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RESEARCH ARTICLE

STRUCTURAL INSIGHTS OF CELL-CELL COMMUNICATION AUTOINDUCER-2 KINASE (LSRK) MODEL FROM *SALMONELLA TYPHI*

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ABSTRACT

Salmonella typhi utilize inter and intra species communication via the process of cell-cell communication, which use to regulate population density with small, diffusible signaling molecules as communication intermediary called Autoinducers-2 (AI-2). Lsrk is the kinase phosphorylate AI-2, be capable to simulate the *lsr* operon. On the other hand, a solved structure of LsrK from *Salmonella typhi* is not available on Protein Data Bank. For that reason, we modelled and validated LsrK through online servers. Secondary structural insights were discussed. These findings provide new knowledge to molecular understanding of Autoinducer-2 kinase within *Salmonella typhi*.

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INTRODUCTION

Several pathogenic bacteria including *Salmonella typhi* utilize inter and intra species communication through Quorum Sensing (QS) system, use to regulate population density (Bassler, 1999; Miller and Bassler, 2001; Ahmer, 2004) with small diffusible signaling molecules as communication mediator called Autoinducers-2 (AI-2) (Beeston and Surette, 2002). AI-2 is produced by LuxS (Taga *et al*., 2003; Xavier *et al*., 2003) and LsrB carries the AI-2 to cells through ABDC cassette (Taga *et al*., 2001). LsrK catalyzes the phosphorylation of AI-2 to phospho-AI-2 (Taga *et al*., 2003; Xavier and Bassler, 2005), which subsequently inactivates the transcriptional regulator LsrR and leads to the transcription of the *lsr* operon (Xue *et al*., 2009). These phospho-AI-2 ring-open form of (S)-4,5-dihydroxypentane-2,3-dione (DPD), which is the pioneer to all AI-2 signaling molecules, at the C5 position and supports to bind LsrR (Xavier *et al*., 2007). LsrE, LsrF and LsrG also involved to control *lsr* operon (Xavier and Bassler, 2005). This phosphorylation induced by LsrK in *salmonella spp* plays a major role in cell density capable to produce Biofilm (Xavier and Bassler, 2005). To understand more about the molecular functions and structural insights were more useful in drug development against typhoid fever and other systematic diseases due to Biofilm formation caused by *S.typhi.*

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MATERIALS AND METHODS

Target sequence Analysis

The amino acid sequence of *Salmonella typhi* LsrK was obtained from Uniprot KB (Apweiler *et al*., 2004) (Accession number: Q8Z2X3).In order to find the structural similarity PSI-BLAST was carried out through BLASTP (Altschul *et al*., 1990) against Protein Data Bank proteins. The secondary structure was analyzed by PREDATOR (Frishman and Argos, 1996), PHD (Rost and Sander, 1993), and GOR4 (Pirovano and Heringa, 2010).

D structure modeling

The structure and function of proteins are determined by their amino acid sequences, and the 3-D structure prediction still remains a significant challenge, with a great command for high resolution structure prediction methods. In this contest with the result of BLAST search the retrieved sequence was subjected to SWISS-MODEL (Schwede *et al*., 2003), I-TASSER (Zhang, 2008) and ROBETTA (Kim *et al*., 2004).

Structure validation and analysis

The modelled structures were subjected to PROCHECK (Laskowski *et al*., 1996), Verify3D (Bowie *et al*., 1991) and ERRAT (Colovos and Yeates, 1993) from SAVES server for validation. The validated 3D model structure insights were analyzed through PDBsum (Laskowskia, 2001). This model submitted to Protein Model Data Base (Castrignanò *et al*., 2006) for further handling.

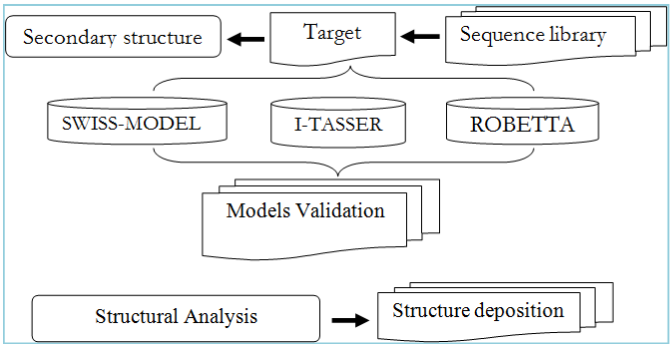

Figure 1. Work flow

RESULTS AND DISCUSSION

Sequence retrieval and similarity search

In order to find the structural similarity, PSI-BLAST was carried out through BLASTP against Protein Data Bank proteins. First five Hits of PSI-BLAST based on the sequence was shown in Table 1.

Table 1. Best five Hits obtained by PSI-BLAST for LsrK (Uniprot ID: Q8Z2X3)

S.No.	Accession number	Identity	Query cover	E-Value
1.	2ZF5	26%	88%	8e-31
2.	3EZW	27%	90%	7e-29
3.	1GLA	27%	90%	3e-28
4.	1BU6	27%	90%	3e-28
5.	1BWF	27%	90%	8e-28

Secondary structure prediction

The secondary structure prediction result has showed that Alpha helix dominated (≥38%) among the secondary structure elements. Then followed by the Random coil (≥37%) and extended strand (≥18%). The details were shown in Table 2.

