

Review

The SOS System: A Complex and Tightly Regulated Response to DNA Damage

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Genomes of all living organisms are constantly threatened by endogenous and exogenous agents that challenge the chemical integrity of DNA. Most bacteria have evolved a coordinated response to DNA damage. In *Escherichia coli*, this inducible system is termed the SOS response. The SOS global regulatory network consists of multiple factors promoting the integrity of DNA as well as error-prone factors allowing for survival and continuous replication upon extensive DNA damage at the cost of elevated mutagenesis. Due to its

mutagenic potential, the SOS response is subject to elaborate regulatory control involving not only transcriptional derepression, but also post-translational activation, and inhibition. This review summarizes current knowledge about the molecular mechanism of the SOS response induction and progression and its consequences for genome stability. Environ. Mol. Mutagen. 60:368–384, 2019. © 2018 The Authors. Environmental and Molecular Mutagenesis published by Wiley Periodicals, Inc. on behalf of Environmental Mutagen Society.

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INTRODUCTION

The environment contains many DNA-damaging agents, both physical (ionizing radiation, UV light) and chemical (alkylating, crosslinking, oxidizing agents, etc.). Moreover, cellular metabolism can produce DNA-damaging byproducts and intermediates, such as reactive oxygen species (ROS). Together, these agents pose a constant threat to an organism's genome. An unrepaired DNA damage presents a very serious challenge to a cell because it may give rise to deleterious mutations or lead to cell death. In response to those threats, organisms have evolved many different mechanisms to deal with DNA damage in an error-prone and error-free manner. *Escherichia coli*, among other bacteria, has evolved an inducible system, termed the SOS response, which allows it to survive sudden increases in DNA damage. The term "SOS response" was first introduced in the 1970s by Miroslav Radman (1974). The SOS response entails the induction of multiple proteins that serve to promote the integrity of DNA; it also includes error-prone factors that allow for improved survival and continuous replication in the presence of extensive DNA damage, but at the cost of elevated mutagenesis. Due to its mutagenic potential, the SOS response is subject to complex regulation.

The SOS response in *Escherichia coli* was last comprehensively reviewed 10 years ago (Friedberg et al., 2006; Cohen et al., 2008; Janion, 2008), and more recently in other bacteria (Kelley, 2006; Erill et al., 2007; Butala et al., 2009;

Kreuzer, 2013; Baharoglu and Mazel, 2014). In the last few years, the significance of the SOS pathway in the evolution of resistance under antibiotic stress and its value as therapeutic target have gained more interest (Cirz et al., 2005; Cirz and Romesberg, 2007; Poole, 2012; Kreuzer, 2013; Fornelos et al., 2016; Williams and Schumacher, 2017).

The principal goal of this review is to summarize current knowledge about molecular mechanisms of the SOS response in *Escherichia coli*. We focused on the molecular basis of the SOS response induction and progression, the role of individual proteins and factors involved in the SOS response as well as consequences of its induction for bacterial genome stability.

SOS RESPONSE REGULATION

The SOS response is initiated by accumulation of single-stranded (ss) DNA during replication of DNA containing lesions (Sassanfar and Roberts, 1990). Single-stranded

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DNA is generated when DNA polymerase stalls at a template lesion while the replicative helicase continues unwinding DNA (Higuchi et al., 2003; Pagès and Fuchs, 2003). Recent studies indicate that the replisome skipping over template lesions and repriming to allow reinitiation of DNA synthesis downstream of a block leaving behind a single-stranded DNA gap is possible during both leading and lagging strand synthesis (Yeeles and Mariani, 2013; Indiani and O'Donnell, 2013; Gabbai et al., 2014). It should be mentioned that during horizontal gene transfer ssDNA is also transiently present and both transformation and conjugative plasmid DNA transfer induce the SOS response (Baharoglu et al., 2012). However, a number of conjugative plasmids encode the PsiB protein, which inhibits the induction of SOS during conjugation (Bagdasarian et al., 1986).

Two proteins play key roles in the regulation of the SOS response: LexA and RecA. LexA protein is composed of two domains separated by a short flexible linker: N-terminal DNA binding domain (NTD), and a C-terminal catalytic domain (CTD) with a serine-lysine catalytic dyad. CTD is also responsible for homodimerization of LexA (Luo et al., 2001; Zhang et al., 2010). During normal growth, the LexA dimer acts as a transcriptional repressor for genes belonging to the SOS regulon by binding to a specific operator sequence (the SOS box) in their promoter region (Walker, 1984). RecA acts as a co-protease to stimulate self-cleavage of LexA as well as other related proteins, such as phage repressors (λ , ϕ 80, P22, 434), UmuD protein and its homologs (Walker, 1984). RecA binds the ssDNA, and in the presence of a nucleoside triphosphate converts to an activated form (RecA* nucleoprotein filament) (Patel et al., 2010, reviewed in Goodman et al., 2016; Jaszczur et al., 2016). RecA* stimulates self-cleavage of LexA at a specific Ala84-Gly85 bond near the middle of the protein, thereby de-activating LexA (Little, 1991), lowering its affinity for the DNA and exposing residues that target LexA for ClpXP and Lon protease degradation (Neher et al., 2003). As a result, the pools of LexA protein begin to decrease, leading to derepression of SOS genes (Little and Mount, 1982). Figure 1 schematically presents the SOS induction process.

The SOS response entails increased expression of over 50 genes that carry out diverse functions in response to DNA damage, including excision repair, homologous recombination, translesion DNA replication, and cell division arrest; some of these genes encode proteins of unknown function (see Table I). In addition, other genes can be upregulated following DNA damage but are believed to be independent of LexA (Fernández De Henestrosa et al., 2000; Courcelle et al., 2001, comprehensively analyzed in Cohen et al., 2008). Not all genes belonging to the SOS regulon are induced at the same time and to the same level. The response is precisely timed and synchronized according to the amount of damage and the time

elapsed since the damage was detected; selective derepression of certain genes might occur in response to even minor endogenous DNA damage, while other genes will be expressed only upon drastic DNA damage and a persistent inducing signal (Fernández De Henestrosa et al., 2000; Courcelle et al., 2001; Quillardet et al., 2003). Mostly error-free repair and maintenance processes characterize the early phase of SOS. The first genes induced are the *uvr* genes for excision of damaged nucleotides, followed by *recA* and other homologous recombination protein coding genes (*ruvAB*, *recN*). Next are *polB* and *dinB* encoding DNA polymerase II and DNA polymerase IV, respectively. The division inhibitor SulA is also induced to give the bacterium time to complete the repairs. Finally, if the damage was extensive and not fully repaired, the error-prone DNA polymerase V (encoded by *umuC* and *umuD* genes) is induced, causing elevated mutation levels but allowing for continuous replication and cell survival (Courcelle et al., 2001; Henrikus et al., 2018b).

The level, timing, and duration of induction of different LexA-regulated genes depends on the strength of different SOS boxes, their number and location relative to the target promoter, and promoter strength. The consensus SOS box sequence is a perfect palindrome: TACTG(TA)₅CAGTA. The deviation of an SOS box from the consensus is characterized by the heterology index (HI). The higher the HI value, the lower the affinity of the LexA repressor to the sequence (Lewis et al., 1994; Fernández De Henestrosa et al., 2000).

