Dynamic modeling of cellular response to DNA damage based on p53 stress response networks

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Abstract

Under acute perturbations from the outside, cells can trigger self-defensive mechanisms to fight against genome stress. To investigate the cellular response to continuous ion radiation (IR), a dynamic model for p53 stress response networks at the cellular level is proposed. The model can successfully be used to simulate the dynamic processes of double-strand breaks (DSBs) generation and their repair, switch-like ataxia telangiectasia mutated (ATM) activation, oscillations occurring in the p53-MDM2 feedback loop, as well as toxins elimination triggered by p53 stress response networks. Especially, the model can predict the plausible outcomes of cellular response under different IR dose regimes.

Keywords: p53; DNA damage; IR; Cellular networks; Modelin

1. Introduction

Under genome stresses such as DNA damage, hypoxia, and aberrant oncogene signals, cells can trigger self-defensive mechanisms to fight against acute perturbations from the outside [1–3]. One of the critical responses is the activation of the p53 tumor suppressor, which is the pivotal anticancer gene within the cell [3,4]. p53 can induce or repress transcription and translation of a series of downstream genes, and further control cell cycle arrest and apoptosis [3–5]. These functions are important to repair DNA damage and to eliminate abnormal cells with DNA damage or deregulated proliferation, especially to modulate the activity of anticancer agents [6–8].

Recently, several models have been proposed to explain the damped oscillations of p53 in cell populations [6–11]. However, the complicated mechanisms of cellular responses to genome stresses need to be further addressed. Based on the previous models [9–14] and stimulated by the impact of bioinformatics approaches on the biomedicine [15], a dynamic model of p53 stress response networks under continuous ion radiation (IR) at the cellular level is proposed along with the kinetics of double-strand breaks (DSBs) generation and repair, ataxia telangiectasia mutated (ATM) activation, p53-MDM2 (murine double minute2) feedback loop, as well as the toxins elimination module. Furthermore, the plausible outcomes of cellular responses were analyzed under different IR dose domains.

The combined approaches of system analysis, control theory, and computer science can simulate the complicated mechanisms of cellular response to genome stresses [15,16]. These methods provide a good link between the diverse areas of biomedicine, mathematics, and bioinformatics [16,17]. Using differential equations and graphic approaches to study various dynamical and kinetic processes of biological systems has provided insights into a series of important biological topics such as enzyme-catalyzed reactions [18–21], diffusion-controlled reactions in enzyme systems [22,23],
protein-folding kinetics [24], inhibition kinetics of processive nucleic acid polymerases and nucleases [25,26], base frequencies in the anti-sense strands [27], hepatitis B viral infections [28], HBV virus gene missense mutation [29], and visual analysis of SARS-CoV [30,31]. In this study, we used differential equations and graphic methods to investigate the dynamic and kinetic processes of cellular responses to DNA damage under continuous IR.

2. Model of p53 stress response networks

2.1. Model overview

Under genome stress, numerous co-factors are involved in enhancing p53-mediated transcription [32]. Interactions among these co-factors make the model more complicated. Therefore, only the vital components and interactions are taken into account in the model. The scheme of the integrated model is given in Fig. 1. In the DSBs generation and repair module, acute IR induces DSBs stochastically and forms DSB–protein complexes (DSBCs) at each of the damaged sites by interaction of the DSB with the DNA repair proteins (RPs). As a sensor of genome stress, ATM is activated by the DSBCs signal transferred from DSBs. ATM activation switches on or off the p53–MDM2 feedback loop, further regulating the downstream regulatory functions of p53, and are used as an indicator of cell cycle arrest and apoptosis in response to genome stress [33,34].

2.2. DSB generation and repair

Under the continuous effect of acute IR, DSBs occur and trigger two major repair mechanisms in eukaryotic cells: homologous recombination (HR) and non-homologous end joining (NHEJ) [35,36]. About 60–80% of DSBs are rejoined quickly, whereas the remaining 20–40% of DSBs are rejoined more slowly [37,38]. As shown in Fig. 2, the module scheme for DSBs repair process. It includes both the fast and the slow repair pathway. Each DSB can be in one of four states: intact DSB (DSB), DBSC, F_r, and F_w. Subscripts ‘1’ and ‘2’ refer to the fast and slow kinetics, respectively.

Fig. 1. The scheme of p53 stress response networks under continuous IR. It is composed of three modules: DSB generation and repair, ATM activation, as well as regulation of the p53-MDM2 feedback loop.

source to transfer the DNA damage to the p53-MDM2 feedback loop by ATM activation [2,39,40].

