Modeling Cellular Self-Repair Mechanism under IR Perturbations Based on KTAP Framework

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Abstract

To illustrate the different kinetics of cellular self-repair mechanism under external perturbations from outer environment, a mathematical model of DNA damage repair process is proposed by using the Kinetic Theory of Active Particles (KTAP) framework. The profile of cellular self-repair process is represented by two sub-populations, each of which is made up of the active particles with different discrete states. The dynamic kinetics of DNA damage generation, repair mRNA transcription, Repair Protein (RP) translation, DSBC synthesis are investigated by the particle interactions between the molecular pairs within DNA and RP sub-systems.

Keywords: *IR, KTAP, Cellular Self-Repair, DNA Damage, Modeling.*

1. Introduction

Generally, a biological system consists of from a few copies to millions of different components with specific interactions [1-3]. Especially, as a unit of a bio-system, a cell also consists of a large number of active molecules, such as, DNA, mRNA, protein etc [4]. By KTAP approach, the description of bio-system essentially means defining the microscopic state of the interacting molecules and their distribution function over the active state [5]. Also, a biological phenomenon can be dealt as the evolution of the dynamics of several interacting modules, especially, in response to acute perturbations from outer environment, a cell can trigger its internal self-defense mechanism by complicated interactions between these "active particles" [6, 7].

Recently, several mathematical frameworks have been proposed to represent the stochastic dynamics of cellular self-defending DNA damage process, such as Monte Carlo simulation methods in [6], as well as ordinary differential equations models in [8-11]. To further investigate cellular self-repair mechanisms under acute perturbation from outer environment, a mathematical framework is proposed by using KTAP approach at single cell level. In this framework, DNA damage and Repair Protein (RP) are dealt as two sub-systems, the dynamic processes of Double Strand Breaks (DSBs) and RP generating, DSB-protein complexes (DSBCs) synthesizing are represented by the particle interactions between the active molecular pairs with different discrete states.

2. Method

As a novel mathematical approach, KTAP can describe the evolution of the probability distribution over the microscopic state, called activity, of several interacting

entities called active particles [1]. Also, KTAP is one of the suitable methods of applied to open systems subject to external actions [2, 3], and the introduction of expression taking into account the external interactions is necessary for derivation of a general mathematical framework of an open system, and suitable for modeling open systems of active particles including the ability to generate new particles in a population [3].

Under acute IR, DNA in a normal cell is broken down, and DSBs occur subsequently. Normally, a cell can trigger its internal self-repair mechanisms to fix genome damage triggered by acute perturbations from outside. RP, a kind of repair enzyme, can bind into the nascent DNA ends and synthesize DSBCs further [12, 13]. As a main signal source of transferring genome stress, DSBC can relay DNA damage to downstream P53 genes and their regulation pathways [14]. By the approach of KTAP, our model focuses on trying to illustrate the cellular self-repair mechanism in response to acute IR perturbation circumstances. Fig 1 is the profile of cellular self-repair mechanisms, it is composed of two populations, DNA damage and repair enzyme, each of which is composed of active particles with different microscopic active states.

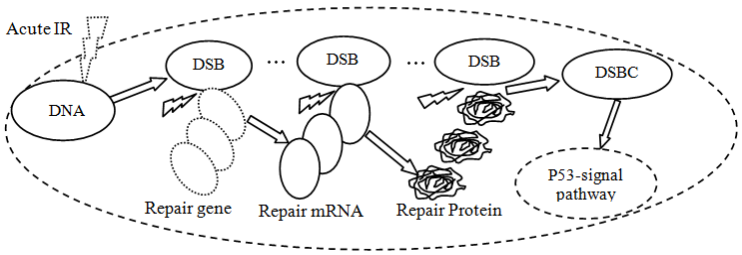

Figure 1. The profile of cellular self-repair mechanisms under IR perturbation. It is composed of two sub-populations, each of which includes active particles with different discrete states. As acute IR is applied into a cell, the resulting DSB occur stochastically, repair mRNA is generated after repair gene interacting with DSB, and repair protein is generated after repair mRNA interacting with DSB. As RP is available, DSBC will be synthesized after RP combing with DSB, which can relay damage signal to downstream genes and their regulation pathways.

As acute IR is applied into a cell, DNA is broken down stochastically, and the resulting DSB occur [14]. As a result of the particle interactions between the molecular pairs of repair gene and DSB, repair mRNA transcription is prompted, and RP translation is accelerated due to the particle interactions between repair mRNA and DSB. Suppose RP is available around damage sites, DSBC can be synthesized after DSB combining with RP. With the cellular self-repair mechanism, most of the DSBs can be correctly fixed, and the correct repair part of DSBCs (rDSBCs) can further transfer the damage signal into downstream gene and their regulation pathways [13, 14]. Whereas, a little part of DSB cannot be repaired correctly, both of disrepair part of DSBCs (mDSBCs) and intact DSBs will be accumulated as a part of cellular toxins, which can seriously weaken cellular viability and self-defense capability, even lead to abnormal and cancerous finally [7-11, 15].