Importantly, *lexA* itself is also a SOS gene. The constant production of LexA during the SOS process ensures that as soon as DNA repair occurs, the disappearance of the inducing signal will allow LexA to reaccumulate and repress the SOS genes (Walker, 1984). In an uninduced cell, roughly 1,300 molecules of LexA are present (Sassanfar and Roberts, 1990). In addition to this loop mechanism, several SOS genes seem to be involved in more precise modulation of the SOS response. For instance, RecX and DinI affect the stability of the RecA filament, thereby influencing the response time and recovery rate of the system (Lusetti et al., 2004a). The RecX protein is known to be a very active RecA inhibitor; it can suppress various RecA activities including ATP hydrolysis, coprotease, and DNA strand exchange reaction at a concentrations hundreds of times smaller than that of the RecA itself (Stohl et al., 2003). It blocks the extension of the RecA filaments (Drees et al., 2004) and promotes RecA filament disassembly (Ragone et al., 2008). Based on the structure of RecX protein complex with the presynaptic RecA filament, Yakimov et al. (2017) designed a novel peptide inhibitor with highly stable α -helical structure capable not only of inhibiting the RecA protein activities *in vitro* but also of suppressing the *E. coli* SOS response *in vivo*. A peptide binding the RecA filament groove may also provide a valuable tool for studying RecA interactions with a wide range of proteins

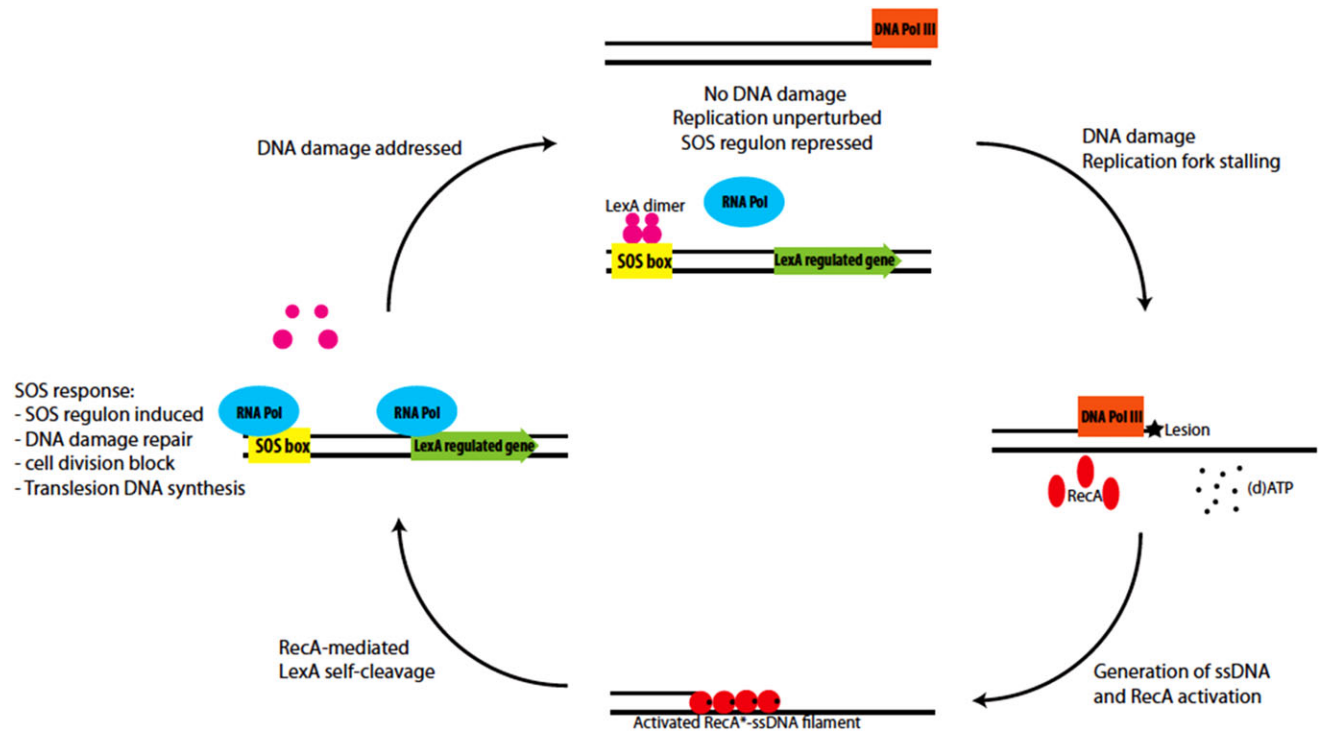


Fig. 1. Schematic representation of the SOS induction process in *E. coli*. During normal growth, the LexA repressor binds to the operator sequence in the promoter region of SOS genes, preventing their expression. Upon DNA damage, ssDNA accumulates when a replication fork stalls during replication of DNA containing lesions. RecA binds the ssDNA, and in

the presence of (d)ATP converts to an activated form (nucleoprotein filament RecA*). RecA* stimulates self-cleavage of LexA, leading to derepression of SOS genes. After the damage has been addressed, elimination of the inducing signal allows LexA to reaccumulate and repress the SOS genes.

interacting with RecA filaments. Function of DinI depends on the concentration of the protein. At concentration stoichiometric with the concentration of RecA, it acts mainly as a positive modulator of RecA function, stabilizing the RecA filament (Lusetti et al., 2004a, b). At high concentrations, it has an opposite effect on RecA - it inhibits both the ability of RecA to induce cleavage of UmuD as well as its recombinase activity (Yasuda et al., 1998, 2001).

The *umuDC* operon was also identified as a key contributor maintaining the temporal precision of the SOS response. The uncleaved UmuD protein and UmuC delay the recovery of DNA replication after DNA damage to allow additional time for accurate repair systems to process the damage (Opperman et al., 1999). Using time-lapse fluorescence microscopy Friedman et al. (2005) investigated the dynamics of SOS response in individual living cells. They showed that the products of the *umuDC* operon are involved in modulating SOS expression by generating discrete activation pulses, whose number increases with the level of DNA damage. McCool et al. (2004) using fluorescent microscopy showed that within the population of DNA metabolism mutants with high basal levels of SOS expression exist subpopulations of cells with various levels of SOS expression. This suggests that in cells where

multiple pathways are available to process DNA intermediates the choice of pathway may affect SOS genes expression levels.

Certain stimuli can indirectly generate the SOS-inducing signal by activation of endogenous DNA damage mechanisms rather than by direct DNA damage, which suggests that SOS might be involved in adaptation to various types of stresses (reviewed by Aertsen and Michiels, 2006). Kubiak et al. (2017) have developed a system for inducible control over the SOS pathway independent of DNA damage and RecA* *in vivo*. They engineered a LexA variant with abolished self-cleavage, but with optimized recognition site for TEV protease placed within the flexible linker between the C- and N-terminal domains. This opens the possibility of addressing questions related to SOS function independently of DNA damage.