In our model, we assume that the same repair enzymes are used in both the fast and slow repair processes. Especially, DSBCs and RPs are treated as the dynamic variables [7–10], and limited RPs are available around DNA damage sites [12–14]. Considering that the misrepair part of DSBs (F_w) has profound consequences for subsequent cellular viability and the cellular response to genome stress [1,3], we obviously distinguish between the correct repair part of DSBs (F_r) and F_w [12–14]. Moreover, we further deal with the total F_w in both repair processes as parts of the toxins within the cell [2,4,15], which can be eliminated by the regulatory functions of p53, and are used as an indicator of outcomes in cellular response to genome stress [32–35].

Some experimental data suggest that the quantity of the resulting DSBs induced by different IR doses obey a Poisson distribution [10]. In accordance with those experiments, we assume that the stochastic number of the resulting DSBs per time scale is proportional to the number generated by a Poisson random function during the period of acute radiation [10]. The DSBs generation process is formulated as follows:

\[
\frac{d[D_T]}{dt} = k_{t} \times \text{Poissrnd}(a_{ir} \times IR)
\]

where \([D_T]\) is the concentration of total resulting DSBs induced by IR in both the fast and the slow repair processes. \(k_{t}\) is the parameter to set the number of DSBs per time scale, and \(a_{ir}\) is the parameter to set the number of DSBs per IR dose.

Moreover, we assume that limited RPs are available around DSBs sites, and 70% of the initial DSBs are fixed by the fast repair process. Each DSB can be in one of the following four states: intact DSB, DBSC, F_r, and F_w. Thus, we have the following differential equations:

\[
\frac{d[D_1]}{dt} = a_1[D_T] + k_{dt1}[C_1] - [RP](k_{dc1}[D_1] + k_{cross}([D_1] + [D_2]))
\]

(2)

\[
\frac{d[D_2]}{dt} = a_2[D_T] + k_{dt2}[C_2] - [RP](k_{dc2}[D_2] + k_{cross}([D_1] + [D_2]))
\]

(3)
Here, we use the superscript the inactive ATM monomer, and ATM*. Here, we assume (Fig. 3), which includes three components: the ATM dimer, ATM is activated from ATM monomers with the cooperative effects of Fig. 3. The module scheme of ATM activation under continuous IR. molecule autophosphorylation [10]. The main formulas are as respectively [38].

\[
\frac{d[C]}{dt} = k_{dc1}[D_1] - k_{cd1}[C_1] - k_{cf1}[C] 
\]

\[
\frac{d[C_2]}{dt} = k_{dc2}[D_2] - k_{cd2}[C_2] - k_{cf2}[C_2] 
\]

\[
\frac{d[RP]}{dt} = S_{rp} + k_{cd1}[C_1] + k_{cd2}[C_2] - [RP](k_{dc1}[D_1] + k_{dc2}[D_2]) 
\]

\[
\frac{d[F_w]}{dt} = k_{fw1}[C_1] + k_{fw2}[C_2] 
\]

where \([D], [C], and [F_w]\) denote, respectively, the concentrations of DSBs, DSBCs, and F_w; \(k_{dc}, k_{cd}, k_{cf},\) and \(k_{fw}\) are the transition rates among the above three states; \(k_{dc}\) and \(k_{cross}\) represent the first-order and second-order repair rates, respectively [38]. \(S_{rp}\) is the basal induction rate of repair mRNA, and subscripts ‘1’ and ‘2,’ respectively, refer to the fast and the slow kinetics.

### 2.3. ATM activation

As a DNA damage detector, ATM exists as a dimer in unstressed cells. After IR is applied, intermolecular autophosphorylation occurs causing the dimer to dissociate rapidly into the active monomers. The active ATM monomer (ATM*) can prompt further p53 expression [37,38]. Especially, toxins are degraded directly by the regulatory functions of ATM*.

Based on the existing model of the ATM switch [10], we present an ATM activation module under continuous IR (Fig. 3), which includes three components: the ATM dimer, the inactive ATM monomer, and ATM*. Here, we assume that DSBCs are the main signal transduction from DSBs to the p53-MDM2 feedback loop through ATM activation, and the rate of ATM activation is a function of the amount of DSBCs and the self-feeding of ATM*. Furthermore, the total concentration of ATM is a constant including the ATM dimer, ATM monomer, and ATM* [10].

