The SOS response and the dissemination of antibiotic resistances

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INTRODUCTION

Horizontal gene transfer (HGT) is the main mechanism bacteria acquire antibiotic resistances [1]. Mobile genetic elements (MGE) such as integrons, transposons, integrative conjugative elements (ICE) or conjugative plasmids have been shown to play a key role in this process, but the regulatory pathways that controlled them remained unclear. Recent discoveries have shown the important role of the SOS response in the regulation of MGE, as well as the ability of these elements to induce the SOS. For all these reasons, the SOS response has been proposed as a potential new target for the development of new drugs and therapies against multi-drug resistant pathogens and to prevent the dissemination of antibiotic resistances [2].

The SOS response

The SOS response is a bacterial global stress response against DNA damage. Two main proteins are involved in this response: LexA, a transcriptional repressor, and RecA, which is activated by binding ssDNA and mediates the autocleavage of LexA, derepressing the genes under the control of the system [3].

Triggering the SOS response

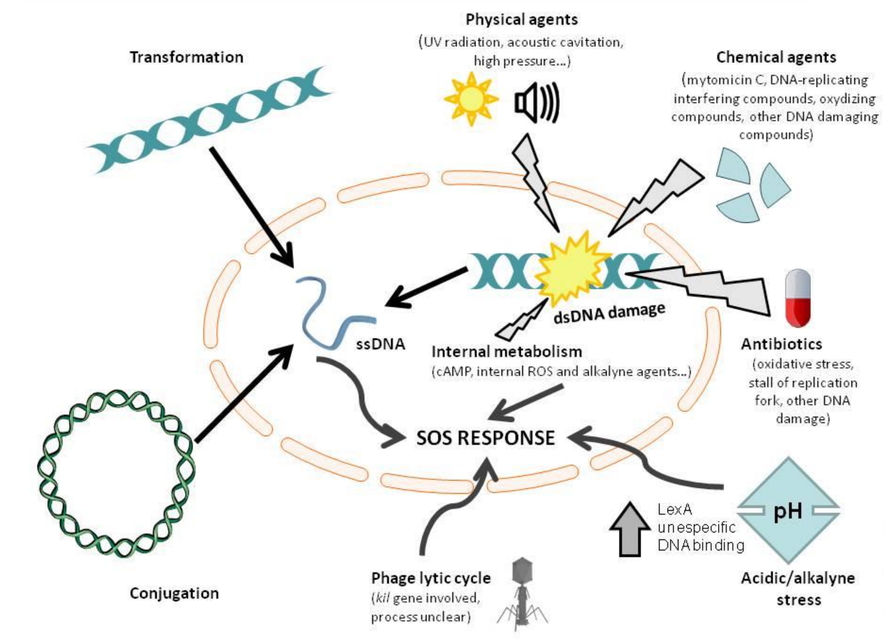

Figure 2: *Agents that can trigger the SOS response*

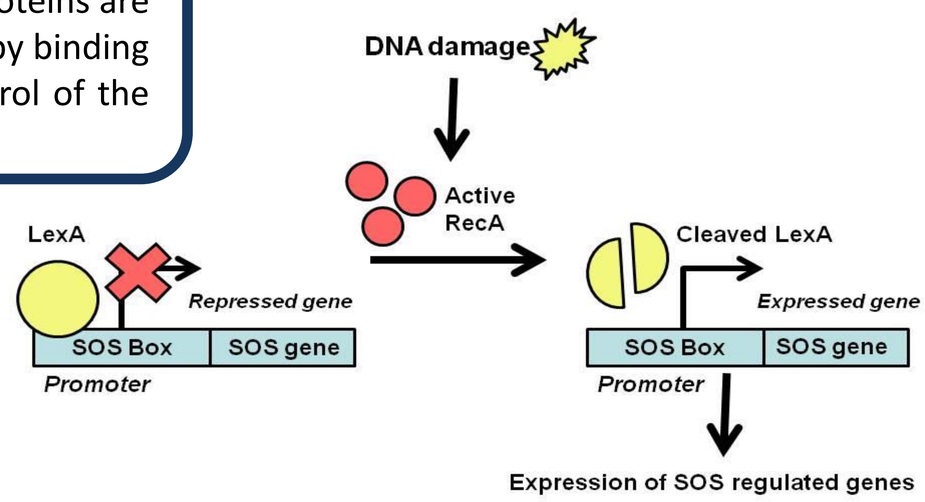

Figure 1: *Schematic representation of the classical SOS response.*

LexA is initially bound to SOS boxes of SOS genes. DNA damage leads to RecA activation, which induces LexA autocleavage, derepressing the expression of the SOS genes.