RecA PROTEIN

RecA is a multifunctional and ubiquitous protein essential for recombination, DNA repair and maintenance. It regulates the synthesis and activity of DNA repair proteins (SOS induction), participates in mutagenesis, and promotes

TABLE I. *Escherichia coli* LexA-Regulated Genes with Known or Potential SOS-Boxes (Based on Fernández De Henestrosa et al., 2000; Courcelle et al., 2001)

Gene	Function
<i>Known SOS box</i>	
<i>cho</i> (<i>ydjQ</i>)	Endonuclease of nucleotide excision repair
<i>dinB</i>	DNA polymerase IV
<i>dinD</i> (<i>pcsA</i>)	DNA-damage-inducible protein
<i>dinF</i> *	DinF MATE Transporter
<i>dinG</i>	ATP-dependent helicase
<i>dinI</i>	DNA-damage-inducible protein
<i>dinQ</i>	Toxic inner membrane peptide DinQ
<i>dinS</i>	DNA-damage-inducible protein
<i>ftsK</i>	Cell division protein
<i>hokE</i>	Toxic polypeptide
<i>lexA</i>	Regulator for SOS
<i>molR</i>	Molybdate metabolism regulator
<i>polB</i>	DNA polymerase II
<i>recA</i>	DNA strand exchange, LexA coprotease
<i>recN</i>	Protein used in recombination and DNA repair
<i>recX</i> *	<i>recA</i> inhibitor
<i>rmuC</i> (<i>yigN</i>)	Predicted recombination limiting protein
<i>ruvAB</i>	Holliday junction helicase subunit A and B
<i>sbmC</i>	DNA gyrase inhibitor
<i>ssb</i>	ssDNA-binding protein
<i>sulA</i>	Inhibits cell division
<i>umuDC</i>	DNA polymerase V
<i>uvrA</i>	Excision nuclease subunit A
<i>uvrB</i>	Excision nuclease subunit B
<i>uvrD</i>	DNA-dependent ATPase I and helicase II
<i>ybfE</i>	DNA-damage-inducible protein
<i>ydjM</i>	Inner membrane protein
<i>yebG</i>	DNA-damage-inducible protein
<i>symE</i> (<i>yjiW</i>)	Toxin-like protein of the SOS response
<i>tisAB</i> (<i>ysdAB</i>)	Toxic peptides induced by SOS
<i>rmuC</i> (<i>yigN</i>)	Putative recombination limiting protein
<i>Potential SOS box</i>	
<i>ymfE</i>	e14 prophage putative inner membrane protein
<i>ymfI</i>	Unknown
<i>ydeO</i>	DNA-binding transcriptional dual regulator
<i>ydeS</i>	Putative fimbrial protein YdeS
<i>yocB</i>	RutC family protein
<i>intE</i>	e14 prophage putative integrase
<i>ogrK</i>	Prophage P2 late control protein
<i>yqgC</i> (<i>afuC</i>)	CP4-6 prophage; ABC transporter ATP-binding protein
<i>yhiL</i>	Unknown
<i>glvB</i>	Putative PTS enzyme II component GlvB
<i>ipbA</i>	Small heat shock protein

*Genes that do not have their own LexA-binding operator sequence, but are co-transcribed with others that do; *dinF* is co-transcribed with *lexA*, whereas *recX* with *recA*.

the central steps of DNA pairing and strand exchange in genetic recombination and recombinational DNA repair. RecA homologs are present in virtually all organisms from bacteria to humans. The human homolog of RecA is RAD51 (Roca and Cox, 1990; Cox, 2007a).

RecA is a small, 352-residue (38 kDa) protein. In an uninduced *E. coli* cell, roughly 7000 RecA molecules are present (Sassanfar and Roberts, 1990). It consists of three

domains: N-terminal, core, and C-terminal. The core domain, with its motif called the RecA fold, shares structural similarities with a range of other proteins (motor proteins, helicases, DNA transport proteins) and contains the ATP-binding site (Story and Steitz, 1992a, b). The C-terminal domain acts as an autoregulator of the RecA protein functions. In the absence of the C-terminal peptide all RecA activities are more pronounced, which makes it a likely interaction point for other proteins that modulate RecA function (Cox, 2007a). Both the recombinase and coprotease functions of RecA require the binding of two effector species: ssDNA and a nucleoside triphosphate (NTP); (Craig and Roberts, 1981; Shibata et al., 1981). RecA coprotease activity does not require NTP hydrolysis (Phizicky and Roberts, 1981; Gruenig et al., 2009). However, RecA protein is a DNA-dependent ATPase (Shibata et al., 1981), and the completion of DNA strand exchange reactions depends on ATP being hydrolyzed. ATP hydrolysis renders the strand exchange a unidirectional process and allows it to bypass structural barriers in the DNA substrates (Shan et al., 1997). A model explaining the involvement of ATP hydrolysis in those activities has been proposed by Cox (2007b). Finally, ATPase activity is necessary for RecA protein to promote replication fork regression, a reaction that may be relevant to RecA function at an arrested replication fork (Robu et al., 2001).

The nucleotide-binding site of a RecA nucleotide filament is located at the interface of two RecA monomers (Chen et al., 2008), therefore a dimer of RecA is required for RecA filament assembly on ssDNA, followed by elongation of the filament by monomer addition. Growth of RecA filament is bidirectional, with preference for the 5' → 3' direction (Bell et al., 2012, reviewed in Bell and Kowalczykowski, 2016). Observations from electron microscopy experiments showed that RecA filament can exist in two different states: an extended state formed on DNA in the presence of ATP or an ATP analog, and a compressed filament formed in the absence of ATP (Egelman and Stasiak, 1993). Efficient formation of RecA filaments in the extended conformation is necessary for SOS induction, even though ATP hydrolysis is not (Gruenig et al., 2009). The LexA binding site on the RecA filament has not been fully elucidated, but current models suggest that LexA may span adjacent RecA monomers across the deep helical groove of the RecA filament (Adikesavan et al., 2011; Kovacic et al., 2013).

Gruenig et al. (2009) proposed that ATP hydrolysis might play an indirect role in negatively regulating the SOS response. They suggested that if the default function of RecA bound to DNA in cells is recombinational repair, then active engagement in recombinational repair might inhibit SOS induction. Temporary suspension of functions requiring the ATPase activity might be required for LexA cleavage to occur. Experiments showing a competition between LexA and a homologous duplex to interact with a RecA-DNA filament support this idea (Rehrauer et al.,

TABLE II. RecA Mutations Affecting SOS Induction

Allele	Recombinase	Coprotease	Reference
<i>recA430</i> (G240S)	+	Defective (λ , UmuD) Reduced activity (LexA)	(Morand et al., 1977; Roberts and Roberts, 1981; Devoret et al., 1983; Burckhardt et al., 1988)
<i>recA441/tif-1</i> (E38K, I298V)	++	Constitutive (42°C) Inducible (30°C)	(Kirby et al., 1967; Castellazzi et al., 1972a; Little et al., 1980; McEntee and Weinstock, 1981; Phizicky and Roberts, 1981)
<i>recA730</i> (E38K)	++	Constitutive	(Witkin et al., 1982; Wang and Tessman, 1985; Wang et al., 1988a).
<i>recA718</i> (E38K, I298V)	+	Constitutive (<i>lexA</i> (Def)) Inducible (<i>lexA</i> ⁺)	(McCall et al., 1987)
<i>recA1203</i> (R169C)	–	Constitutive (LexA) Inducible (λ)	(Wang and Tessman, 1986)
<i>recA1730</i> (S117F)	–	Inducible (λ , UmuD) Reduced activity (LexA) (when overexpressed)	(Dutreix et al., 1989, 1992).
<i>recA453</i> (promoter down)	–	Deficient	(Castellazzi et al., 1972b)
<i>recAo</i> (operator, increased basal transcription level)	+	Inducible	(Clark, 1982; Ginsburg et al., 1982)
<i>recA2201</i> (K72R)	–	Reduced activity	(Rehrauer and Kowalczykowski, 1993; Shan et al., 1996; Gruenig et al., 2009)
<i>recA4159</i> (K72A)	–	– Abolishes cSOS in <i>recA730</i>	(Renzette and Sandler, 2008; Šimatović et al., 2016)
<i>recA4142</i> (F217Y)	+	Constitutive	(Šimatović et al., 2016)
<i>recA</i> D112R, N113R	+	Inducible (LexA, λ) Defective (UmuD)	(Gruber et al., 2015)

