Mycobacterial Diseases
ISSN: 2161-1068

Saravanan and Patra, Mycobact Dis 2016, 6:1
DOI: 10.4172/2161-1068.1000204

Short Communication open access journal

Rv3802c in Tuberculosis Therapeutics

Parameswaran Saravanan and Sanjukta Patra*

Department of Biotechnology, Indian Institute of Technology Guwahati, Guwahati, Assam, India

***Corresponding author:** Patra S, Department of Biotechnology, Indian Institute of Technology, Guwahati - 781039, Assam, India, Tel: 91-361-2582213; Fax 91-361-2582249; E-mail: sanjukta@iitg.ernet.in

Rec date: February 29, 2016; **Acc date**: April 20, 2016; **Pub date**: April 25, 2016

Importance of Rv3802c in the Context of Tuberculosis Therapeutics

The recent upsurge of life-threatening multidrug- and extreme drug- resistant tuberculosis along with HIV co-infection urge the need of new drug targets and drugs to cripple the survival and infection of *Mycobacterium tuberculosis* [1-5]. The current scenario of tuberculosis might be dealt by targeting pathogen's enzymes that participate in both cell wall and lipid metabolism [6-8].

Rv3802c is such a drug target which gained importance due to its genetic location in a mycolic acid synthesis proved essentiality from mutagenesis experiments [9]. Conditional disruptions of MSMEG_6394, functional homolog of Rv3802c in *M. smegmatis* lead to loss of cell wall integrity and internal structure of cell. Recent research effort revealed that tetrahydrolipstatin, a human lipase inhibitor binds irreversibly to both MSMEG_6394 and Rv3802c and exhibting antitubercular activity [10,11]. All these evidences point to the suitability of Rv3802c as promising drug target.

Methodology

Our current study begins with the 3D structure prediction of Rv3802c by utilizing the experimental structure of MSMEG_6394 of *M. smegmatis* (PDB Id: 3AJA, chain A; 2.9 Å) with bound inhibitor tetrahydrolipstatin with the help of Modeller 9v7. Stepwise similarity-based virtual screening was the method of choice to identify potential inhibitors against Rv3802c.

This screening was carried out with AutoDock4.2 using lamarckian genetic algorithm with AutoDock. Lipases Rv0183 and Rv3802c were chosen as drug targets for multi-targeting strategy which are involved in the pathogen's lipid and cell wall metabolism respectively [12,13]. Contact footprinting studies were carried out with AuPosSOM to design effective potential dual inhibitors against Rv0183 and Rv3802c. The detailed methodology could be found in our published research work [14,15].

Our Attempt to Target Rv3802c for Drug Discovery

Sequence analysis revealed that Rv3802c has no sequence homolog in human. Sequence analysis also identified the conserved "nucleophilic elbow" (Gly-Phe-Ser-Gln-Gly; Gly173-Gly177) and other structurally and functionally important amino acids. Homology modeling confirmed that Rv3802c is a member of cutinase family of α/β hydrolases with six-stranded parallel beta sheets covered by helices and "lid" sits atop of active site (Figure 1).

Apart from conserved catalytic residues (Ser175, Asp268 and His299), strict conservation was observed at the active site namely Trp84, Glu85, Ser86, Thr127, Ala128, Gln129, Met140, Phe174 and Ala300 which might be involved in substrate binding and recognition. The comparison of Rv3802c model with human MGL [PDB Id: 3HJU, chain A] and cutinases [PDB id: 1CEX, chain A] identified Thr83 and Gln176 as the putative oxyanion hole residues which might be involved in the substrate binding and in stabilizing the tetrahedral intermediate for catalysis.

