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Investigation of allosteric mechanism of PTC inactivation by ribosomal antibiotics via molecular-dynamics simulations .

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The ribosome is a target of about half of clinically used antibiotics. They affect crucial functional sites of the ribosome, the most common of which is the peptidyltransferase center (PTC). Various classes of antibiotics bind in the nascent peptide exit tunnel (NPET) triggering translation arrest — inactivation of the PTC in the presence of both aminoacylated tRNA, and this arrest is peptide sequence dependent, i.e. antibiotics in cooperation with nascent peptides cause allosteric inactivation of the PTC.

However, molecular mechanism of this allosteric coupling is still unclear. Meanwhile, this allosteric interaction is crucial for the NPET antibiotics action: even good affinity to the conventional binding site does not necessary provide the PTC function affection (for example, [1]). So, understanding of an allosteric coupling of the PTC with other sites of the ribosome would be valuable information for rational drug design and new antibiotics sites seaching.

In our research we obtained MD simulation trajectories of the *E.coli* ribosome with one of the most well-studied antibiotic erythromycin and without it in the presence of peptide. First, we described a MD-fit structure of the PTC which differed from the cryoelectronic one but these differences are in better coherence with experimental data and could provide an interesting catalysis mechanism with protone shuttle. This PTC structure appeared in several non-erythromycin trajectories accompanied by other structure features, for example, the A-site finger and A-tRNA "elbow" contacts, which are not observed in the structural data. Allosteric communication network is obtained via noncovalent interactions analysis displaying a dense cluster near the PTC.

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References

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