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Kinetic aspects of enzyme-mediated repair of DNA single-strand breaks

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ABSTRACT

In cells and bacteria, DNA can be damaged in different ways. The efficient damage repair, mediated by various enzymes, is crucial for their survival. Most frequently, the damage is reduced to single-strand breaks. In human cells, according to the experiments, the repair of such breaks can mechanistically be divided into four steps including (i) the break detection, (ii) processing of damaged ends, (iii) gap filling, and (iv) ligation of unbound ends of the broken strand. The first and second steps run in parallel while the third and fourth steps are sequential. The author proposes a kinetic model describing these steps. It allows one to understand the likely dependence of the number of breaks in different states on enzyme concentrations. The dependence of these concentrations on the rate of the formation of breaks can be understood as well. In addition, the likely role of unzipping and zipping of the fragments of broken ends of the strand in the ligation step has been scrutinized taking the specifics of binding of DNA stands into account.

1. Introduction

In mammalian cell in general and human cells in particular, DNA damage is continuously induced by intrinsic reactions, including oxidation and hydrolysis, and by environmental factors, e.g. UVB light, and may also take place during medical treatments such as chemotherapy [reviewed by Hakem (2008), Hoeijmakers (2009), Ciccia and Elledge (2010), and Bautista-Nino et al. (2016)]. The role of DNA damage is usually negative because it contributes to aging (Bautista-Nino et al., 2016) and neurological dysfunction (Caldecott, 2008), may result in cancer (Hoeijmakers, 2009), and, during reproductive periods, represents also a threat to the ability to faithfully transmit genetic information (Ciccia and Elledge, 2010). To respond to these threats, there exist multiple DNA repair pathways depending on the type of damage. A few of them are as follows: (i) direct reversal of chemical modifications of nucleotides; (ii) repair of base pair mismatches; (iii) repair of oxidized and alkylation lesions in the nucleus and mitochondria, as well as single-strand breaks (SSBs); (iv) nucleotide excision repair, to correct transcription-disturbing bulky adducts; (v) homologous recombination; and (iv) non-homologous end joining, which corrects SSBs and double-strand breaks (DSBs) as well (Bautista-Nino et al., 2016). Of the different types of DNA damage, SSBs are the most common, arising at a frequency of tens of thousands per cell per day [reviewed by Caldecott (2008, 2014)]. DSBs are much less frequent [reviewed by Gursoy-Yuzugullu et al. (2016) and Mladenov et al. (2016)]. The time scale of DNA repair, τ_r, depends on the type of damage and the gene specifics and is in a wide range. For repair of DSBs, τ_r is often between 10 min and 1 h but may be much longer, up to a few hours (Iliakis et al., 2004; Durante et al., 2013; Ebert et al., 2016). The repair of SSBs is usually performed faster, with τ_r from a few sec to a few min (Boye et al., 1974; Chauleau and Shuman, 2013; Woodrick et al., 2015).

Mechanistically, DNA repair is related to the function of a multitude of genes [see e.g. the review by von Stechow et al. (2013) from the perspective of systems biology], but practically it is mediated by a few enzymes (Hakem, 2008; Hoeijmakers, 2009; Ciccia and Elledge, 2010; Bautista-Nino et al., 2016). Although the general principles of enzymatic reactions are now well established [reviewed retrospectively by Cornish-Bowden (2013) and Xie (2013); see also recent reviews focused on stochasticity and conformational changes (Schwabe et al., 2013; Grima et al., 2014), reversibility (Noor et al., 2013), feedback inhibition and cooperativity (Cárdenas, 2013), and membrane-pathway specifics (Zhdanov and Höök, 2015)], the understanding how enzymes mediate DNA repair is still incomplete. The progress in this area may help to defend healthy cells or use facilitation of the DNA damage by

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inhibition of the repair enzymes (e.g., PARP) as a tool for suppression of the population of cancer cells [the latter strategy is reviewed by Sonnenblick et al. (2015)].

To rationalize the mechanistic aspects of DNA repair, one can employ kinetic models describing this process. In the current literature, one can find a few generic mean-field (MF) models of this category. In particular, Karschau et al. (2011) proposed a three-variable one-enzyme model focused on SSBs in bacteria. Aiming at the mutagenic elements of the *Escherichia coli* DNA repair system, Hilbert et al. (2011) introduced a two-variable model describing the dynamics of DNA damage and activation level of mutagenic gene repair (the corresponding reaction scheme does not include enzymes explicitly). Kumala et al. (2013) and Lakomiec et al. (2014) used two complementary four- and five-variable models to describe DSBs of circular minichromosome in human Raji cells (the schemes employed by these authors do not include enzymes explicitly either). There are also kinetic models focused on genetic networks where DNA damage and repair are just ordinary steps of a whole reaction scheme. For example, the effect of DNA damage on cell cycle dynamics was analyzed by Qi et al. (2007), Iwamoto et al. (2011), Zhang et al. (2013), Sun and Cui (2014, 2015), and Alam et al. (2015). From the perspective of the experimental studies of SSB and DSB repair in human cells [the former is reviewed by Caldecott (2008, 2014), while the latter is reviewed by Gursoy-Yuzugullu et al. (2016) and Mladenov et al. (2016)], all these models are highly simplified.

