Bacterial SOS Response and its role in the acquisition of antibiotic resistance and virulence factors

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INTRODUCTION

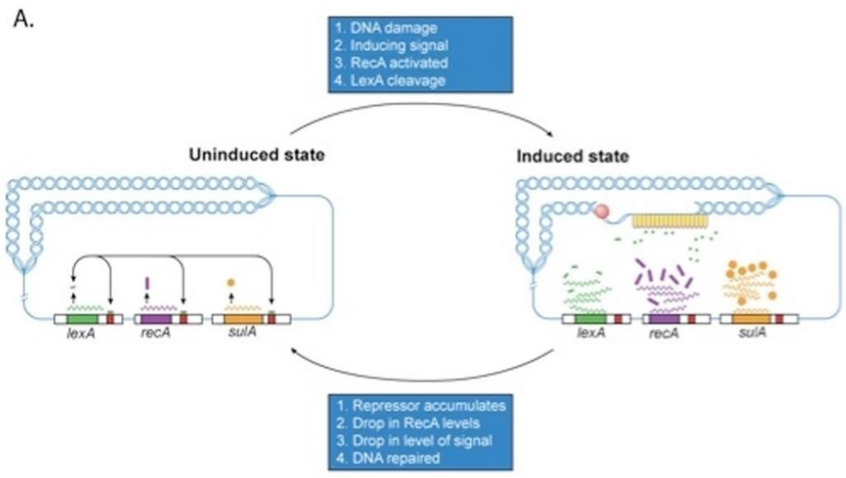

Figure 1. Model of the SOS induction. Edited from Lyle A. Simmons *et al.* [2]

First described in *Escherichia coli* and named by Miroslav Radman in 1974 when he postulated the existence of an "error-prone" replication mechanism triggered by DNA damage or replication fork blockages[1]. The SOS response is controlled by two main proteins: the repressor LexA and the activator RecA. RecA binds to single-stranded DNA to form a nucleoprotein filament which leads to the autocleavage of LexA[2]. More than 40 genes are under control of this regulon, including low-fidelity polymerases[1] (Figure 1). The inducing signal that activates RecA and the SOS system is based on the unwinding activity of the RecBCD enzyme[3].

The SOS response can be triggered by various endogenous and exogenous factors, as UV irradiation, chemical compounds or organic mutagens, among others. This review is focused on the antibiotic-induced SOS response and the secondary effect that this system has in bacteria.

The mechanisms of action of the antibiotics are a determinant factor for the activation or not of the SOS system. Thus, each drug would have a different effect depending on the specie we study and its target on the cells.

Direct Activation of the SOS Response

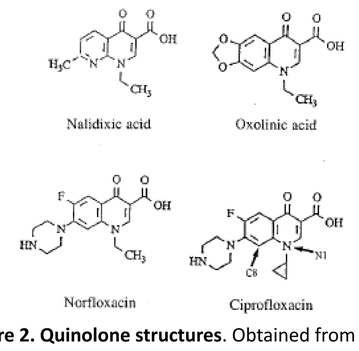

Figure 2. Quinolone structures. Obtained from Darlika and Zhao[4]

The antibiotics that induce directly the SOS system are those that target DNA or blocks the replication fork by targeting some enzyme related to it.

Quinolones: These antibiotics (Figure 2) target two essential replicative enzymes (DNA gyrase and DNA Topoisomerase). Their interference with these enzymes prevent the advance of the replication fork and induce the generation of single-stranded DNA[4].

