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Computational Modelling of LdcA and LtgD from Neisseria gonorrhoeae and analysing their interactions with novel small molecule inhibitors: a computational drug discovery approach

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Author(s)

Ravi Kant, n/a

Senior Research Fellow

Dr.B.R. Ambedkar Centre for Biomedical Research (ACBR), University of Delhi, New Delhi (India)

Hannah Tilford, n/a

Research Fellow

1Neisseria Research Group, Molecular Microbiology, School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, England, SO16 6YD

James Ng, n/a

Researcher

1Neisseria Research Group, Molecular Microbiology, School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, England, SO16 6YD

Gwennan Rucinski, n/a

Researcher

1Neisseria Research Group, Molecular Microbiology, School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, England, SO16 6YD

Joshua Watkins, n/a

Researcher

1Neisseria Research Group, Molecular Microbiology, School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, England, SO16 6YD

Tigran Abramyan, n/a

Researcher

717 Market Street, Suite 800, San Francisco, CA 94103, USA

Stephanie Contreras, n/a

Researcher

717 Market Street, Suite 800, San Francisco, CA 94103, USA

Alejandra Vera, n/a

Researcher

4Escuela de MedicinaVeterinaria, Facultad de Ciencias de la Vida, Universidad Andres Bello, 7100 Talcahuano, Chile

Myron Christodoulides, n/a

Professor & Section Head

Southampton General Hospital, University of Southampton, England

Background

Neisseria gonorrhoeae (Ng)-LdcA and Ng-LtgD are indispensable enzymes that are mainly responsible for converting cell wall tetrapeptide-stem peptidoglycan to release tripeptide-stem peptidoglycan. Both these are significant and promising targets for developing new antimicrobials and novel drug molecules. In the current study, we demonstrated that Ng-LdcA and Ng-LtgD could be targets to develop anti-gonococcal drugs. The study also confirms the biological activities of the lead compounds identified through virtual screening of libraries provide by Atomwise, with stability confirmed with Molecular Dynamics simulation studies.

Aim/Methods

Since the crystal structure of LdcA and LtgD for Neisseria gonorrhoeae was not available, we generated the homology model using various authenticated web servers. The templates to generate the models for both the proteins were selected based on the query coverage and percentage similarity score, and 5Z01 (native E.coli structure for LdcA) and 1D0K (native E.coli structure for LtgD) were used. We identified the ligand binding active sites in the modelled protein structures and characterized the models using a conventional drug discovery pipeline. Thus, we provide data on MIC and MBC values, toxicity and other biological parameters.

Results

The best homology model generated was selected based on the ERRAT and PDBsum scores, and validation of the selected model by Ramachandran plot revealed that 90%of the residues fall in the most favored region. Root-mean-squared deviation (RMSD) of 1.20 A0was calculated by superimposition of query and template structures. Quality factor of 84% for the protein models was obtained using ERRAT. Six potential lead compounds were identified through a high-throughput virtual screening process. These ligand molecules were subjected to energy minimization and were docked to the target proteins to access their binding affinities and docking scores. The six lead compounds showed high efficacy in killing MDR gonococci in vitro.

Conclusions

In this study, we have characterized two gonococcal drug targets and identified the potential compounds that interact with the active site of LdcA and LtgD proteins, opening new avenues for the development of new anti-gonococcal drugs.