As a detector of DNA damage, ATM activation plays an important role in triggering the regulatory mechanisms of p53 stress response networks [34,41,42]. After acute IR is applied, phosphorylation of inactive ATM dimers is promoted first by DSBCs and then rapidly by means of the positive feedback from ATM*, accounting for the intermolecular autophosphorylation [10].

The modules shown in Fig. 3 are as follows:

\[
\frac{d[ATM]}{dt} = \frac{1}{2} k_{dim}[ATM]^2 - k_{undim}[ATM] 
\]

\[
\frac{d[ATM_1]}{dt} = 2k_{undim}[ATM] - k_{dim}[ATM]^2 
\]

\[
\frac{d[ATM^*]}{dt} = k_{af}[ATM] - k_{af}[ATM^*] 
\]

\[
f(C, [ATM^*]) = a_1C + a_2[ATM^*] + a_3C[ATM^*] 
\]

where \([ATM], [ATM_1], and [ATM^*]\) represent the concentrations of the ATM dimer, ATM monomer, and active ATM monomer, respectively; \(k_{undim}\) is the rate of ATM undimerization, and \(k_{dim}\) is the rate of ATM dimerization; \(k_{af}\) is the rate of ATM monomer inactivation, and \(k_{af}\) is the rate of ATM monomer activation. In addition, \(f\) is the function of ATM activation, the term \(a_1C\) implies the fact that DSBs somehow activate ATM molecules at a distance, \(a_2[ATM^*]\) indicates the mechanism of autophosphorylation of ATM, and \(a_3C[ATM^*]\) represents the interaction between the DSBCs and ATM* [2,10].

### 2.4. Regulation of the p53-MDM2 feedback loop

The p53-MDM2 feedback loop is the vital part in the integrated networks. As shown in Fig. 4, p53 and its principal antagonist, Mdm2, is trans-activated by p53 and form a p53-MDM2 feedback loop. ATM* can elevate the transcriptional activity of p53 by prompting phosphorylation of p53 and degradation of the MDM2 protein [9].

To account for a decreased binding affinity between inactive p53 and p53*, we assume that MDM2-induced degradation of inactive p53 is faster than that of p53* [10,12]. Only p53* can regulate the target genes to eliminate the toxins within the cell [9,10,19]. This negative feedback loop can produce oscillations in response to sufficiently strong IR doses [9–14]. The formulas used in this module are as follows:

- \(p53_a\)
- \(p53_k\)
- \(p53_r\)
- \(p53^*\)
- \(Mdm2_a\)
- \(Mdm2_k\)
- \(Mdm2_r\)
- \(Mdm2^*\)

Fig. 4. The scheme of the p53-MDM2 feedback loop. ATM* elevates the transcriptional activity of p53 by prompting phosphorylation of p53 and degradation of the MDM2 protein. The increase in MDM2 proteins promotes a fast degradation of p53 and a slow degradation of p53*. Especially, toxins are degraded directly by the regulatory functions of p53*.
where \([p53^{*}]\), \([p53]\), and \([p53]^{*}\) represent the concentrations of p53 mRNA, p53 protein, and active p53, respectively. \([MDM2^{*}]\), \([MDM2]\), and \([Toxins]\) represent the concentrations of MDM2 mRNA, MDM2 protein, and \(F_w\) within the cell, respectively; \(S_{p53}\) and \(S_{MDM2}\) are the basal induction rate of p53 mRNA and that of MDM2 mRNA, respectively. The other parameters are presented in Tables 1–3.

### 3. Simulation results and discussion

To ensure the accuracy of the simulation results, let us consider the fact that the valid parameter sets should obey the following rules [9,10,41]: (i) the model must contain oscillations. This is important as there has been experimental evidence that oscillations occur between p53 and MDM2 after cell stress; (ii) the mechanism used to mathematically describe the degradation of p53 by MDM2 is accurate only for low concentrations of p53; and (iii) the concentration of p53* is much higher than that of inactive p53 after the system reaches an equilibrium. Based on these three rules and the existing parameter sets used in [10], we obtained the kinetics of p53 stress response networks under continuous IR dose using the simulation platform in MATLAB. The detailed parameter sets used in our model can be found in Tables 1–3.