Table 2. Details of secondary structure elements of LsrK

Secondary Structure	PREDATOR (%)	PHD (%)	GOR4 (%)
Alpha helix	38.8	50.19	43.58
Extended strand	12.45	12.26	18.11
Random coil	48.68	37.55	38.30

Structure modeling and Validation

LsrK model was generated based on the crystal structure of glycerol kinase from *Cellulomonas sp*. NT3060 (PDB ID: 2D4W) chain A with sequence similarity of 25.67% was selected as highest quality template in SWISS MODEL (Homology modelling). The global and per-residue model quality has been assessed using the QMEAN (Benkert *et al*., 2011) score is -4.79, Figure 2. Predicted local similarity with target and templates were shown in Figure 3.

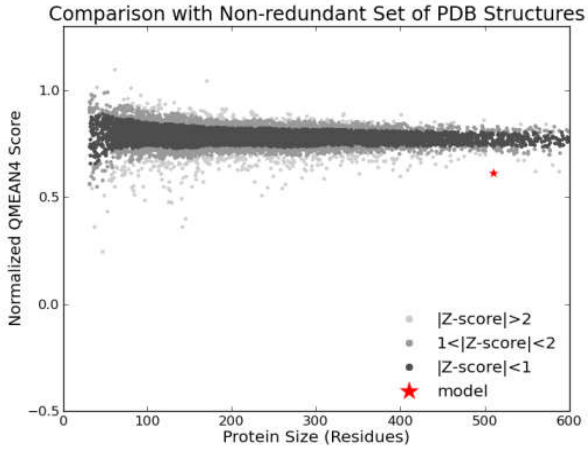

Figure 2. Predicted global and per-residue model quality has been assessed using the QMEAN with Non redundant set of PDB structures

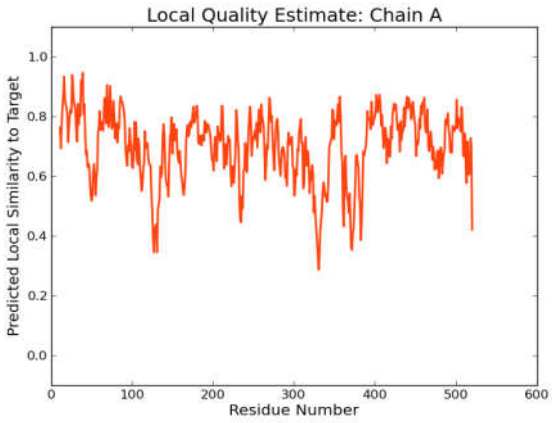

Figure 3. Predicted local similarity with the target and templates with the Range of 11-520

I-TASSER builds the whole structures by *ab initio* modelling and highest Z-score 3.94 was selected for threading program and C-score was 0.34. ROBETTA provides the modeled structures fully automated and evaluated through CAMEO by both *ab initio* and comparative methods. LsrK models were validated through PROCHECK, ERRAT and ROBETTA, particulars shown in Table 3. Model from ROBETTA shows 90.7% of the residues in the most favoured region, 08.0 % in the allowed region, 0.9% in the generously allowed region and 0.4% in disallowed regions. Validation through Verify3D and ERRAT also shows ROBETTA structure was more reliable with score of 89.62% and 93.94.Validated Structure and Ramachandran plot were shown in Figure 4 and Figure 5 respectively.

Table 4. LsrK Modelled structure validation results

Validation	Swiss-model	I-Tasser	Robetta
PROCHECK : Ramachandran Plot			
Most favoured regions	87.4%	73.5%	90.7%
Additional allowed regions	09.7%	22.2%	08.0 %
Generously allowed regions	02.0%	03.0%	00.9%
Disallowed regions	00.9%	01.3%	00.4%
Verify3D	77.06%	86.04%	89.62%
ERRAT Overall quality factor	88.84	93.67	93.94

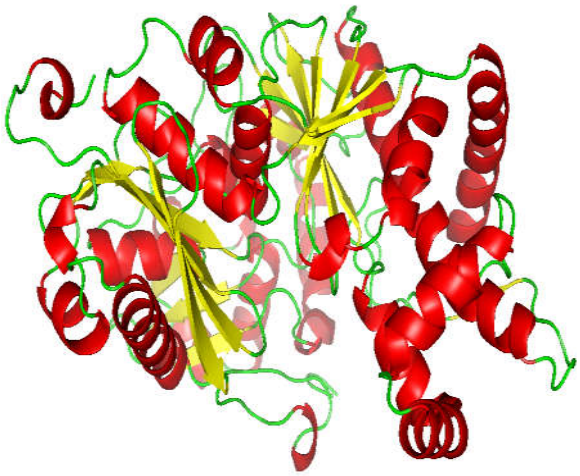

Figure 4. LsrK Modelled structure. Helixes were represented as red colour, sheets in yellow colour and Loop in Green colour

