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

Marta Arch Sisquella, Grau en Microbiologia
Universitat Autònoma de Barcelona

INTRODUCTION

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. 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. More than 40 genes are under control of this region, including low-fidelity polymerases (Figure 1). The inducible signal that activates RecA and the SOS system is based on the unwinding activity of the RecBCD enzyme.

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

Conclusions

The widely extended use of the antibiotics for the treatment of infectious diseases has 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 also 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 these procedures and the development of new drugs that do not activate the SOS system.

Figure 1. Model of the SOS induction. Edited from Lyle A. Simmons et al. 1

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

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

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.

Indirect Activation of the SOS Response

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

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

EFFECTS OF THE ANTIBIOTIC-INDUCED SOS RESPONSE

Horizontal gene transfer

Virulence (Staphylococcus aureus)
SaPI is an S. aureus pathogenicity island that encode toxic shock syndrome (TSST-1) and integrates near the pyrB gene. SaPI is related with the temperature phase 80s, that when is induced promotes the excision and the encapsulation for the transduction of the island (Figure 4). The Sti repressor binds to SaPI promoters and blocks its cycle. When the 80s is induced by the SOS response (following the same mechanism as ph13) a phage protein interacts with Sti and prevents its union to the promoters.

Chromosomal changes

Virulence (Staphylococcus aureus)
Fibronectin binding proteins (FnBPs) are necessary for the attachment and encoded by two genes, one of them (fnbA) 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.

Antibiotic resistance (Vibrio cholerae)
The STX is an integrating conjugative element (ICEs) that encode resistance to several antibiotics and requires of recA for its excision and transfer (Waldor). SetfR is the repressor of the genes needed for the excision (setF and setR). Its interaction with the active RecA filament leads to an auto-hydrolisis of SetR and permits the transfer of the STX element (Figure 5).

Antibiotic resistance (Persisters)
Persisters: non-hereditable phenotype acquired via reversible epigenetic changes exhibit a subpopulation of susceptible bacteria which permit to survive lethal doses of antibiotics.

Persisters is induced by antibiotics and is highly related with the SOS system, as demonstrated when a culture is treated with a SOS inducer as mitomycin C (Figure 7).

CONCLUSIONS

The Bibliography