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Review

Some aspects of the SOS response system — A critical survey

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The SOS system and SOS mutagenesis are frequently studied, or exploited to obtain an increase in mutagenicity of bacteria. Here a short survey is made of the phenomenon of SOS response with special attention to latest and less discussed data, especially the induction of the SOS system in response to cell starvation or mutation of certain genes and the role of inducible DNA polymerases.

HISTORICAL ASPECTS

The discovery of the SOS response system evolved from studies on the effect of UV irradiation on *Escherichia coli* and consideration of seemingly unconnected data. It was observed that reactivation and mutagenesis of UV-irradiated phage λ were increased when the phage infected an *E. coli* host that had been previously irradiated [1]. Later Radman [2] termed this phenomenon W-reactivation or Weigle-reactivation. Furthermore, UV-irradiation caused induction of prophage λ in bacterial lysogens (transition of phage λ from the lysogenic to lytic development) [3], filamentation of cells [4], and mutation in bacteria [5]. All of these data led Miroslaw Radman [2] (see also [6, 7]) to put forward the hypothesis on inducible SOS repair that is related to mutagenesis. He proposed that when bacteria are exposed to stress they can produce many defence proteins which genes are normally in a repressed state and that allow repair of damaged DNA and reactivation of DNA synthesis, and that these processes are connected with mutation. Since emotionally he was bound with the sea he called this phenomenon the SOS response, after Save Our Souls, the telegraph signal given in Morse alphabet when a ship in deadly danger. Knowing that the re-

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Abbreviations: HI, heterology index; NER, nucleotide excision repair; SSB protein, single-strand binding protein.

pressor of λ phage is proteolytically cleaved in the course of prophage induction [8] and that mutations in *lexA* and *recA* genes abolish the SOS response, Gudas & Pardee [9] proposed that the SOS system is repressed by LexA protein and derepressed by RecA protein. After these proteins were purified it was shown in *in vitro* experiments that RecA does cleave the CI repressor of phage λ as well as LexA protein, although repressor of phage is cleaved with at least 10 times slower activity [10–12].

The functioning of the SOS system seems to be simple and, in general, operates as proposed by Little & Mount [13]. The SOS genes are scattered at different sites on the chromosome and their expression is based on interplay of the two proteins LexA and RecA. LexA is a repressor that binds to the SOS box of the operator sites of both *lexA* and *recA* and all of the genes belonging to the SOS system and represses their transcription. The SOS genes therefore are regulated negatively and are normally transcriptionally repressed.

PHYSIOLOGY OF SOS INDUCTION

An increase in expression of the SOS genes begins when DNA is damaged, or when replication of DNA is blocked and single stranded DNA accumulates. A cascade of reactions starts when RecA protein, in the presence of dATP or ATP, forms filaments on a single strand of DNA and acquires protease activity, RecA*. The level of ATP and dATP during SOS induction is increased several folds [14–17]. RecA* facilitates cleavage of LexA repressor and CI repressor of λ phage, as well as processing of UmuD protein to mutagenic UmuD′ which assists UmuC in its DNA pol V polymerase activity. LexA, phage λ repressor and UmuD are all able to autocleave themselves. RecA*, therefore, functions as a co-protease. A decrease in the level of LexA repressor frees the operator sites and facilitates gene expression. To identify the genes belonging to the SOS regulon, Kenyon & Walker [18] (see also [19]) first employed Mu d1(*Ap,lac*) phage constructed by Casadaban & Cohen [20]. Phage Mu is easily inserted into the chromosome of *E. coli* K12 and causes gene mutation. The *lac* operon carried by Mu phage is promoterless, so that when it randomly integrates in the right orientation to the promoter of an SOS gene, β-galactosidase encoded by *lacZ* is expressed after damage to DNA with e.g., UV light or mitomycin C.

In this way Kenyon & Walker [18] made estimates of the number of the damage inducible genes (*din*) which were later identified. This strategy (fusion of SOS genes with *lacZ* as a reporter gene) has since been frequently exploited to investigate the SOS response (e.g. [21]). The earliest-recognised SOS genes were *recA, lexA, uvrA, uvrB* (but not *uvrC*), *lon* and others [12].

HETEROLOGY INDEX (HI)

LexA repressor binds to SOS boxes with sequences 20-nucleotides long situated near or inside the promoter site of the SOS-induced genes, and its binding prevents accessibility to RNA polymerase.