3. Result

To represent the framework of the cellular self-repair mechanism based on KTAP, we denote two populations, DNA damage and repair enzyme, by two

sets, $I_1^u = \{u_1^1, u_1^2, u_1^3, u_1^4\}$ and $I_2^u = \{u_2^1, u_2^2, u_2^3\}$, in which the elements in set I_1^u denote the active particles of DNA, DSB, rDSBC, and mDSBC, respectively, and the elements in set I_2^u denote the active particles of repair gene, repair mRNA, and RP, respectively.

3.1 DSBs Generation Induced by IR

As the first part of this model, the continuous function of acute IR, denoted as $g^{(p)}(t)$, is dealt as an external action applied into a single cell from outer environment. The profile of DSBs generation induced by continuous IR is shown in Fig 2. As external function of acute IR, $g_1^{(p)}$, is applied into a cell, DNA is stochastically broken into two pieces of DSBs, each of which is dealt as a new DNA. Therefore, the kinetics of DSB generation and DNA increasing without cellular self-repair mechanisms can be represent by the formulations as the followings:

$$\frac{df_1^2}{dt} = c_{11}^e P_{11}^2 g_1^{(p)} f_1^1, \quad (1)$$

$$\frac{df_1^1}{dt} = k_1^{1,2} f_1^2, \quad (2)$$

where c_{11}^e is the rate of DNA interacting with the external IR action P_{11}^2, $k_1^{1,2}$ is the rate of DSB conversion into a new DNA. f_1^1, and f_1^2 are the distribution functions of DNA and resulting DSB within a cell, respectively.

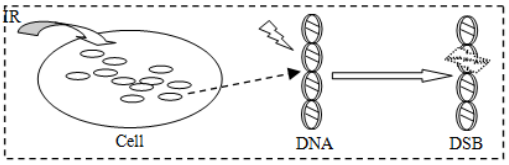

Figure 2. The Profile of DSBs Generation Derived from DNA under Continuous IR

In accordance with the fact the stochastic number of resulting DSBs induced by per IR dose within each time scale obeys the principle of a Poisson random distribution, whose average is proportional to the radiation dose [6-11, 13], we deal that the external proliferating transition density function P_{11}^2, and the kinetics of DSB generation process under external action function $g_1^{(p)}$ are denoted as follows:

$$P_{11}^2 = k_t \, poissrnd(a_{IR}[IR]), \quad (3)$$

$$\frac{df_1^2}{dt} = c_{11}^e k_t \, poissrnd(a_{IR}[IR]) f_1^1, \quad (4)$$

where $[IR]$ is the strength of IR dose; c_{11}^e is the rate of DNA population interacting with the external proliferating/destructive IR perturbation; k_t is the parameter to set the number of DSBs generation within each time scale, and a_{IR} is to set the number of DSBs induced by per IR dose.

3.2 Repair mRNA Transcription and RP Translation

In the process of repair mRNA transcription and RP translation, both of the RP and DSB are dealt as dynamic variables, which means that there are limited repair proteins available around increasing damage sites. As shown in Fig 3, the dynamic processes of

repair mRNA transcription and RP translation are prompted by particle interactions between molecular pairs of DSB and repair gene, as well as DSB and repair mRNA, respectively.

The kinetics of repair mRNA transcription is accelerated by particle interactions between active molecular pairs of DSB and repair gene, and the kinetics of RP translation is prompted by particle interactions between the molecular pairs of DSB and repair mRNA. The processes of repair mRNA transcription and RP translation can be written by the following equations:

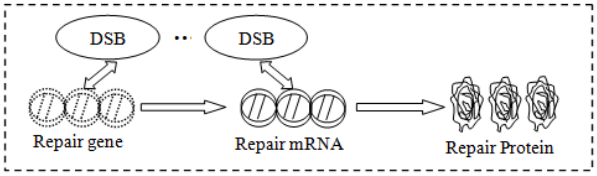

Figure 3. Repair mRNA and RP generation process with particle interactions between the molecular pairs of DSB and repair gene, as well as DSB and repair mRNA, respectively.

$$\frac{df_2^2}{dt} = s_2^{12} f_2^1 + \eta_{12}^{21} B_{12}^{21}(2) f_1^2 f_2^1 - d_2^2 f_2^2, \quad (5)$$

$$\frac{df_2^3}{dt} = s_2^{23} f_2^2 + \eta_{12}^{22} B_{12}^{22}(3) f_1^2 f_2^2 - d_2^3 f_2^3, \quad (6)$$

where s_2^{12} is the basal transcription rate of repair mRNA from repair gene, s_2^{23} is the basal induction rate of repair protein from repair mRNA; d_2^2 and d_2^3 is the self-degradation rates of repair mRNA and repair protein; f_2^1, f_2^2 and f_2^3 are the distribution functions of repair gene, repair mRNA and repair protein, respectively; η_{12}^{21}, and η_{12}^{22} are the encounter rates of DSB with repair mRNA, as well as DSB with repair gene, respectively. B_{12}^{21}, and B_{12}^{22} are the probability densities of repair gene falling into repair mRNA, and repair mRNA falling into repair protein after interacting with DSB, respectively.