SOS-mediated regulation of HGT

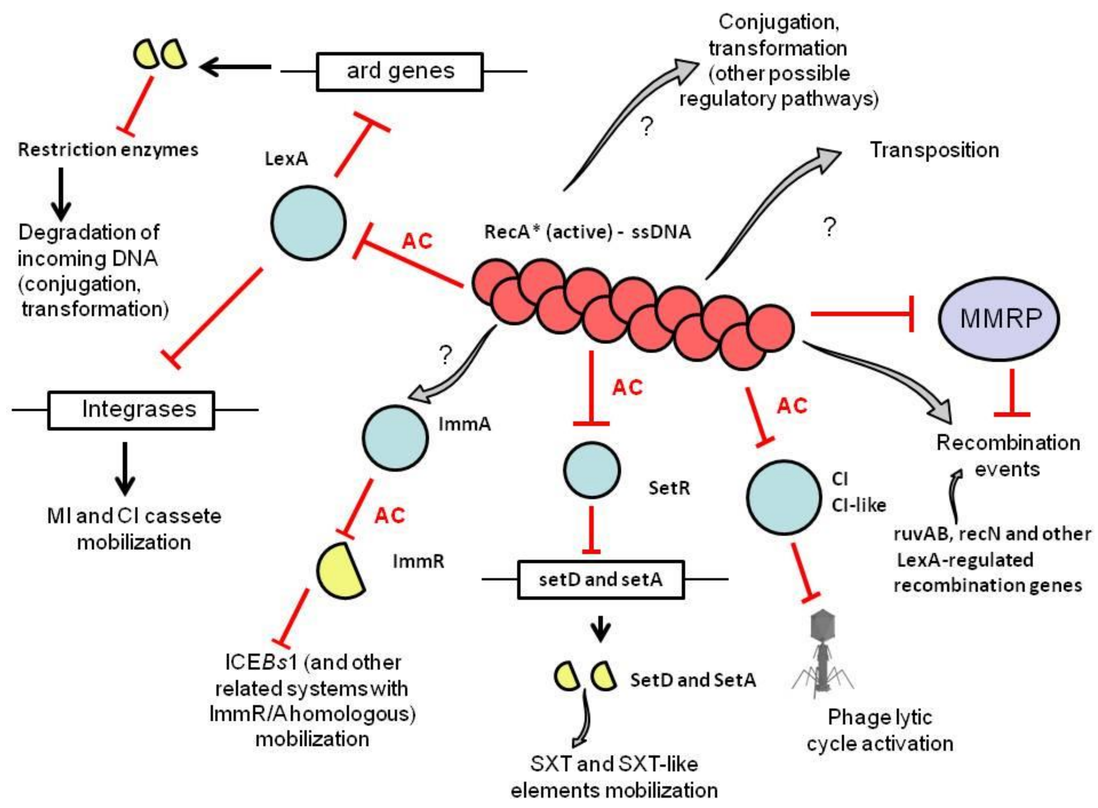

Figure 3: *SOS-mediated regulation of mobile genetic elements.*
The molecular mechanism is indicated if known. Red arrows means inhibition, and the "AC" means inhibition by autocleavage induction. The "?" symbol in some of the arrows mean that the molecular mechanism is unknown or unclear.

Mobile genetic elements

GME	Self-transferable?	Function in antibiotic resistance dissemination
Integrons	No	Gene capture Adaptative gene reorganization
Conjugative Plasmids	Yes	Gene dissemiantion Dissemination of other GME
Transposons	No	Transposition of genes and integrons
ICE	Yes	Gene dissemination Dissemination of other GME
Bacteriophages	Yes	Gene capture and dissemination.
Free DNA (transformation)	No	Gene capture

SOS as a target for future treatments

SOS target	LexA	RecA
Proposed treatment	Phage-mediated overexpression of an uncleavable LexA version	Drug mediated inhibition of RecA biochemical activity
Details	Phage use presents clincal problems	RecA regulates LexA AND other repressors Highly conserved among bacteria No human closely related homologous

Conclusions

1. Mobile genetic elements play a key role in antibiotic resistance dissemination.

2. The SOS response increases the antibiotic resistance acquired through DNA mutation.

2. The SOS response also regulates the mobilization and transference of the MGE containing antibiotic resistance genes.

4. Inhibitors of RecA are promising approaches to fight against antibiotic resistance dissemination and multi-drug resistant bacteria.

References

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3. Erill I, Campoy S, Barbé J (2007) Aeons of distress: an evolutionary perspective on the bacterial SOS response. *Microbiol Rev*. 31:637-656