All SOS boxes show a palindromic structure and a high degree of homology, but they are distinct in sequence and this non-identity causes LexA repressor to bind to the *din* promoters with a different strength. Recently Lewis *et al.* [22], on the basis of 19 sequenced SOS boxes, defined their consensus as $TACTG(TA)_5CAGTA$, and calculated mathematically for every SOS box a heterology index (HI) that indicates the relative binding strength of LexA repressor to a given gene promoter. They calculated that binding of LexA repressor to the SOS box would occur when the HI value is below 15. When its HI is higher, a gene is more easily expressed.

Some of the SOS genes and the timing of their expression are shown in Table 1. In the first phase, among the expressed genes are

lexA, encoding SOS repressor protein, genes *uvrA, uvrB, uvrD* whose products (together with *uvrC*-encoded protein) are involved in single strand nucleotide excision repair (NER), and *ruvA* and *ruvB* genes whose products are involved in recombinational DNA repair. One of volved in RecF-dependent recombination and double strand repair [30, 31].

Knowledge of the role of RecA protein in recombination much preceded our knowledge of its role in de-repression of the SOS system and in SOS mutagenesis [32]. Among the lat-

Table 1. Some of the SOS genes in *E. coli* and the sequence of their expression in response to SOS induction*

Gene	Function of gene product	Copy number/cell non-induced	induced	Heterogeneity index (HI)
Expressed as the first				
lexA	Repressor of SOS genes	1300	7540	6.34;7.02
uvrA	UvrABC-excinuclease (NER repair)	20	250	6.98
uvrB	UvrABC-excinuclease (NER repair)	250	1000	6.11
uvrD	Helicase II	5000–8000	25000–65000	8.80
polB	DNA polymerase II	40	300	12.09
ruvA	RuvAB-helicase,	700	5600	9.19
ruvB	Recombinational repair	200	1600	9.19
dinI	Inhibitor of UmuD processing	500	2300	6.24
Expressed as the second				
recA	SOS derepressor, recombinational repair	1000–10000	100000	4.31
recN	RecN, recombinational repair	?	?	5.16;9.38;11.47
Expressed as the last				
sfiA	(*sulA*) cell division inhibitor	?	125-fold increase	4.65
umuD	UmuD' (unit Pol V)	180	2400	2.77
umuC	UmuC (Pol V)	0	200	2.77

*Based on papers by Kuzminow [23] and Fernandez de Henestrosa *et al.* [24]. Genes expressed in the last phase are *cea, caa* coding for colicin E1 and colicin A in the colicinogenic plasmids Col. They may be regarded as genes of apoptosis, since their expresion causes lysis and death of the cells.

the first expressed is also the *dinI* gene coding for an inhibitor of UmuD → UmuD′ processing [25], and *polB (dinA)* encoding DNA polymerase II [26], enabling resumption of DNA synthesis when replication is stalled [27]. In the next phase are expressed *recA* and *recN* genes, whose protein products are involved in DNA recombinational error-free repair. RecA, therefore, is involved in induction of the SOS response (*via* RecA*), in DNA recombination, single and double strand DNA repair, and recombination dependent replication [23, 28, 29]. RecN is interest expressed genes are *sulA* (*sfiA*) encoding a cell division inhibitor and causing filamentous cell growth, *umuD* and *umuC* genes encoding error-prone DNA polymerase V [33], and genes *cea* and *caa of* colicinogenic plasmids coding for colicin E1 and colicin A, respectively. *cea* and *caa* can be regarded as apoptosis genes because their induction causes lysis and death of the cells. Only a few genes has more then one SOS box; namely *lexA*, (two sites) and *recN*, (three sites) included in Table 1 and (not indicated in Ta-

ble 1) *ydjM* (two sites). These genes are regarded as being more tightly regulated.