1996). UmuD'C complex may also play a role in modulating the recombinational activity of RecA. Sommer et al. (1993) have demonstrated that at a high enough concentration relative to the number of residual RecA filaments not resolved by recombinational repair, the UmuD'C complex will switch repair from recombination to SOS mutagenesis. Many different proteins, including RecF, RecO, RecR, DinI, RecX, RdgC, PsiB, and SSB, have either a demonstrated or probable role in modulating where and when RecA-mediated recombination events occur, and thus may play a role in determining which pathway is undertaken (Cox, 2007a). Furthermore, it was shown recently that RecA directly interacts with topoisomerase I in *E. coli* and stimulates its activity (Banda et al., 2016). DNA topoisomerase I removes negative supercoiling of DNA. Excessive negative supercoiling can affect global transcription and result in growth inhibition. Formation of an active RecA filament is required for the stimulating effect. This suggests that the functional interaction between RecA and topoisomerase I may be responsible for RecA-mediated modulation of the relaxation-dependent transcriptional activity in response to DNA damage (Reckinger et al., 2007; Banda et al., 2016), especially that mutations in *E. coli topA* gene were demonstrated to diminish the SOS response to DNA damage and antibiotics treatment (Thi et al., 2011; Yang et al., 2015).

Many mutants of the RecA protein have been identified up to date. Table II summarizes the properties of those most relevant for SOS induction. The RecA1730 (S117F)

mutant displays a unique split phenotype: it is deficient in recombination, mutagenesis, and LexA cleavage but retains the ability to cleave λ repressor and UmuD protein (Dutreix et al., 1989, 1992). However, despite its ability to cleave UmuD, RecA1730 fails to activate pol V for DNA synthesis (Schlacher et al., 2005, 2006). Interestingly, *in vitro* it is still able to activate the polV-related polymerase Ruma₂B encoded by the integrating-conjugative element (ICE) R391 (Gruber et al., 2015), and IncN plasmid R46-encoded MucAB (Frank et al., 1993). Overproduction of RecA1730 restores recombination, LexA cleavage and UV survival *in vivo* (Dutreix et al., 1989). RecA residues 112–117 are located at a surface exposed at the 3'-proximal end of RecA filament (Sommer et al., 1998). This region is critical to the activation of pol V. Recently, a new RecA mutant in this region was described (RecA D112R N113R), displaying an improved separation of function phenotype compared with RecA S117F (RecA1730): abolished activation of pol V, with other RecA functions minimally affected (Gruber et al., 2015).

LESION TOLERANCE PATHWAYS

During DNA replication, polymerases may encounter DNA lesions that block processive DNA synthesis. When DNA polymerase stalls at a template lesion while the replicative helicase continues unwinding DNA, single-stranded DNA is generated (Higuchi et al., 2003; Pagès and Fuchs,

2003). Bacterial replicase is able to re-prime downstream of a DNA lesion, even on the leading strand, leaving behind a single-stranded DNA gap (Yeeles and Mariani, 2011, 2013; Indiani and O'Donnell, 2013). With the help of recombination mediator RecFOR complex (or, to a lesser extent, recBCD), SSB is displaced from these gaps, and replaced by RecA (Clark, 1973; reviewed in Kowalczykowski, 2000). The RecA-ssDNA filaments constitute a signal for SOS induction (Sassanfar and Roberts, 1990), play a role in the activation of Translesion Synthesis (TLS) polymerases Pol V (Schlachter et al., 2005) and Pol IV (to a lesser extent [Godoy et al., 2008]), and are a key intermediate in the initiation of gap repair *via* homologous recombination (Cox, 1999). Subsequently, the gaps are either filled by error-prone Translesion Synthesis involving specialized TLS polymerases (Pol II, Pol IV, or Pol V), or using an error-free Damage Avoidance (DA) pathway involving homologous recombination with the undamaged sister chromatid (Homology Directed Gap Repair: HDGR) (Laureti et al., 2015, reviewed in Fuchs, 2016).

TLS and DA are referred to as DNA damage tolerance (DDT) pathways, as the lesion is bypassed and not removed from the template. The balance between TLS and DA is very important since it defines the level of mutagenesis during lesion bypass. The choice of the pathway that is utilized is influenced by multiple factors. However, it is presently not fully understood exactly how the balance between error-free and mutagenic pathway is regulated, and which are the factors in charge of this regulation.

TLS POLYMERASES

In *E. coli* chromosome replication is performed by DNA polymerase III holoenzyme. During normal growth conditions three accessory DNA polymerases are expressed at significant levels: two high fidelity polymerases - DNA Pol I and DNA Pol II, and one error-prone polymerase—DNA Pol IV. DNA Pol V, the second error-prone polymerase is expressed at almost an undetectable level (Woodgate and Ennis, 1991). Participation of these accessory polymerases in *E. coli* chromosome replication and their effect on the fidelity of DNA replication and ability to copy damaged DNA was reviewed in (Walsh et al., 2011; Fijalkowska et al., 2012; Vaisman et al., 2012a; Goodman et al., 2016; Jaszczur et al., 2016; Henrikus et al., 2018b). Upon DNA damage the level of three TLS DNA polymerases, DNA polymerase II, DNA polymerase IV, and DNA polymerase V is elevated, as part of the *E. coli* inducible SOS response (Napolitano et al., 2000).

As shown in Figure 2, TLS polymerases have more spacious active site compared with the replicative polymerases. They can accommodate mismatched base pairs and bulky DNA lesions. In consequence, they can bypass damaged template but exhibit much lower fidelity than the cell's replicase. Crystal structures of TLS polymerases have been determined, providing a molecular basis for understanding their biochemical properties (reviewed by Yang and Woodgate, 2007, Yang and Gao, 2018; Goodman and Woodgate, 2013).

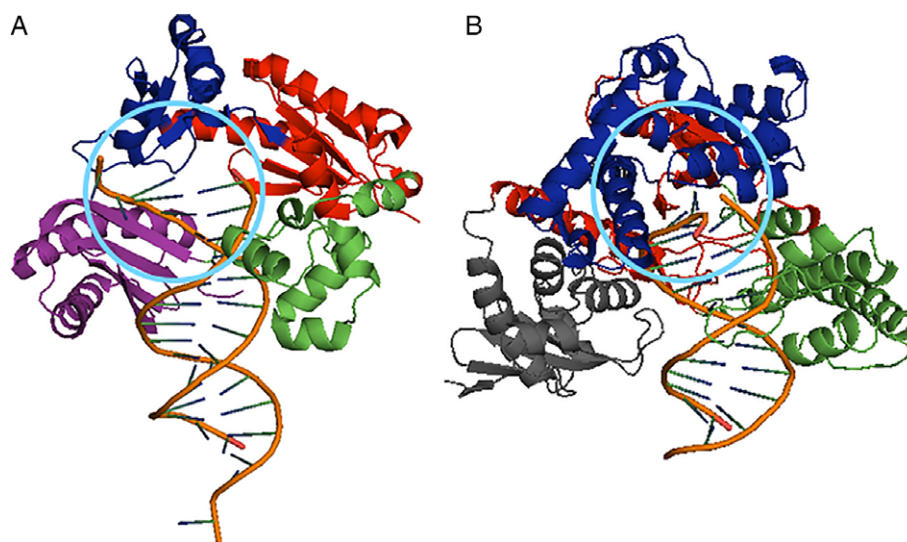


Fig. 2. Comparison of two DNA polymerase structures. (A) low fidelity *E. coli* DNA Pol IV and (B) high fidelity *Thermus aquaticus* DNA polymerase I (Klentaq1). Encircled are polymerase catalytic active sites. The polymerase domains are labeled in red (palm), blue (finger), green (thumb), gray (N-terminal domain of Klentaq1), purple (little finger

domain, unique for Y-family polymerases). The images were generated using PyMol (DeLano, 2002) based on the crystal structure of DNA Pol IV from *E. coli* in complex with DNA (PDB ID code 5YYD) and the ternary complex structure of the large fragment of *Thermus aquaticus* DNA polymerase I (PDB ID code 3KTQ).

