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Detuning of the ribosome conformational landscape promotes antibiotic resistance and collateral sensitivity

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Around 50% of the current antibiotic arsenal targets the ribosome, thus resistance to ribosome-targeting antibiotics poses severe challenges to antimicrobial treatments. Here, we characterize a 12-nucleotide deletion in the rplF gene encoding the uL6 ribosomal protein, which was identified in a tobramycin-resistant strain of Pseudomonas aeruginosa isolated from a cystic fibrosis patient. To understand this resistance, we determined multiple structures of wild-type and mutant ribosomes characterizing their conformational landscape. Our analysis reveals how detuning of the ribosome dynamics alters spontaneous rotational movement circumventing inhibition. The mutation compromises the 50S assembly, triggering structural instability and inducing a different rotational dynamic of the 70S. We found 3 new binding sites of tobramycin, and a fourth one exclusive of the mutant, which acts as an allosteric activator to skip inhibition. Our data also illustrate why the mutation enhances sensitivity to chloramphenicol, providing evidence of a molecular mechanism leading to collateral sensitivity. Our work reveals the complex scenario faced to combat ribosome antibiotic resistance, as minor changes generated in regions far away from the antibiotic docking site can derail translation inhibition. This information may be used for the development of new antibiotics that target the effects of the mutations restoring the antimicrobial effect.

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