THE NUMBER OF SOS GENES

Knowledge of functional elements of the SOS genes and of the entire sequence of chromosomal DNA in *E. coli* has provided a new approach to search for putative SOS genes [24, 34]. In the most recent paper Fernandez de Henestrosa *et al.* [24] by taking into account localisation of the putative SOS box to a gene or a promoter site and the value of the HI index, computationally searched the whole genome of *E. coli* strain MG1655 for candidates of SOS-regulated genes. They find 69 such sites of which 24 were already known, 7 were classified as novel genes that encode proteins and are transcriptionally regulated by LexA, and the remainder awaits definition. Meanwhile, in Phil Hanawalt's laboratory, by using DNA chip technology it has been found that downstream of *dinB* there are three others SOS genes that were unknown (Roger Woodgate, personal communication; see also [75]). Since three SOS genes have more than one sos box, the whole number of the all SOS genes in *E. coli* chromosome most probably does not exceed of 68. Assuming that the total number of genes in *E. coli* genome is 4300, the whole number of all the SOS genes accounts from 0.76% (for 32 genes) to 1.58% (for 68) of genes of the entire genome [24]. However, functions for most of them remain to be established.

CELLULAR METABOLISM AND THE SOS RESPONSE

Induction of the SOS response takes place under a variety of physiological states of bacteria, in response to changes of pH, transition from exponential to stationary growth, and starvation of the cells [35–37]. Further, chronic induction (or sub-induction) of the SOS genes is observed in response to mutations in certain genes (see Table 2). Therefore, induction of the SOS system is not a desperate attempt to stay alive, but rather is a reaction of the cells to inhibition of DNA synthesis [23].

INDUCTION OF THE SOS RESPONSE IN STARVED BACTERIA — THE EFFECT OF GLUCOSE

Recently Taddei *et al.* [36] demonstrated that induction of the SOS response occurs in bacteria that were starved on plates. To show this they used lysogenised with phage λ MT1-derived bacteria bearing *c*I-*cro-gal* fusion, in which the *c*I and *cro* genes were fused to a promoterless bacterial *gal* gene so that expression of *gal* was dependent on expression of *cro*. The lysogenic state of bacteria depends on production of the CI repressor encoded by the *c*I gene. The genes, *cro* and *c*I mutually repress each other. Therefore, the bacterial cells were either in the lysogenic state and had the phenotype $\lambda^{+}gal^{-}cro^{-}$, or when the SOS system was induced and the CI repressor was cleaved, the *gal* gene was transcribed and the phenotype was $\lambda^{-}gal^{+}cro^{+}$. Since the bacteria were kept on plates containing galactose whose products of metabolism stained the bacteria red, induction of the SOS system could be directly visualised on the plate. This result was then confirmed in bacteria bearing the gene fusion *recA::lacZ* in which induction of SOS was measured by the level of β-galactosidase when bacteria were starved and then incubated in liquid growth medium. The authors have found that induction of the SOS response is *cya*-dependent; it does not occur in a cya^{-} mutant and addition of cAMP reverses the effect of a *cya* mutation. They also found that addition of glucose inhibits SOS induction.

The gene *cya* codes for adenyl cyclase that synthesises cAMP from ATP, and glucose inhibits cAMP production. It is well known that

cyclic AMP and CAP (catabolite gene activator) protein is involved in repression or de-repression of many catabolic genes. Induction of the SOS system (at least in starved bacteria) may, therefore, depend on the level of cAMP.

MacPhee first noticed that in *E. coli* K12 glucose inhibits induction of spontaneous [38] and *mucAB*-mediated UV-induced mutation when bacteria were irradiated at stationary phase [39]. To explain these effects the authors considered three possibilities: glucose either represses error-prone repair or enhances error-free repair, and/or at least one component of the SOS mutational pathway is extremely sensitive to classical cAMP-mediated catabolite repression. It is also possible that glucose shifts the SOS response to another, possibly an error-free, metabolic system. The concentration of cAMP probably plays a pivotal role in this process hence the effect of glucose may be especially pronounced when the level of cAMP is low. Clearly, further studies are needed to resolve this problem.