All three *E. coli* TLS polymerases interact with the β -clamp (Hughes et al., 1991; Sutton et al., 1999, Sutton and Duzen, 2006; Wagner et al., 2000; Bunting et al., 2003; Patoli et al., 2013). Both error-free and mutagenic bypass activities of the *E. coli* TLS polymerases strictly depend upon the integrity of their β -clamp binding motif (Becherel et al., 2002). Therefore, the β -clamp plays a pivotal role during the TLS process acting as the common platform to which the TLS polymerases are directed when normal replication is stalled at a lesion site. Discrete β clamp-DNA interaction regions were shown to contribute to its ability to manage actions of its different partner proteins, particularly Pol IV and Pol V, allowing *E. coli* to tolerate specific classes of DNA damage (Nanfara et al., 2016). It has been reported by Indiani et al. (2013) that RecA protein acts as a switch to regulate the occupancy of polymerases in a moving replication fork during TLS. It severely inhibits fork progression by Pol III replisomes, but stimulates replication performed by Pol II and Pol IV by relieving the SSB induced repression of TLS replisomes.

Pol II

DNA polymerase II, encoded by the *polB* gene, is a B-family TLS polymerase possessing a 3'-5' exonuclease activity; therefore, it replicates both undamaged and damaged DNA quite accurately (Cai et al., 1995). In the presence of β -clamp, γ -clamp loader and SSB, Pol II has a processivity of approximately 1,600 nucleotides incorporated per template binding event (Bonner, 1992). It is present at 30–50 molecules per cell, which is comparable to the estimated concentration of Pol III HE (30 molecules/cell). Upon SOS induction it can be further induced about sevenfold (Qiu and Goodman, 1997). Genetic studies have shown that Pol II is involved in the repair of DNA damaged by UV irradiation (Masker et al., 1973) and oxidation (Escarceller et al., 1994), the repair of inter-strand cross-links (Berardini et al., 1999), and is pivotally involved in the replication restart after UV irradiation (Rangarajan et al., 1999). It has also been shown that, although Pol II is a proofreading-proficient enzyme, it can carry out error-prone translesion synthesis at certain lesions, such as abasic sites and AAF adducts (Paz-Elizur et al., 1996; Becherel and Fuchs, 2001).

Wang and Yang (2009) have provided new insights into possible mechanisms of TLS by Pol II, showing that small protein cavities near the active site in Pol-II are capable of accommodating looped out template nucleotides. The two looped-out nucleotides can remain extra-helical as Pol II continues downstream DNA synthesis. By looping out DNA lesions, Pol II has no preference for a lesion type and thus can have a broad substrate range. The authors thus proposed that Pol II might be able to act as a second polymerase in TLS following incorporation of nucleotides

opposite a lesion catalyzed by a replicational or Y-family polymerase.

Banach-Orlowska et al. (2005) proposed that the role of Pol II in DNA replication of undamaged DNA is that of a back-up polymerase to Pol III HE. It can substitute for Pol III HE when the latter has difficulties extending a mismatched primer terminus and removing the terminal mismatch. Exchange of the *E. coli* replicative DNA polymerase Pol III core with translesion polymerase Pol II and Pol IV was demonstrated *in vitro* (Kath et al., 2016; Zhao et al., 2017). Delmas and Matic (2006), using a *dnaEts* allele, have shown that at nonpermissive temperature replication is reduced, and Pol II is able to carry out the remaining chromosomal replication. They also suggested that Pol II plays an important role in evolutionary fitness, as the *polB* gene is more evolutionarily constrained than the *dinB* and *umuC* genes, and the level of selective constraint may reflect the frequency by which each polymerase is required to assure survival. Pol II also contributes considerable genetic diversity during periods of rapid growth (Corzett et al., 2013).

It was shown that RpoS is a positive regulator of *polB* (Pol II) expression, required for full expression of the *polB* gene even when the SOS response is derepressed. The fact that its expression is controlled by the two major stress response regulons emphasizes the key role of this polymerase as an important factor in genome stability (Dapa et al., 2017).

Pol IV

DNA polymerase IV (DinB), encoded by the *dinB* gene, belongs to the Y family of polymerases. It is a low-fidelity DNA polymerase lacking intrinsic proofreading activity. In normally growing cells the concentration of Pol IV is fairly high (250 molecules/cell) and increases by about 10-fold upon SOS induction; therefore, under conditions of DNA damage it is the most abundant DNA polymerase in *E. coli* (Kim et al., 2001). Pol IV is able to carry out error-free or error-prone translesion synthesis, depending upon the nature of damage and the sequence context (Napolitano et al., 2000). It has been shown to participate in TLS and mutagenesis induced by N2-dG adducts, oxidative damage, and alkylating agents (Fuchs et al., 2004; Benson et al., 2011). DinB replicates both undamaged templates and an apparent cognate substrate, an N2-dG adduct, with an error frequency of 10^{-3} – 10^{-5} /bp (Jarosz et al., 2006). In the presence of the β -clamp its processivity reaches 300–400 nucleotides (Wagner et al., 2000).

Kath et al. (2014) proposed a comprehensive model of the regulation of Pol IV access to replication fork by the β clamp. Pol IV, at relatively low concentrations during normal growth, is able to associate in an inactive mode with the clamp rim site and compete with the weakly bound ϵ subunit of Pol III for its cleft, which allows rapid exchange

and translesion synthesis after Pol III stalls at a lesion site. At high concentrations (corresponding to up-regulated levels during the SOS response), Pol IV occupies a secondary contact on β , promoting dissociation of Pol III. Scotland et al. (2015) showed that the switch requires that Pol IV contact not only two discrete sites on the β clamp protein, but Pol III as well. Impaired Pol III–ssDNA interactions (e.g., when polymerase encounters a hairpin-stem duplex) influence the susceptibility of Pol III HE to Pol IV-mediated polymerase exchange (Le et al., 2017). Using single-molecule time-lapse microscopy to directly visualize fluorescently labeled pol IV in live cells, Henrikus et al. (2018a) recently demonstrated that over 90% of foci induced by DNA damage form outside of replisome regions, suggesting that pol IV predominantly carries out non-replisomal functions, consistent with the postreplicative TLS in gaps behind the replisome model. However, Pol IV's access to ssDNA gaps is restricted to the first 100 min after induction of the SOS response. Furthermore, few foci were observed in an absence of damage in an SOS-constitutive mutant expressing high levels of pol IV, which indicates that access of pol IV to DNA is dependent on the presence of damage, and not concentration-driven competition for binding sites. The interactions of pol IV with the β -sliding clamp are likely to be involved during post-replicative TLS by pol IV, as it is assumed that when the replisome skips a lesion it leaves a β -sliding clamp behind at the gap. The authors raise the question, however, how these interactions could be modulated to provide access to gaps during early stages of the SOS response, while excluding pol IV in late stages of the SOS response.

