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Comparative modeling of class 1 lysyl tRNA synthetase from *Treponema pallidum*

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Abstract:

Lysyl tRNA synthetases facilitate amino acylation and play a crucial role in the essential cellular process of translation. They are grouped into two distinct classes (class I and class II). Class I lysyl tRNA synthetase is considered as a drug target for syphilis caused by *Treponema pallidum*. Comparative genome analysis shows the absence of its sequence homolog in eukaryotes. The structure of class I lysyl tRNA synthetase from *Treponema pallidum* is unknown and the difficulties in the *in vitro* culturing of *Treponema* makes it non-trivial. We used the structural template of class I lysyl tRNA synthetase from the archaea *Pyrococcus horikoshii* for modeling the *Treponema pallidum* lysyl tRNA synthetase structure. Thus, we propose the usefulness of the modeled class I lysyl tRNA synthetase for the design of suitable inhibitors towards the treatment of syphilis.

Keywords: *Treponema pallidum*; lysyl tRNA synthetase; modeller; syphilis; comparative modeling

Background:

Syphilis is a STD (sexually transmitted disease) caused by *Treponema pallidum*. The understanding of host-pathogen interactions remains unclear due to difficulty in culturing the organism *in vitro*. Syphilis is an exclusive human pathogen and its pathogenesis from animal study provides limited inference. **[1]** The availability of the complete genome sequence of *Treponema pallidum* provides ample opportunities for the computational analysis towards the identification of potential drug targets.

Lysyl tRNAs are essential for protein biosynthesis by ribosomal mRNA translation. They are synthesized by lysyl tRNA synthetases (a group of enzymes of two unrelated protein families, namely, class I and II). Known lysyl tRNA synthetases are class II in bacteria/eukaryotes and class I in archaea. A recent genomic analysis showed the presence of the archaeal type class-I lysyl tRNA synthetase in *Treponema pallidum and Borellia* species. **[2]** The difference between the lysyl tRNA synthetases of spirochetes and their hosts is for potential exploitation towards the development of anti-spirochete therapeutics. The X-ray crystal structure of class-I lysyl tRNA synthetase from the archaea *Pyrococcus horikoshii* is known. **[3]** Here, we use this structure as a template for the modeling of class-I lysyl tRNA synthetase from *Treponema pallidum*. We discuss the modeled structure as a potential drug target for syphilis caused by *Treponema pallidum*.

Methodology:

Lysyl tRNA synthetase sequence:

The protein sequence for class I lysyl tRNA synthetase of *Treponema pallidum* (O83650) was obtained from the SWISS PROT database.

Template selection:

The sequence was then searched against PDB (protein databank) protein sequences **[4]** using BLASTP **[5]** and a potential template structure (PDB-ID: 1IRX) was identified at an E-value (expect value) cut-off of 3e-110.

Molecular modeling:

An ensemble of 20 models for the class I lysyl tRNA synthetase from *Treponema pallidum* was generated using MODELLER by satisfaction of spatial restraints. **[6]**

Model evaluation:

The backbone of 20 models were overlapped well with the template structure and the most reliable structure was chosen based on least objective function value and stereo chemical quality of the models using the PROCHECK analysis. **[7]** In addition, the superimposition was also performed using the *SUPERPOSE command* in MODELLER and the RMSD (root mean square deviation) between predicted model and template is 0.7 angstrom. The predicted model quality assessment was checked using Ramachandran plot analysis for phi and psi torsion

angles. The analysis shows that 92.5 % of residues are found to be in the allowed region of the plot which is more than the average cut-off of 90% in most reliable models. **[8]** The bond lengths and bond angles analyses of the modeled structure satisfies the small molecule experimental data described by Kabsch *et al*.,. **[9]**

Utility of the study:

Here, we illustrate the potential use of molecular models towards the likely design of inhibitors for the class I tRNA synthetase enzyme from *Treponema pallidum*. The study is highly pertinent where the difficulty of solving the structure of the protein is high (culturing of *Treponema pallidum* is difficult in this case).

Conclusion:

A molecular model of the class I lysyl tRNA synthetase from *Treponema pallidum* is documented in this study. The model is believed to provide valuable insights towards the design of an inhibitor for class I lysyl tRNA synthetase for the treatment of syphilis. However, further computational docking and high throughput screening experiments are required in detail for extracting more useful information.

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