Herein, we propose and analyze a more complete SSB-repair model (Section 2) based primarily on the mechanistic concepts validated by numerous experimental studies of SSB repair in the latter cells [as comprehensively reviewed in Caldecott (2008, 2014)]. Mathematically, the model represents a set of the MF kinetic equations describing various stages of SSB repair. The whole process is considered to be catalyzed sequentially or in parallel by four enzymes. As usual, the rates of the elementary steps are expressed via the corresponding rate constants, populations of damaged DNA fragments in different states, and concentration of enzymes. The total number of equations is large, and the analysis of the corresponding transient kinetics is beyond our present goals. Under steady-state conditions, the equations can, however, be easily solved as shown below.

The specifics of DNA is that the complementary fragments of its strands are weakly bound as manifested in their local rapid reversible unzipping and zipping [reviewed by Frank-Kamenetskii and Prakash (2014) and Manghi and Destainville (2016)]. For this reason, the details how some of the steps of DNA repair occur are of interest from the perspective of statistical physics and theory of rate processes. In our work, one of such steps, ligation of the broken-strand ends, is discussed in more detail in this context (Section 3).

To articulate the novelty of our kinetic model of SSB repair, it is instructive to outline the already mentioned three-variable one-enzyme model proposed earlier by Karschau et al. (2011). The latter model schematically shown in Fig. 1 operates with the number of damaged DNA fragments, n_d, not associated with repair enzymes, number of fragments under repair, n_r, and population of unbound repair enzyme, n_e. The corresponding kinetic equations are as follows:

$$\frac{dn_d}{dt} = w - k_a n_e n_d, \tag{1}$$

$$\frac{dn_r}{dt} = k_a n_e n_d - k_r n_r, \tag{2}$$

$$\frac{dn_e}{dt} = -\frac{dn_r}{dt} = k_r n_r - k_a n_e n_d, \tag{3}$$

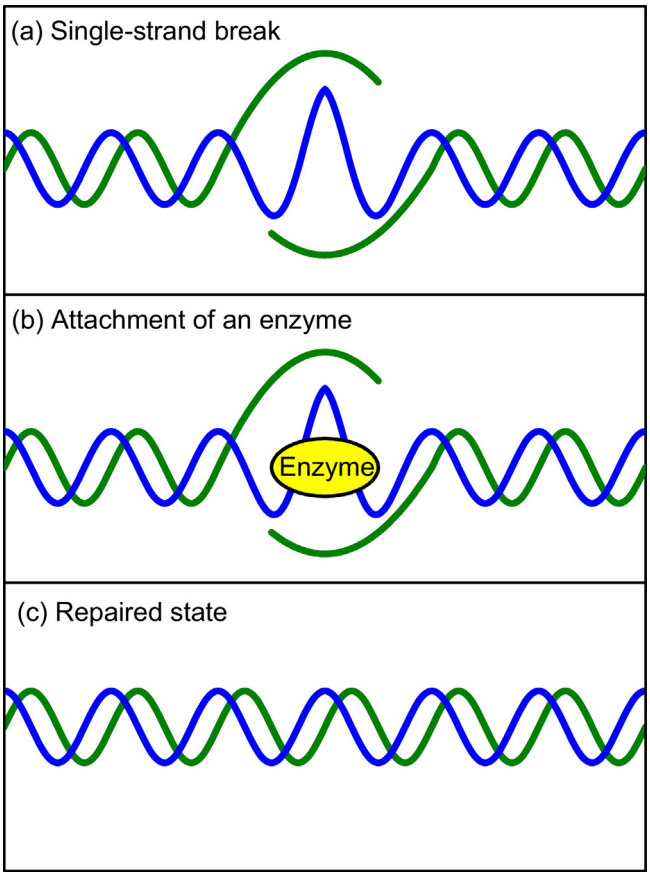

Fig. 1. Scheme of repair of single-strand DNA break: (a) single-strand break, (b) attachment of an enzyme, and (c) repaired double helix. The simplest model proposed by Karschau et al. (2011) for bacteria implies that the repair is performed by one enzyme via step (b). In human cells, step (b) is repeated a few times with participation of different enzymes (Caldecott, 2008, 2014). In the model employed herein, the whole process is considered to be catalyzed by four enzymes. The first two enzymes act in parallel, while the third and fourth enzymes react sequentially.

where w is the rate of damage of normal bases (this term is proportional to the DNA length and the concentration of damage-induced species or intensity of radiation), k_a is the rate constant for repair-enzyme attachment to a damaged DNA fragment, and k_r is the repair rate constant. Concerning these model and equations, one can notice that the proposed repair mechanism does not include the steps of enzyme formation and degradation (this is acceptable if these steps are slow on the time scale of the DNA repair). Under steady-state conditions, n_e represents the corresponding enzyme population, while the numbers of damaged fragments and fragments under repair are given by

$$n_d = \frac{w}{k_a n_e} \quad \text{and} \quad n_r = \frac{w}{k_r}. \tag{4}$$

The total number of damaged fragments is represented as

$$n_t = n_d + n_r = \frac{w(k_r + k_a n_e)}{k_r k_a n_e}. \tag{5}$$

2. Kinetic model

2.1. Reaction steps

We focus on SSBs induced directly e.g. by reactive oxygen species with disintegration of oxidized deoxyribose (sugar damage). Following the review by Caldecott (2008 and 2014; see there, respectively, Figs. 2 and 1), we consider that the SSB repair