ROLE OF THE SOS SYSTEM IN PRODUCING ADAPTIVE MUTANTS

The experimental conditions applied by Taddei *et al.* [36] resemble those used to induce adaptive mutations, which occur when cells are starved and are non- or very slowly-dividing and are different from those arising in dividing cells (for reviews see [40–44]). The finding that in starved cells the SOS system is induced raises the question whether and to what extent error-prone SOS mutagenesis participates in adaptive mutations. This mechanism may occur and be pronounced in at least all cases when lactose or another cAMP-forming sugar (not glucose) is supplied as a sole carbon source. The effect of starvation and the role of the carbon source on induction of the SOS functions were investigated in *E. coli* AB1157 (*argE*3) starved on a plate for arginine from 1 to 10 days (Janion *et al.*, to be published elsewhere). The starved bacteria were then collected and we examined whether or not they were in SOS-inducing phase. Bacteria were examined either directly after being starved or after further incubation in a different liquid growth media. The results showed that starvation could induce the SOS response, but only when bacteria after being starved were incubated in growth medium containing 0.2% glycerol instead of 0.5% glucose as a sole carbon source. This seems to indicate that during starvation signals for SOS system induction are formed, but to induce the SOS response the cells must be in a dividing state and under conditions that allow production of a high concentration of cAMP (that is, in the presence of glycerol but not of glucose). These data confirm those of Taddei *et al.* [36] and seem to indicate that the starving conditions applied by these authors were not so stringent as supposed and that some of the cells, perhaps due to prophage induction and bacterial lysis, were in a dividing state.

These data point to the complexity of SOS induction and pose the question whether there is any connection between the nature of the SOS-inducing signals and the SOS response. It may be that different responses depend on the strength and nature of the SOS-inducing signal, and that the SOS-inducing signals in starved cells require cAMP for their activation. A putative role of the SOS response in mutagenesis induced under starvation condition (adaptive mutants) remains to be determined.

CHRONIC INDUCTION OF THE SOS SYSTEM AND INDUCING SIGNALS

A number of physical and chemical agents induce the SOS response. The best documented is UV radiation and the role of cyclobutane pyrimidine dimers and 4,6-pyrimidine photoproducts generated by UV in mutagenesis and the SOS induction. Among

the chemicals inducing SOS signals are mitomycin C (MC) causing cross-link formation, methyl methanesulphonate (MMS) causing formation of 3meA and apurinic sites [45], 4-nitro-quinoline *N*-oxide (4-NQO), benzo(*a*)pyrene and many others that cause adduct formation and introduction of a variety of non-coding base adducts in DNA. It has been also found (or deduced) that mutations in certain genes that are involved in DNA repair or in replication can cause a chronic induction or sub-induction of the SOS response. A list of these genes, certainly incomplete, is included in Table 2. All of these genes are involved either in DNA metabolism, or repair. The gene *dam* codes for DNA adenine methylase and is part of the *dam*-directed mismatch repair system [57]. In dam^+ bacteria only unmethylated 3′-GATC-5′ sequences in the newly synthesised strand of DNA are incised, whereas in dam^- they are incised in both of the strands [58]. p*olA* (*dinA*) codes for DNA polymerase I (Pol I), a main DNA repair enzyme that functions in NER repair and in processing of Okazaki fragments arising in the course of DNA synthesis on the lagging strand [59]. *ligA* codes for DNA ligase that seals nicks in DNA. *uvrD* codes for DNA helicase II involved in NER and in mismatch repair. Mutations in *dam*, *lig*, *polA* and *uvrD* genes cause increased single strand interruptions in DNA and replication fork collapse. *dnaQ* (*mutD*) codes for the epsilon subunit with 3′-5′-exonuclease (proofreading) activity of DNA polymerase III, a main polymerase of *E. coli;* its defect disturbs DNA synthesis. Chronic induction of the SOS response *in dnaQ* mutants may be due to increase in the number of gaps in DNA as a result of intensification of mismatch repair activity. *priA* encodes a protein required for primosome assembly and its defect causes instability of replication forks and delay of DNA replication. Mutants in *recN* are defective in transductional and conjugational recombination and in RecF-mediated recombinational repair (recombination connected with double strand repair).

Table 2. Genes whose defects cause chronic derepression of SOS system

Gene	Gene product /Function/References
dam	DNA-adenine methylase involved in *dam*-directed mismatch repair [46–49]
lig	DNA ligase seals nicked DNA [50]
pol I	DNA polymerase I participates in NER repair and processing of Okazaki fragments [51]
uvrD	DNA helicase II required for NER and DNA mismatch repair [52, 53]
dnaQ	*(mutD)* ε subunit of DNA polymerase III with 3′-5′-exonuclease corrector activity [54]
priA	Protein required for primosome assembly [55]
recN	Recombinational protein [56]
xth,nfo,nth	Exonuclease III, endonuclease IV that jointly remove 90% of abasic sites and endonuclease III with DNA glycosylase and abasic lyase activity (Janion *et al*., to be published)

The genes *xth* and *nfo* code for exonuclease III and endonuclease IV that jointly remove 90% of abasic sites from DNA. *nth* codes for DNA glycosylase that removes oxidised bases (mainly pyrimidines) from DNA and incises abasic DNA (abasic lyase activity). In the *xth*, *nfo* and *nth* mutant the level of abasic sites and nicks greatly increases [60–63]. Permanent induction of the SOS response in all of these mutants is not dependent on the presence of glucose; in other words glucose in the medium is not able to prevent chronic induction of the SOS response.

