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Article

Study of interactions between the *E. coli* ribosome, CmlAL leader peptide and chloramphenicol by molecular dynamics simulations.

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CmlAL leader peptide regulates biosynthesis of CmlA1 efflux pump, which moves out chloramphenicol from the bacterial cell. CmlAL stops own biosynthesis in the presence of chloramphenicol, which causes conformational changes in mRNA, leading to the opening of the CmlA start codon and its synthesis. The mechanism of CmlAL action is similar to the mechanism of action of Erm family leader peptides, which regulate the synthesis of the corresponding methyltransferase. Toe-printing biochemical experiments have shown, that CmlAL synthesis stops at the M_1STSKNAD$_8$ sequence in the presence of chloramphenicol, so that the next lysine residue remains at the A–site of the ribosome [1]. However, the structure of the emerging peptide–ribosome–chloramphenicol ternary complex has not been experimentally established due to the extreme complexity of this problem.

We attempted to model this ternary complex for the E. coli ribosome using molecular dynamics simulations. Upon that, we proceeded from the assumption, that chloramphenicol is bound in the noncanonical binding site, that we previously identified [2]. We found that chloramphenicol is retained in this site in the presence of CmlAL, which has a stable conformation supported by multiple hydrogen bonds with the 23S rRNA bases. At the same time, the alanine residue of CmlAL contacts with chloramphenicol, but CmlAL does not form stable hydrogen bonds with chloramphenicol. Thus, chloramphenicol presses CmlAL to the wall of the nascent peptide exit tunnel, supporting their interactions, rather than holding CmlAL itself.

Simulations were performed on the Lomonosov-II supercomputer using the Amber14sb force field and the GROMACS 2019 package. This research was funded by the Russian Science Foundation, project 2–24–20030.

References

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