In addition to its translesion synthesis activity, Pol IV is proposed to aid in restarting stalled and collapsed replication forks (Goodman, 2002; Mallik et al., 2015). Difficulties in replication can lead to breakage of the fork. Recombinational reactions restore the integrity of the fork through strand-invasion of the broken chromosome with its sister. Extension of the invading 3' strand by Pol IV may be required to stabilize the D-loop, prior to reestablishment of a DNA polymerase III-dependent replication fork (Lovett, 2006; Pomerantz et al., 2013). Furthermore, DinB has been suggested to act as an equivalent of the eukaryotic intra-S-phase checkpoint effector, as the increased expression of *dinB* and *recA* plays role in limiting the progression of an unperturbed replication fork during the SOS response (Furukohri et al., 2008; Uchida et al., 2008; Tan et al., 2015). Additionally, Cohen et al. (2009) proposed that Pol IV contributes to the recovery of arrested transcription events caused by DNA damage through its interaction with NusA, a modulator of RNA polymerase, which is associated with the RNA polymerase throughout the elongation phase of transcription. They hypothesized that if an RNA polymerase encounters a gap in the transcribed strand opposite a lesion, it would stall and NusA might then recruit a TLS polymerase to fill in the gap (Cohen et al.,

2009). In a subsequent article they suggested that this process of transcription-coupled translesion synthesis might contribute to the generation of stress-induced mutations (Cohen et al., 2010).

In normally growing cells, Pol IV was shown not to contribute to the error rate of chromosomal DNA replication (Kuban et al., 2004; Wolff et al., 2004), most likely due to limited access to the normal replication fork. Tashjian et al. (2017) have shown *in vitro* that DinB performs poor DNA synthesis with RNA primers and that it is additionally impeded upon interaction with RecA. They postulate that poor synthesis of DinB using RNA primers might represent a mechanism to prevent DNA synthesis by DinB when it is not needed.

Pol V

DNA polymerase V, the product of the *umuDC* operon (Reuven et al., 1999; Tang et al., 1999), is a member of the Y family of polymerases. It is an error-prone DNA polymerase lacking proofreading activity. Previous studies have indicated that under SOS-induced conditions most mutagenesis results from the action of this polymerase (Kato et al., 1982; Schlacher et al., 2005). DNA polymerase V is a heterotrimer, consisting of catalytic subunit UmuC and a dimer of UmuD', a product of RecA-facilitated autodigestion of UmuD (Burckhardt et al., 1988; Nohmi et al., 1988; Shinagawa et al., 1988; Tang et al., 1999). It is estimated that there are approximately 180 molecules of UmuD and approximately 15 molecules of UmuC in an undamaged cell. During SOS induction, the levels of UmuD and UmuC increase to approximately 2,400 and 200 molecules per cell, respectively (Woodgate and Ennis, 1991). The active form of DNA polymerase V is UmuD'₂C-RecA-ATP, termed the mutasome (Pol V Mut) (Schlacher et al., 2005; Jiang et al., 2009). The presence of β -clamp/ γ -clamp loader complex was shown to stimulate Pol V Mut processivity *in vitro* (Karata et al., 2012).

Pol V catalyzes TLS through several types of lesions, including TT cis-syn cyclobutane dimers (CPD), TT (6–4) photoproducts, abasic sites, and covalent adducts like N-2-acetylaminofluorene-dG (Tang et al., 2000; Fujii et al., 2004). Pol V is a highly error-prone DNA polymerase: it replicates undamaged templates with an error frequency of 10^{-3} – 10^{-4} /bp, and has an error frequency of 10^{-2} for TT cyclobutane dimers (Tang et al., 2000). It can bypass AAF, CPDs and TT (6–4) photoproducts with processivity of approximately 15 nucleotides (Fujii and Fuchs, 2009). Furthermore, it was shown that wild-type DNA Pol V efficiently incorporates ribonucleotides into DNA *in vitro* (Vaisman et al., 2012b).

Due to the strong mutagenic potential of this enzyme, Pol V activity is tightly controlled (reviewed in Goodman, 2016; Goodman et al., 2016). The first level of control is LexA-dependent transcriptional regulation. The *umu*

operon is tightly regulated by LexA repressor ($HI = 2.77$) (Lewis et al., 1994). Successively, both UmuD and UmuC proteins are rapidly degraded by the Lon protease (Frank et al., 1996). Activated RecA (RecA*) promotes the autocatalytic cleavage of the UmuD molecules that escaped proteolysis to yield UmuD' (Nohmi et al., 1988). UmuD and UmuD' exist as homodimers, but their subunits can readily exchange to form UmuDD' heterodimers preferentially. Murison et al. (2017) measured the kinetics of exchange of a number of fluorescently labeled single-cysteine UmuD variants and demonstrated that somewhat different molecular surfaces mediate homodimer exchange and heterodimer formation. Importantly, in the heterodimer context, UmuD' is specifically degraded by the ClpXP protease (Frank et al., 1996). Therefore, accumulation of UmuD' in the cell is only possible after severe DNA damage. Consequently, the appearance of active Pol V is delayed until roughly 45 min after the initial DNA damage, giving the cell time to repair the damage via error-free repair mechanisms.

Formation of Pol V Mutasome (UmuD'₂C-RecA-ATP complex) requires RecA* nucleoprotein filament (Schlachter et al., 2005; Jiang et al., 2009; Patel et al., 2010). Acting as a catalyst, RecA* transfers a RecA monomer, containing a single ATP molecule, from its 3'-proximal end to inactive Pol V, forming an active mutasome complex. Once synthesis has proceeded far enough, ATP hydrolysis by Pol V Mut will dissociate the complex from the primer-template DNA. The released Pol V can then be reactivated for another round of synthesis if ssDNA and RecA* are still present (Jiang et al., 2009; Gruber et al., 2015). It was shown that Pol V can be activated by RecA* acting *in trans* (Jiang et al., 2009). Rehrauer et al. (1998) analyzed the interaction between the purified Umu(D')₂C complex and RecA protein and found that the Umu(D')₂C complex can bind along the entire length of the RecA nucleoprotein filament. Polymerase V function is also regulated by its intrinsic DNA-dependent ATPase activity. Binding of the polymerase to the primer-template DNA requires an ATP molecule. After DNA synthesis, ATP hydrolysis triggers the dissociation of Pol V from the DNA. No such ATPase activity or autoregulatory mechanism has previously been found for a DNA polymerase. Restricting low-fidelity DNA synthesis performed by polymerase V to short fragments is necessary to limit mutations, especially in rapidly dividing cells. Keeping Pol V processivity in check appears to be the role of its internal ATPase activity (Erdem et al., 2014). Another layer of regulation on Pol V activation occurs after synthesis when the UmuC subunit of Pol V is sequestered transiently at the membrane. Release into the cytosol and final activation depends on RecA*-mediated cleavage of UmuD to generate the UmuD' subunit of Pol V (Robinson et al., 2015).