Indirect Activation of the SOS Response

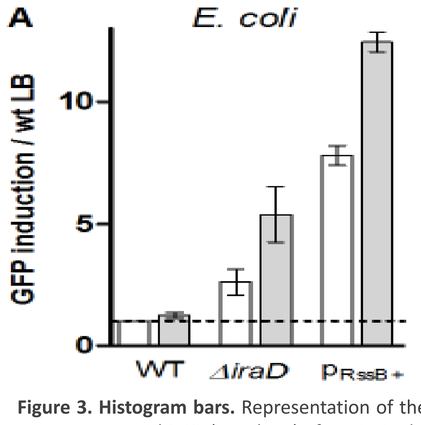

Figure 3. Histogram bars. Representation of the GFP induction differences between growth in LB (white bars) and growth in presence on antibiotic (grey bars) of an strain deficient for IraD and a strain overexpressing RssB. Edited from Zeynep et al. [5]

Antibiotics that do not directly affect DNA replication can induce an SOS response in some microorganisms due to the existence of intermediated factors.

Aminoglycosides: stimulate the production of reactive oxygen species (ROS) which target and damage DNA. These drugs induce the SOS response in the *Vibrionaceae* family, but not in *Escherichia coli*, due to the RpoS regulon[5] (Figure 3). ClpXP regulator interact with RssB to repress RpoS genes, but IraD prevents this union and stabilize RpoS expression. It has been proved that *iraD* gene is not conserved in the *Vibrionaceae* family and make them more sensitive to ROS damage[6].

EFFECTS OF THE ANTIBIOTIC-INDUCED SOS RESPONSE

Horizontal gene transfer

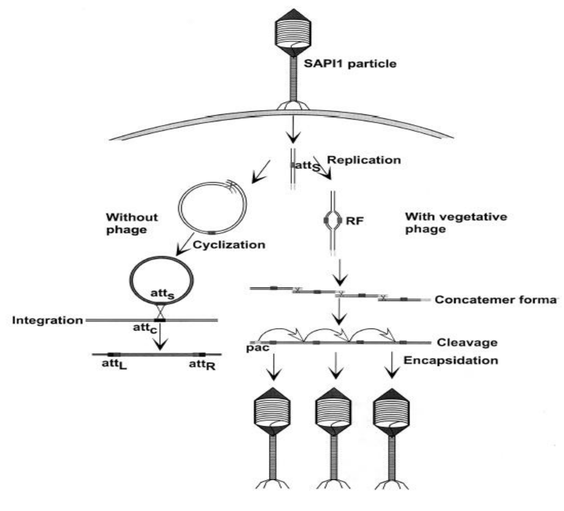

Figure 4. Model of the SaPI1 cycle. In absence of the active bacteriophage the SaPI1 inserts into the chromosome. When the phage is induced the SaPI1 is excised and encapsulated in order to be transduced to another cell. Edited from Ruzin *et al.*[8]

Virulence (*Staphylococcus aureus*)

SaPI1 is an *S. aureus* pathogenicity island that encode toxic shock syndrome (TSST-1) and integrates near the *tyrB* gene[7]. SaPI1 is related with the temperate phage 80α, that when is induced promotes the excision and the encapsulation for the transduction of the island (Figure 4) [8]. The Stl repressor binds to SaPI1 promoters and blocks its cycle. When the 80α is induced by the SOS response (following the same mechanism as phi13) a phage protein interacts with Stl and prevents its union to the promoters[9]

Chromosomical changes

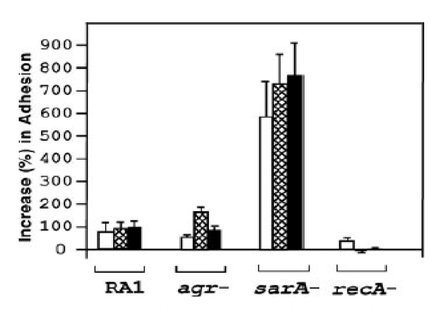

Figure 6. Adhesion to coverslips by different regulator-deficient strains. Each bar represents a different amount of fibronectin in the coverslips from less to more. Edited from Bisognano *et al*.[11]

