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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

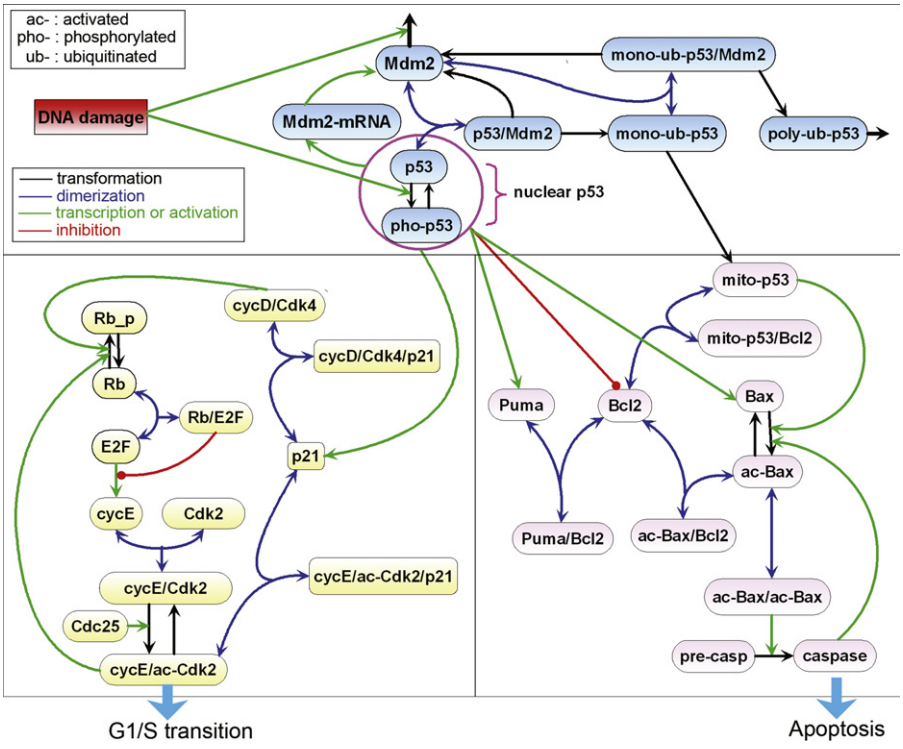

Fig. 1. The p53 DNA damage response network. Proteins with similar functions are grouped into one node denoted by their representative members.