The chronological activity of *umuD* gene products in the SOS response has been described as a primitive DNA damage

checkpoint: uncleaved UmuD in combination with UmuC provides protection from DNA damage by acting in a noncatalytic fashion to delay resumption of the cell cycle after DNA damage to allow additional time for accurate repair pathways to act (Opperman et al., 1999; Sutton and Walker, 2001). Specifically, UmuD₂ has been shown to disrupt the interaction between the β processivity clamp and α -subunit of DNA polymerase III (Silva et al., 2012; Chaurasiya et al., 2013).

For many years, the accepted model for Pol V-dependent TLS assumed the displacement of the high fidelity Pol III HE from the replisome, blocked at the lesion site, by Pol V (Indiani et al., 2013). However, a more recent model suggests that Pol III can skip over the lesion and reinitiate DNA synthesis downstream (Yeeles and Mariani, 2011, 2013), while β -clamp is left behind at the lesion site and can recruit Pol V Mut to perform TLS (Robinson et al., 2015). Recent observation that after UV irradiation in the RecA⁺ cells there is no significant co-localization between Pol V Mut and Pol III HE *in vivo* provides evidence supporting this model (Robinson et al., 2015).

UmuD protein also acts as a modulator of polymerase IV (DinB) replication fidelity. DinB is known to strongly promote 1-bp deletion events (Wagner and Nohmi, 2000). Godoy et al. (2008) reported that DinB-dependent -1 frameshift mutagenesis can be suppressed by overproduction of UmuD and elevated by *umuD* deletion. Full-length UmuD is required to control DinB's mutator potential, since a noncleavable UmuD variant is fully proficient for suppression of -1 frameshift mutagenesis. RecA is essential for this process to occur *in vivo*, but its role is distinct from its function in promoting UmuD autocleavage. Interestingly, RecA and UmuD₂ enhance the ability of DinB to extend from a correctly paired terminus. Godoy et al. (2008) suggest that in uninduced cells and during the early stages of SOS induction, UmuD₂ and RecA act in concert to restrict the -1 frameshift mutagenic activity of DinB and increase its catalytic proficiency on properly paired templates. During the late phase of SOS induction this control is relaxed, so under conditions of chronic SOS induction DinB becomes mutagenic.

SOS MUTATOR EFFECT

In addition to mutagenesis resulting from translesion synthesis (targeted mutagenesis), SOS induction is also characterized by increased mutagenesis on nondamaged DNA. This phenomenon, named "SOS mutator effect," occurs in the absence of any DNA damaging treatment (untargeted mutagenesis) in certain strains in which there is a constitutive expression of the SOS regulon (*recA441*, *recA730*, and others) (Witkin, 1976; Witkin et al., 1982; Tessman and Peterson, 1985). Studies investigating the mutational specificity of the SOS mutator in *recA441* (Miller and Low, 1984; Yatagai et al., 1991) and *recA730*

(Watanabe-Akanuma et al., 1997) alleles demonstrated that transversion mutations are favored ($G \cdot C \rightarrow T \cdot A$ and $G \cdot C \rightarrow C \cdot G$, and $A \cdot T \rightarrow T \cdot A$, respectively). The nature of the errors recovered under SOS-induced conditions in both *recA441* and *recA730* strains appears to be similar to those recovered when the proofreading exonuclease of DNA polymerase III is defective (*mutD5* and *mutA/mutC*) (Yatagai et al., 1991; Watanabe-Akanuma et al., 1997). A study of the SOS mutator in mismatch repair-defective strains showed a synergistic effect of mismatch repair deficiency and the *recA730* mutation on spontaneous mutagenesis (at the *rpoB* locus). This indicates that these mutations are introduced near or at the replication fork and therefore strongly suggests that they arise through correctable, non-targeted, replication errors (Caillet-Fauquet and Maenhaut-Michel, 1988). Fijalkowska et al. (1997) showed that deficiencies in DNA excision repair or abasic site repair do not enhance the SOS mutator effect in *recA730* strains and that SOS-induced errors are corrected by the mismatch repair system as efficiently as normal replication errors. Given the transversion specificity of the SOS mutator activity and that Pol III HE is very inefficient in extending from terminal mismatches (especially transversions) (Mendelman et al., 1990; Joyce et al., 1992) it was suggested that the SOS mutator effect results from the transient stalling of Pol III HE at terminal mismatches. This may result in the dissociation of Pol III, providing an entry point for SOS TLS polymerases and leading to the increased probability of mismatch extension by Pol V and Pol IV (Fijalkowska et al., 1997; Maliszewska-Tkaczyk et al., 2000). Overproduction of DNA Pol IV leads to mutator effect preferentially during lagging strand synthesis, most likely resulting from Pol IV-dependent extension of mismatches introduced by polymerase III holoenzyme (Kuban et al., 2005). In addition, it was postulated that under constitutive expression of the SOS regulon in a *recA730* strain, after an error is introduced by Pol III and it dissociates from the mismatched terminus, Pol V is preferentially recruited to continue replication (as mutator effect is nearly completely Pol V-dependent) (Maliszewska-Tkaczyk et al., 2000). However, Pol V may not be processive enough to fix the mutation. Therefore Pol IV may play a role in fixing Pol V errors by extending the primer, protecting it against nuclease activity or proofreading-proficient enzymes (Kuban et al., 2006). Recently, it was shown that in the *recA730* background under normal growth conditions Pol V Mut co-localizes with Pol III HE, suggesting that Pol V can replace Pol III during replication of undamaged DNA (Robinson et al., 2015).

Maliszewska-Tkaczyk et al. (2000) showed that the spontaneous SOS mutator creates mutations preferentially in the lagging strand due to the greater dissociability of the lagging-strand polymerase, which enables Pol V and Pol IV to replace Pol III at the 3' terminus more easily than on the leading strand. Therefore, the authors propose that the

enhancement of untargeted mutagenesis in SOS-induced cells results from a disproportionately large increase in replication errors in the lagging strand. Curti et al. (2009) analyzed *rpoB* spectra in a *recA730* *lexA(Def)* *mutL* background and showed that all three TLS polymerases can interfere with the ability of Pols I and III to complete their function and modulate the extent of spontaneous mutagenesis occurring on the *E. coli* chromosome.

ROLE OF dNTP POOLS IN SOS INDUCTION

Little *in vivo* information is available about the possible role of the cellular dNTPs in RecA activation, although a number of studies have addressed the role of alternative cofactors using *in vitro* experiments (Phizicky and Roberts, 1981; Weinstock and McEntee, 1981; Menetski et al., 1988; Wang et al., 1988a; Ellouze et al., 1999; Wigle et al., 2006). Various (d)NTP species show different efficiencies in promoting RecA coprotease activity *in vitro* (Phizicky and Roberts, 1981; Weinstock et al., 1981a). dATP and ATP are the most active; dATP might be the primary cofactor *in vivo*. *In vitro*, other nucleotide triphosphates are competitive inhibitors of dATP-promoted RecA coprotease activity (Weinstock and McEntee, 1981; Weinstock et al., 1981b). It was suggested that the chemical nature of the nucleobase is important for the stability of the RecA-ssDNA complex: adenine promotes strong RecA-DNA binding, while other bases promote only weak binding, leading to enhanced dissociation of the filament (Ellouze et al., 1999). Of the two possible RecA filament states, only one explains the interaction between LexA and RecA that promotes LexA cleavage (VanLoock et al., 2003), and the efficient formation of RecA filaments in the active conformation is necessary for SOS induction (Gruenig et al., 2009).