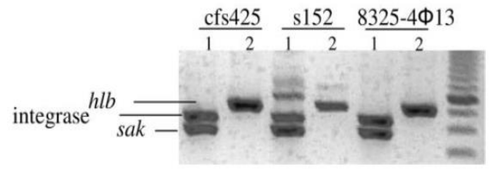

Figure 6. Multiplex PCR. Detection of hlb, phi13 integrase and phage-encoded protein sak before (lanes 1) and after (lanes 2) ciprofloxacin treatment. Edited from Goerke *et al.*[14]

Virulence (*Staphylococcus aureus*)

Fibronectin binding proteins (FnBPs) are necessary for the attachment and encoded by two genes, one of them (*fnbB*) under LexA repression, among other regulator networks. Thus, in presence of ciprofloxacin RecA induce the autocleavage of LexA and permits the expression of this virulence factor (Figure 6). This mechanism permit that the subpopulation of survivors to antibiotics have a major invasive ability[11].

Hemolysin β: the *attP* site of the prophage phi13 is located in the *hlb* gene preventing its expression. The cI-like repressor of the lytic cycle has a C-terminal domain that interact with RecA and adopt a particular conformation in which a catalytic residue interact with the cleavage site[13] (following the same mechanism as LexA). When the phage is induced, the *hlb* gene can be expressed[14].

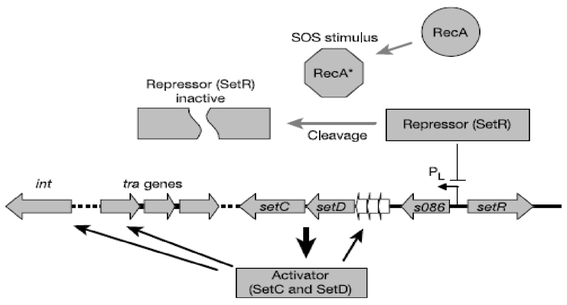

Figure 5. Model of the regulatory network by which the SOS response enhance the SXT transfer. Edited from John W. Beaber *et al*[10].

Antibiotic resistance (*Vibrio cholerae*)

The SXT is an integrating conjugative element (ICEs) that encode resistance to several antibiotics and requires of *recA* for its excision and transfer (Waldor). SetR is the repressor of the genes needed for the excision (*setC* and *setD*). Its interaction with the active RecA filament leads to an auto-hydrolysis of SetR and permits the transfer of the SXT element (Figure 5)[10].

Antibiotic resistance (Persisters)

Persistence: non-hereditable phenotype acquired via reversible epigenetic changes exhibit by a subpopulation of susceptible bacteria which permit to survive lethal doses of antibiotics.

Persistence is induced by antibiotics and is highly related with the SOS system, as demonstrated when a culture is treated with a SOS inducer as mytomycin C (Figure 7)[15].

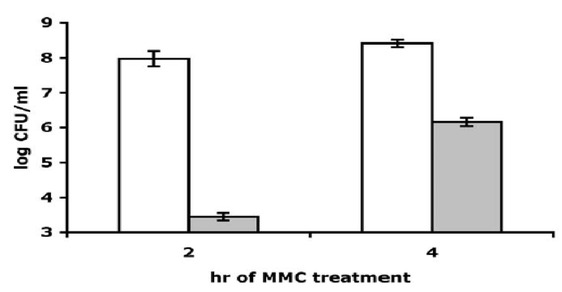

Figure 7. Persistence induced after Mitomycin C treatment. Open bars represent total viable cells and grey bars are the persisters fraction. Edited from Tobias Dörr *et al.*[15]

CONCLUSIONS

The widely extended use of the antibiotics for the treatment of infectious diseases has had a major role in the appearance of resistances, which directly challenge our ability to battle against these diseases. The wrong and excessive use of these compounds not only enhance the appearance of resistances, but in this review is proved that they also play a key role in the spread of virulence factors among bacteria and could aggravate the infectious agent we are trying to treat, as is the case of one of the cystic fibrosis pathogens, *S. aureus*. The main conclusions of this review is the importance of keep studying the molecular basis of this procedures and the development of new drugs that do not activate the SOS system.

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