#### 3.1. Cellular response under continuous IR

During the simulation process, we applied 5-Gy IR to generate the DSBs fraction. To agree with the experimental results that showed 30–40 DSBs per Gy occurred in a single cell [10], the stochastic number of resulting DSBs was generated using a Poisson random function with a mean of 35x as a continuous IR dose of x-Gy was applied. Fig. 5(a) displays a stochastic trace of the resulting DSBs versus the constant radiation time, and Fig. 5(b) shows the kinetics of ATM activation triggered by DSBCs transfer, and the ATM* switch to the “on” state and the tendency to reach the saturation state after about 15 min at 5-Gy IR. The step-like traces suggest that the ATM module can produce an on–off switching signal and further transfer the damage signal to the p53-MDM2 feedback loop [7–14].

Meanwhile, Fig. 5(c) shows the dynamic traces of p53 and MDM2 in response to continuous applications of 5-Gy IR from time zero. Upon the activation by ATM*, and decreased degradation by Mdm2, the total amount of p53 proteins increases quickly. Due to p53-dependent induction of Mdm2 transcription, the increase in Mdm2 proteins is sufficiently large to lower the p53 level, which in turn reduces the amount of the MDM2 proteins. The oscillation pulses shown in Fig. 5(c) have a period of about 400 min, the phase difference between p53 and MDM2 is about 100-min, moreover, the first pulse is slightly higher than the second, which is quite similar to the experimental observations [17–19] and the simulation results [7–14].

#### 3.2. Cellular response under different IR doses

During the simulation process, we applied 2-, 6-, and 10-Gy IR to analyze the different kinetics of cellular response to different IR doses. As shown in Fig. 6(a), RPs available around damage sites keep increasing under 2-Gy IR, whereas, RPs begin to decrease from initial value as the IR dose increases to 6-Gy. Fig. 6(b) shows that the rate of DSBCs synthesis begins to decrease after about 70 min of 10-Gy IR. Meanwhile, as shown in Fig. 6(c), without the degradation effect of p53*, \(F_w\) are accumulated dramatically at IR doses above 6-Gy. These simulations suggest that the capabilities of cellular response to fight against DNA damage begin to decrease at a certain IR dose threshold.

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Table 1

| Parameters | Description | Constant |
|-----------|-------------|----------|
| \(k_1\) | The rate of DSBs generation per time scale | 0.01 |
| \(d_1\) | The number of DSBs generation per IR dose | 35 |
| \(d_1\) | The percentage of DSBs processed by fast repair (D1) | 0.70 |
| \(d_2\) | The percentage of DSBs processed by slow repair (D2) | 0.30 |
| \(k_{d1,1}\) | The rate of DSBs transition to DSBCs in D1 | 2 |
| \(k_{d1,2}\) | The rate of DSBs transition to DSBCs in D2 | 0.2 |
| \(k_{d1,3}\) | The rate of DSBCs transition to DSBCs in D1 | 0.5 |
| \(k_{d2,1}\) | The rate of DSBCs transition to DSBCs in D2 | 0.05 |
| \(k_{d1,2}\) | The rate of DSCs transition to Fi in D1 | 0.001 |
| \(k_{d2,2}\) | The rate of DSCs transition to Fi in D2 | 0.0001 |
| \(k_{d1,2}\) | The rate of DSCs transition to Fi in D1 | 0.001 |
| \(k_{d2,2}\) | The rate of DSCs transition to Fi in D2 | 0.0001 |
| \(k_{cross}\) | The rate of DSB binary mismatch in second-order kinetics | 0.001 |
3.3. Prediction for cellular response under IR

The p53-MDM2 feedback loop is vital for the control of downstream genes and regulation pathways to fight against genome stress [8,9,33]. In response to the input signal of ATM*, the p53-Mdm2 module generates one or more oscillations. The response traces of the p53 protein under continuous applications of 2-, 6-, and 10-Gy IR from time zero are shown in Fig. 7(a), which shows that two or more pulses of p53 and MDM2 are generated after increasing the IR doses. Our simulations are fully in accordance with the observations that, on average, the greater the number of p53 pulses, the more severe the damage that can be triggered [8,9,33], whereas the intensity of the oscillations begins to decrease under 10-Gy IR. Meanwhile, Fig. 7(b) shows the kinetics of $F_w$ elimination induced by the degradation functions of p53*, compared with Fig. 6(c). $F_w$ are eliminated dramatically and tends towards dynamic equilibrium versus radiation doses of 2- and 6-Gy IR, whereas $F_w$ begin to decrease at the first climax, and then maintain a higher level under continuous application of 10-Gy IR. These simulations suggest that p53* does play important roles in fighting against DNA damage, whereas the abilities of the cellular response to fight against genome stress begins to decrease as the IR dose overtakes a certain