Addition of nucleosides or free bases to the growth medium can affect the SOS induction in the cell (Kirby et al., 1967; Witkin, 1974; Tessman and Peterson, 1980; Llagostera et al., 1985). The inducing activity of *recA* mutant proteins is inhibited by cytidine plus guanosine, and the addition of adenine reverses this inhibition. Various RecA coprotease-constitutive mutants show different levels of resistance toward G + C inhibition: the greater the constitutive coprotease strength, the more resistant the mutant to the G + C inhibition (Tessman and Peterson, 1985; Wang et al., 1988a). This may be explained by the fact that certain *recA* mutants have higher affinity for ssDNA (Wang et al., 1988b). Since the addition of nucleosides to the growth medium affects the ratio of NTPs in the cell (Ruff et al., 1971), it is possible that the proportion of various NTPs in the cell may play an important role in the activation of RecA coprotease activity, and therefore modulate SOS system induction. A recent study provides evidence in favor of that hypothesis. After the observation that "SOS mutator effect" resulting from constitutive SOS induction

(*recA730* mutation) was suppressed in the strains affected in nucleotide metabolism (dCTP deaminase, *dcd* or nucleoside diphosphate kinase, *ndk* deletion), the issue was further explored by microarray studies allowing expression analysis of the complete spectrum of SOS inducible genes (SOS regulon). Remarkably, in the presence of the *ndk* or *dcd* deficiency (that changes the levels of particular nucleotides) a near complete shutdown was observed of the entire SOS system. The effect is mediated most likely through the direct role of the dNTPs in the activation of the RecA protein coprotease activity facilitating the LexA repressor cleavage (Maslowska et al., 2015).

Several studies have reported dNTP elevations of several-fold for each of the four dNTPs after treatment of *E. coli* with UV light, which also effectively induces the SOS system. The pattern of nucleotide pool alterations after UV irradiation was the same in wild-type strains and in *recA*[−] and *umuC*[−] strains (Suzuki et al., 1983; Das and Loeb, 1984). This dNTP increase results from an increase in expression of the *nrdAB* genes (Gon et al., 2011) encoding the ribonucleotide reductase (RNR), the main enzyme involved in dNTP synthesis, and a corresponding increase in the RNR protein level. This induction of RNR in response to UV light irradiation is consistent with previous reports on the inducibility of the *nrdAB* operon by DNA damage in a LexA-independent manner (Gibert et al., 1990; Courcelle et al., 2001). An increase of dNTP pools contributes to the specificity of UV-induced mutagenesis (Suzuki et al., 1983; Das and Loeb, 1984). Elevated dNTP pools are essential for efficient translesion synthesis across specific replication-blocking lesions by Pol II and Pol V (Gon et al., 2011).

The rNDP reductase overexpression without UV treatment does not initiate the SOS response (Wheeler et al., 2005). However, a study by O'Reilly and Kreuzer (2004) found that certain mutations in nucleotide metabolism genes cause SOS constitutive phenotype. The strongest effect was found for *purF* (first enzyme in the purine biosynthesis pathway), *dcd*, and *thyA* mutants. The *thyA* mutant, when starved of thymine, loses colony-forming ability. This so-called thymineless death (TLD) is a unique biological phenomenon, since starvation of bacteria of other growth factors, such as amino acids or vitamins, stops growth but does not cause cell death. TLD leads to a variety of damage to DNA and was found to be associated with SOS induction in earlier studies (Ahmad et al., 1998). Recently, it has been shown that starvation for dGTP can kill *E. coli* cells in a manner sharing many features with TLD—increased time of starvation increases DNA replication stress causing induction of the SOS system (Itsko and Schaaper, 2014, 2016).

CONTROL OF SOS FACTORS BY OTHER STRESS RESPONSES

Bacteria have global response systems to adapt and survive many environmental stresses (Foster, 2007;

Micevski and Dougan, 2013). Stress response pathways were shown to be involved in the control of SOS factors, including stringent response and general stress responses regulated by alternative sigma factors RpoS and RpoH.

RpoS is an alternative sigma factor (σ^S), a subunit of RNA polymerase that directs RNA polymerase to gene promoters. Its activity is triggered by entry into stationary phase as well as different stress conditions that inhibit growth. The RpoS regulon involves over 70 genes, most of them encoding proteins that help the cell survive insults encountered by non-growing cells. Therefore, RpoS is considered to be a regulator of a general stress response (reviewed in Hengge, 2009). The activity of Pol IV is regulated by RpoS both in stationary-phase and in exponential-phase cells. The RpoS-dependent induction of Pol IV in stationary phase is independent of LexA inactivation (Layton and Foster, 2003). In growing cells RpoS regulates Pol IV activity indirectly via one or more intermediate factors, including SbcCD nuclease and RecB (Storvik and Foster, 2011). RpoS is also a positive regulator of *polB* (Pol II) expression, required for full expression of the *polB* gene even when the SOS response is derepressed (Dapa et al., 2017).

RpoH (σ^{32}) is the primary sigma factor controlling the heat shock response during log-phase growth. The RpoH regulon contains approximately 30 genes. It is induced not only by temperature, but also by other conditions that result in unfolded proteins (reviewed in Yura et al., 2000). The *groEL/ES* operon encoding the molecular chaperone GroE belongs to this regulon. Levels of DNA Pol V are dependent on GroE because it interacts with UmuC and protects it from degradation (Donnelly and Walker, 1992). GroE is also required for normal and induced levels of Pol IV. However, lack of direct interaction between GroE and Pol IV suggests that GroE is required for the stability or activity of some other positive effector of Pol IV (Layton and Foster, 2005).

The *E. coli* stringent response, mediated by the alarmone (p)ppGpp, is responsible for reorganizing cellular transcription in response to nutritional starvation and other stresses, resulting in reduced growth rate (reviewed in Dalebroux and Swanson, 2012). Transcription profiling showed that the stringent response in *E. coli* induces genes involved in the SOS response (*recA*, *ruvA*, *sbmC*, *sulA*, *umuD*, and *yebG*) (Durfee et al., 2008). The (p)ppGpp alarmone can increase the pause time of transcription elongation complexes at some positions, blocking proper fork migration during DNA replication. This may result in increased regions of single-stranded DNA which in turn induce the SOS response (Trautinger et al., 2005).

The links between SOS and other global responses to DNA damage, protein damage, and starvation provide evidence that the ability to increase genetic diversity has evolved to promote survival during stress.

CONCLUDING REMARKS

The SOS response allows the cell to survive sudden increases in DNA damage by inducing the expression of multiple factors that serve to promote the integrity of DNA. It is therefore a very important system that needs to be regulated at a large number of different levels. These levels of regulation ensure the timely induction, progression, and termination of the response.

Decades of studies have yielded many advances in our knowledge about the SOS response. However, the current understanding of precise molecular mechanisms regulating this important process is far from complete. Studying the molecular mechanism of bacterial SOS response provides an essential source of concepts for the understanding of DNA repair regulation networks and mechanisms influencing the fidelity of replication. Identifying new levels and new means of regulation of the SOS response might reveal links with other cellular global regulation networks and unsuspected consequences of the SOS induction.

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Author contributions

All authors contributed to the literature review and manuscript writing. In addition, KHM prepared figure and tables.

Conflict of interest

The authors declare that they have no conflicts of interest.

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