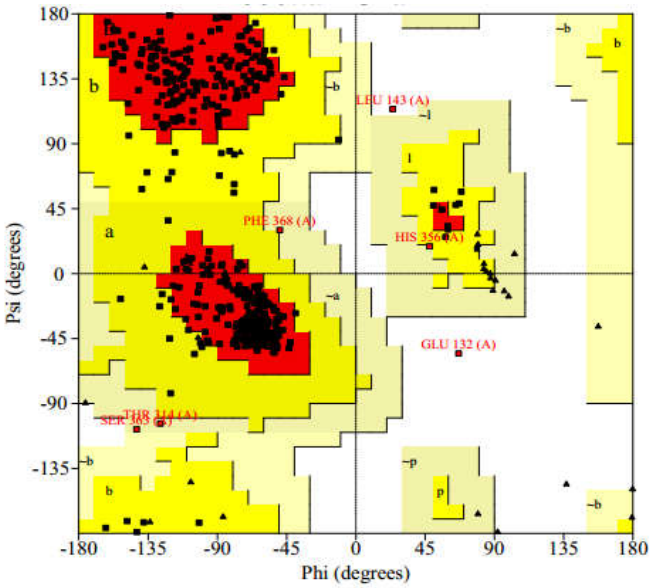

Figure 5. Ramachandran Plot for the modeled LsrK, red, yellow and white regions represent the favoured, allowed and the disallowed regions respectively

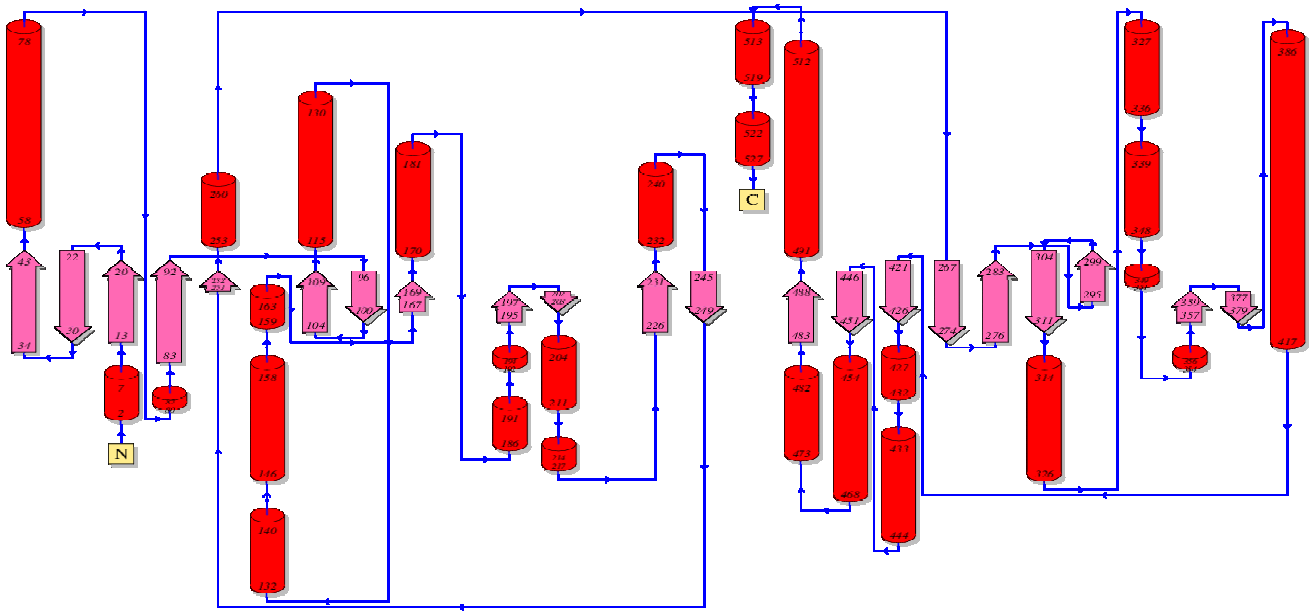

Figure 5. Secondary structure insights of LsrK. Pink colour represent the helix and red colour shows the helix

Structure analysis

In order to find out the structural insights, LsrK validated structure was subjected to PDBsum server. PDB ID: K796 was generated with PDBsum page generation service. Secondary structure was analyzed from N- terminal to C- terminal shown in Figure 5. The modeled 3-D structure was submitted to Protein Model Data Base (ID: PM0081030) for further studies.

Conclusion

LsrK is one of the key components in *lsr* operon of *Salmonella typhi* Quorum sensing system. The structural aspects of LsrK plays a crucial role in understanding the molecular level mechanism of cell to cell communication in *S.typhi*. The comparative analysis of secondary structure analysis, 3-D modelling and structural insights put forward to LsrK can be a good target in computational biology. It also gives support researchers experimentally determine the structure.

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