Abstract

Vga(A) and Msr(A) are resistance proteins belonging to the ARE subfamily of ABC -F proteins. They confer resistance to inhibitors of the peptidyltransferase center. It has been proposed that the mechanism of resistance is based on interaction with a transmembrane partner that forms the functional transporter. Their ribosomal function has been described by cryoelectron microscopy of ribosome complexes with ABCF mutants unable to hydrolyze ATP. However, the exact mechanism of resistance is not yet known.

We have produced the mutant proteins combining the four amino acid residues in Vga(A) and Vga(A)$_{LC}$ at the linker tip, and we were the first to describe the effects of substrate specificity of the single mutants. Amino acid positions 212 and 220 are important for resistance to lincosamides and pleuromutilins, respectively, while position 219 is responsible for resistance to streptogramin A. Each amino acid property plays a critical role in conferring antibiotic specificity, as confirmed by the fact that amino acid substitution at position K218T in the Vga(A) protein causes the shift in resistance from streptogramins to lincosamides and pleuromutilins.

The mechanism of resistance conferred by Vga(A) is ribosomal protection. This is supported by the fact that the rate of [3H]-lincomycin accumulation in the Vga(A)-expressing strain is very similar to that of the erm(C)-expressing strain. At the same time, we confirmed this hypothesis in an in vivo experiment in which we were the first to detect an unmutated Vga(A)$_{LC}$ on the 50S and 70S subunits of the bacterial ribosome.

Although Vga(A) and Msr(A) belong to the same ARE subfamily, their interaction with other resistance mechanisms might differ. While co-expression of Vga(A) and Erm(C) leads to a decrease in MIC and growth defects, an increase in MIC was observed in the case of Msr(A) and Erm(C). Although several high-quality scientific articles have been published in recent years on the mechanism of resistance of ARE ABC-F proteins, the molecular nature of this mechanism is not yet fully understood.

Key words

Vga(A), Msr(A), ARE ABC-F proteins, *Staphylococcus*, lincomycin, erythromycin, ribosomes