Most of these genes (Table 2) are known as mutator genes [64, 65]. The relationship be-

tween their SOS-inducing power and mutator activity and the participation of the error-prone DNA polymerases in their mutator potency has not been yet clearly defined. It may be suspected that the SOS-induced error-prone repair pathway would be less effective in *dnaQ* mutants bearing a defect in proofreading activity than, e.g., in *xth nfo nth* mutant which is defective in repair of apurinic sites. Introduction of frequent mismatches in DNA is sufficient for the increased mutagenicity in $dnaQ^-$ strains, but nevertheless error-prone DNA polymerases may further contribute to an increase in mutations.

SOS-INDUCED DNA POLYMERASES

Five different DNA polymerases have been found in *E. coli* so far, and are numbered from pol I to pol V. The non-inducible polymerases are pol I, the main DNA repair enzyme that fills gaps in the course of DNA repair and in discontinuous DNA synthesis on the lagging strand, and pol III, the main DNA polymerising enzyme [59]. The remaining pol II, pol IV and pol V polymerases encoded by *polB*, *dinB* or *umuDC*, respectively, are induced during the SOS response and are a part of the SOS mutagenic pathway. Some characteristics of these three inducible enzymes are shown in Table 3. The most important for SOS-induced mutagenesis is the operon *umuDC*. Its inactivation in *E. coli* causes non-mutability of UV-irradiated cells [66, 67]. To achieve mutagenic activity UmuD must be previously processed to UmuD′ and form a $UmuD'_2UmuC$ complex [68, 69]. The enigma of the function of the $UmuD'_2C$ proteins was resolved quite recently by showing that this complex alone (as well as pol II and pol IV) possesses an intrinsic DNA polymerase activity [33]. Currently it is supposed that Pol II catalyses restart synthesis of the damaged DNA after its replication has been blocked in an error-free process [27, 70]. Pol IV does not seem to play a role in targeted SOS-UV-induced mutagenesis but causes untargeted –1 frameshift mutations in phage and in F′ plasmid DNA. Pol V is the most error-prone of all *E. coli* DNA polymerases. It copies with a base substitution error rate of about 10^{-3}–10^{-4} whereas the accuracy of pol IV is 10- to 15-fold greater. RecA* is absolutely required for synthesis of DNA by pol V; its activity in the presence of SSB (single-strand binding) protein, ATP, and the β and complex of pol III increases 15 000-fold after addition of RecA* [71–73]. However, recently Napolitano *et al.* [74] have shown that all of the SOS-inducible DNA polymerases may be involved in induced mutagenesis and that this depends on the nature of the DNA lesion and its sequence context. Bypassing of *N*-2-acetylaminofluorene-guanine adducts requires pol II for –2 frameshift mutations, and is error-free for pol V; while bypassing of a benzo(*a*)pyrene adduct leading to –1 frameshifts requires activity of both pol IV and pol V. All the induced polymerases are not processive but distributive. They synthesise only a short fragment of six to eight nucleotides across a non-coding lesion and then are released and pol III resumes their work.

Table 3. SOS-induced DNA polymerases

Gene	Gene product and its function
polB	(*dinA*) DNA Pol II reactivates replicative DNA complex
dinB	DNA Pol IV induces of mutations in λ phage and in episom F′
umuDC	DNA Pol V ($UmuD'_2C$), error prone translesion DNA polymerase, to its full activity requires RecA*, SSB protein and the β and γ complex of DNA pol III

Summing up, our knowledge about the SOS system seems to be almost complete, and all of the genes controlled by the SOS regulon should be known soon. Some questions remain to be answered, of which one of the most enigmatic is the role of glucose and of cAMP in SOS induction.

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