| Table 2 |
|---|
| The parameters used in the module of the ATM activation process. |

| Parameters | Description | Constant |
|---|---|---|
| $k_{dim}$ | ATM dimerization rate | 8 |
| $k_{undim}$ | ATM undimerization rate | 1 |
| $k_{af}$ | ATM phosphorylation rate | 1 |
| $k_{ar}$ | ATM dephosphorylation rate | 3 |
| $a_1$ | Scale of the activation function of ATM phosphorylation | 1 |
| $a_2$ | Scale of the activation function of ATM phosphorylation | 0.08 |
| $a_3$ | Scale of the activation function of ATM phosphorylation | 0.8 |

| Table 3 |
|---|
| The parameters used in the p53-MDM2 feedback regulatory loop. |

| Parameters | Description | Constant |
|---|---|---|
| $S_{p53}$ | Basal induction rate of p53 mRNA | 0.01 |
| $S_{mdm2}$ | Basal induction rate of MDM2 mRNA | 0.002 |
| $k_{tp}$ | Translation rate of p53 mRNA | 0.12 |
| $k_{yr}$ | Dephosphorylation rate of p53* | 0.2 |
| $k_{app}$ | ATM*-dependent phosphorylation rate of p53 | 0.6 |
| $k_{mp}$ | Mdm2-dependent degradation rate of p53 | 0.1 |
| $k_{app}$ | p53-dependent Mdm2 transcription rate | 0.03 |
| $k_{mpd}$ | Mdm2-dependent degradation rate of p53* | 0.02 |
| $k_{mat}$ | ATM*-dependent degradation rate of Mdm2 | 0.01 |
| $k_{mpp}$ | Translation rate of Mdm2 mRNA | 0.02 |
| $d_{pr}$ | Degradation rate of p53 mRNA | 0.02 |
| $d_{pp}$ | Basal degradation rate of p53 | 0.02 |
| $d_{pp}$ | Basal degradation rate of p53* | 0.008 |
| $d_{mrd}$ | Degradation rate of Mdm2 mRNA | 0.01 |
| $d_{mrd}$ | Basal degradation rate of Mdm2 | 0.003 |
| $k_{rp}$ | Michaelis constant of ATM-dependent p53 phosphorylation | 1.0 |
| $k_{mp}$ | Michaelis constant of p53-dependent Mdm2 transcription | 1.0 |
| $k_{d}$ | Threshold for Mdm2-dependent p53 degradation | 0.03 |
| $n$ | Hill coefficient of the Mdm2 transcription rate | 4 |
| $k_{at}$ | Threshold of ATM-dependent Mdm2 degradation | 1.60 |
| $k_{d}$ | Threshold of Mdm2-dependent p53* degradation | 0.32 |
maximal threshold under different circumstances, such as in different cell types.

Moreover, our model can quantitatively predict how perturbations of some vital parameters in the system affect the cellular response under some abnormal circumstances. As shown in Fig. 7(c), a plausible prediction is made that an abnormal basal transcription rate of p53 ($S_{P53}$) will disable cellular response under 5-Gy IR. The oscillations of $p53^*$ will consequently disappear as $S_{P53}$ decreases from its abnormal initial value (Fig. 7(c)). $F_w$ are accumulated dramatically without normal elimination effects of $p53^*$, which means that the cellular self-defense mechanisms in response to genome stress have been broken due to the abnormal $S_{P53}$ within the abnormal cell.

If oscillations are of importance for triggering the cellular self-defense mechanisms of DNA damage repair or
abnormal cell apoptosis, this prediction implies that cells with abnormal basal transcription rates of high Mdm2 or low p53 should be associated with enhanced tumorigenesis [8,10]. In addition, our model can predict the consequences of perturbations in other vital components, for example, eliminating ATM will lead to an enhanced variability in the number of oscillations in response to a given IR dose.

4. Conclusions

A set of differential equations, combined with graphic approaches, was proposed to model the p53 stress response networks under continuous IR. Our model demonstrated that ATM exhibits a strong sensitivity and switch-like behaviour in response to the number of DSBs. Also, the p53-MDM2 feedback loop will produce oscillations, and the number and amplitude of the oscillations are different according to cell type and the IR dose [10]. Especially, plausible predictions are made for toxins elimination under different IR doses, and the outcomes of cellular response under some abnormal circumstances. Our model, although simple, does provide a mathematical framework for the theoretical analysis and prediction of the cellular response to DNA damage under continuous IR.

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