. The phase diagram of the cell fate as functions of the damage level and the damage duration. The green line is the onset of cell cycle arrest. The red line is the onset of apoptosis. The integers on the steps of the red line indicate the number of oscillation periods after which the cell will start apoptosis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

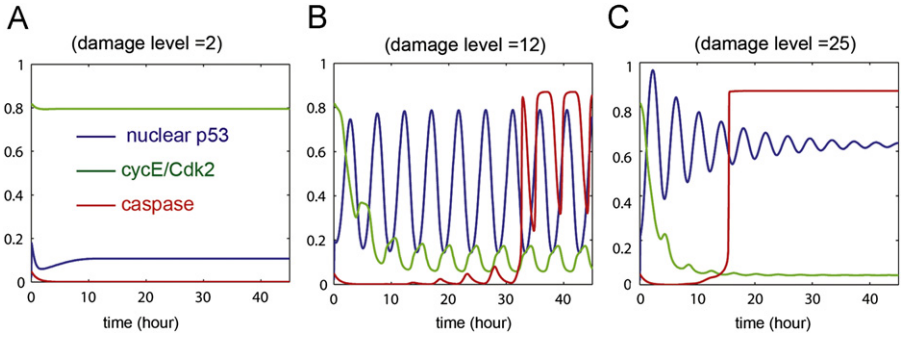

Fig. 4. Dynamics behavior of key proteins for low (A), intermediate (B) and high (C) damage levels. High caspase levels correspond to apoptosis; low cycE/Cdk2 levels correspond to G1 cell cycle arrest.

3.2. The possible function of the nuclear p53 oscillation

An oscillatory or pulsatile nuclear p53 have the characteristic property of a high peak value, but a much lower value of the time integration compared with a constant profile of the same peak value. If the pro-survival modules are activated/maintained by the instantaneous and/or peak values and the apoptosis is triggered by the time integration, oscillating nuclear p53 would effectively activate the pro-survival modules with its high peak value and at the same time not accelerating the pace of apoptosis. Indeed, as shown in Fig. 2A, p53 oscillation appears in the intermediate levels of damage—under potentially reparable damage, the cell prefers survival with high p53 peak value yet low integral value. Furthermore, a low valley value of p53 between the peaks may give the cell a chance to reset certain programs. In general, an oscillating nuclear p53 brings itself a larger dynamic range while keeping the accumulation of the mitochondria p53 at a controlled pace.

Note that under severe damages, the nuclear p53 takes high steady-state values (Fig. 2A). In this case, the cell goes faster into the apoptotic phase than with an oscillatory p53, even when the high steady-state concentration of the p53 is lower than the peak value of oscillation (compare Fig. 4C with 4B). Cell death is therefore preferred under high damage levels.

3.3. General strategy for cell decision-making in stress response

Some other stress response pathways seem to share the similar structure with that of the p53 network. For example, the Nf-κB pathways involve both pro-survival and pro-death responses and the oscillatory behavior of some key regulators was observed (Ashall et al., 2009; Hoffmann et al., 2002; Krishna et al., 2006). In the endoplasmic reticulum unfolded protein response pathways, the same regulators were shown to activate both the protective and the apoptotic responses (Han et al., 2009; Lin et al., 2007), and the cell fate depends on the strength and the duration of the stress (Degterev et al., 2003). Our proposed cell-fate decision-making strategy for the p53 network may also apply to these systems and may be rather general in stress response systems of eukaryotes. The theory can be verified or falsified with quantitative experiments, for example, by simultaneously monitoring the p53 concentrations in the nucleus and the cytoplasm, their dynamic behaviors, and the probability of apoptosis with varying degrees of irradiation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtbi.2010.11.041.

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