Title	**Conformational sampling of aminoacyl-tRNA during selection on the bacterial ribosome**
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Abstract	Aminoacyl-tRNA (aa-tRNA), in a ternary complex with Elongation Factor-Tu (EF-Tu) and GTP, enters the aminoacyl (A) site of the ribosome *via* a multi-step, mRNA codon-dependent mechanism. This process gives rise to the preferential selection of cognate aa-tRNAs for each mRNA codon and consequently the fidelity of gene expression. The ribosome actively facilitates this process by recognizing structural features of the correct substrate, initiated in its decoding site, to accelerate the rates of EF-Tu-catalyzed GTP hydrolysis and ribosome-catalyzed peptide bond formation. Here, the order and timing of conformational events underpinning the aa-tRNA selection process were investigated from multiple structural perspectives using single-molecule fluorescence resonance energy transfer (smFRET). The time resolution of these measurements was extended to 2.5 and 10ms, a 10–50-fold improvement over previous studies. The data obtained reveal that aa-tRNA undergoes fast conformational sampling within the A site, both before and after GTP hydrolysis. This suggests that the alignment of aa-tRNA with respect to structural elements required for irreversible GTP hydrolysis and peptide bond formation plays a key role in the fidelity mechanism. These observations provide direct evidence that the selection process is governed by motions of aa-tRNA within the A site, adding new insights into the physical framework that helps explain how the rates of GTP hydrolysis and peptide bond formation are controlled by the mRNA codon and other fidelity determinants within the system.
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