Consider the fact that RP generation is effected by the number of initial repair gene and resulting DSBs, as well as the capability of cellular damage repair mechanisms, η_{12}^{2*} and $B_{12}^{2*}(3)$ can be represent by the equations as the followings:

$$\eta_{12}^{21} = \frac{f_1^2}{f_1^2 + f_2^1}, \quad (7)$$

$$B_{12}^{21}(2) = \frac{(T_2^1 - f_1^2) f_2^2}{(f_1^2 + f_2^1)}, \quad (8)$$

$$\eta_{12}^{22} = \frac{f_1^2}{f_1^2 + f_2^2}, \quad (9)$$

$$B_{12}^{22}(3) = \frac{(T_2^2 - f_1^2) f_2^3}{(f_1^2 + f_2^2)}, \quad (10)$$

where T_2^1, and T_2^2 are the quantity thresholds of repair mRNA and repair protein generation, which denote that the rate of repair mRNA transcription and repair protein translation begin to decrease as the quantity of the resulting DSB overpass the capability that cellular repair mechanism can deal with maximally.

3.3 DSBCs Synthesis Kinetics

The profile of DSBC synthesis process is shown in Figure 4, in which the particle interactions between the molecular pairs of DSB and RP trigger the binding of RP into the nascent DNA ends, and then synthesize into DSBC. Whereas, some DSBC being unstable state might be reversibly broken into DSB and RP again [13, 14], especially, some part of DSB can not be fixed correctly by cellular self-repair mechanism. Due to the reason that toxins, which include both mDSBC and intact DSB within a cell, can seriously weaken the cellular viability and cellular self-defense capability, mDSBC is obviously distinguished from rDSBC during DSBC synthesis process.

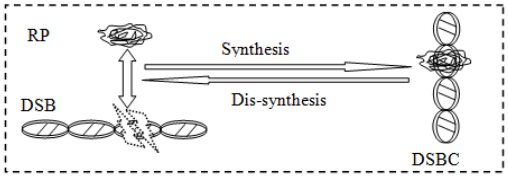

Figure 4. The Profile of DSBC Synthesis and Dis-synthesis Kinetics

Moreover, DSBC synthesis is dealt as a result of particle interactions between the molecular pairs of DSBs and RP, and the number of rDSBC is dealt as an indictor for reflecting the cellular capability of transferring damage signal. Meanwhile, the quantities of both mDSBC and intact DSB are dealt as cellular toxins within a cell. The kinetics of rDSBC and mDSBC synthesis can be denoted by the formulation respectively as the followings:

$$\frac{df_1^3}{dt} = \sum_{i=1}^{2}\sum_{j=1}^{2} \eta_{21}^{32} w_{ij} B_{(ij)21}^{32}(3) f_1^2 f_2^3 - k_1^3 f_1^3, \tag{13}$$

$$\frac{df_1^4}{dt} = \sum_{i=1}^{2}\sum_{j=1}^{2} \eta_{21}^{32} w_{ij} B_{(ij)21}^{32}(4) f_1^2 f_2^3 - k_1^4 f_1^4, \tag{14}$$

where η_{21}^{32} is the encounter rate of RP and DSB; k_1^3, and k_1^4 are the dis-synthesis rates from rDSBCs and mDSBCs into DSB and RP again, respectively; w_{ij} indicate the probability density for DSBC synthesis, and $B_{(ij)21}^{32}$ is the rate of DSBC transfer from DSB after interaction with RP, in which the subscript i refers to the fast and slow repair kinetics, and j refers to the first and second order process, respectively. In addition, we can derive the following equations:

$$\eta_{21}^{32} = \frac{f_1^2}{f_1^2 + f_2^3}, \tag{15}$$

$$\sum_{i=1}^{2}\sum_{j=1}^{2} w_{ij} = 1, \tag{16}$$

$$\sum_{i=1}^{2}\sum_{j=1}^{2} (B_{(ij)21}^{32}(3) + B_{(ij)21}^{32}(4)) = 1. \tag{17}$$

3. Conclusion

By using the KTAP framework, a mathematical model of cellular self-repair mechanism is proposed under IR perturbations. The kinetics of DSB generation, repair

mRNA transcription, RP translation, DSBC synthesis are represented by particle interactions between molecular pairs with different discrete microscopic states in the DNA and RP sub-systems. Our model is flexible and suitable for illustrate the complex interactions between molecular particles within different sub-systems, and provide a mathematical framework to investigate the dynamic kinetics of cellular self-repair mechanisms in response to IR perturbations from outsides.

Acknowledgements

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