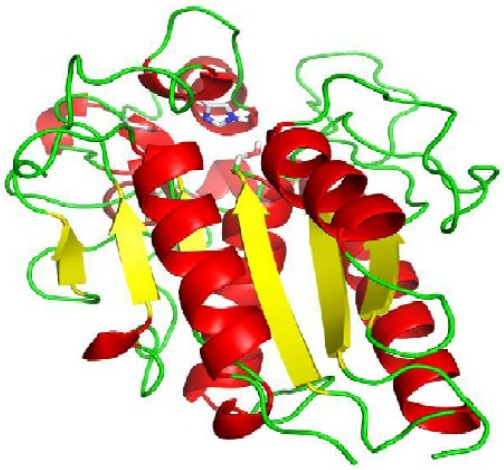

Figure 1: 3D predicted structure of Rv3802c with catalytic residues in stick representation.

Virtual screening followed by comparative docking studies of Rv3802c with its human monoglyceride lipase has been carried out to identify mycobacteria-specific potential inhibitors.

Two diverse molecules, ZINC43860875 and ZINC28262919 were identified as potential mycobacteria-specific inhibitor against RV3802c with difference in predicted free energy of binding (ΔG) of -3.78 and -2.60 respectively. Multi-targeting strategy is one among the effective approach to combat tuberculosis with minimal adverse effects.

With this strategy it is also harder for *Mycobacterium tuberculosis* to survive and evolve into more drug-resistance strains. Potential dual inhibitors of tetrahydropyranyl and dibenzofuranone derivatives were discovered targeting respective substrate binding pocket of Rv0183 and Rv3802c (Figure 2).

Molecule ZINC43860875 is the best hit with ΔG of -10.80 and -10.97 kcal/mol against Rv0183 and Rv3802c respectively. Based on contact footprinting studies, several molecules were designed with better ΔG through modification of functional groups that favor van der Waals and ionic interactions. The current study paves way towards

design and development of new multi-target inhibitors to combat tuberculosis.

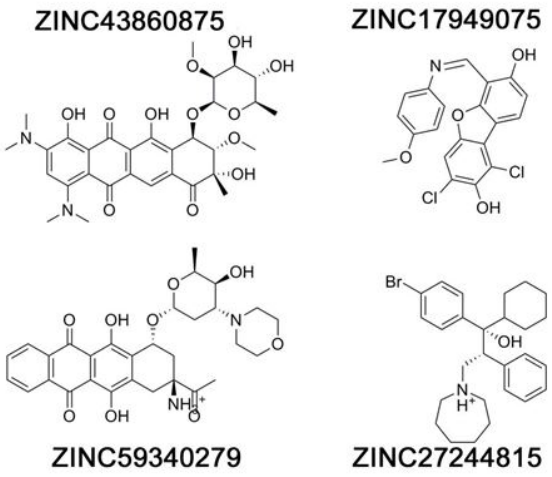

Figure 2: Discovered dual inhibitors of Rv0183 and Rv3802c.

Concluding Remarks

Targeting cell wall and lipid metabolism of *M. tuberculosis* simultaneously could be promising arsenal to combat tuberculosis. The therapeutic utility of the identified potential multi-target inhibitors against Rv0183 and Rv3802c could be validated by the TB research community. Knowledge about Rv3802c of *M. tuberculosis* can open a new horizon towards understanding cutinases and PE-PPE enzymes of the pathogen as well as for tuberculosis therapeutics [16,17].

On the other hand, structure activity relationship of identified potential inhibitors might provide insight into the discovery of reversible inhibitors for lipases, which is an emerging area in biotechnology. Research on Rv3802c, its potential inhibitors and synergistic effects with DOTS (directly observed treatment, short-course) therapy needs to be intensified to pave a way to eradicate tuberculosis [18].

References

1. World Health Organization (2015) Global tuberculosis report 2015. World Health Organization, Geneva.
2. Russell DG, Barry CE, Flynn JL (2010) Tuberculosis, what we don't know can, and does, hurt us. Science 328: 852-856.
3. Berry M, Kon OM (2009) Multidrug- and extensively drug-resistant tuberculosis: an emerging threat. Eur Respir Rev 18: 195-197.
4. Janbaz KH, Qadir MI, Ahmad B, Sarwar A, Yaqoob N, et al. (2012) Tuberculosis-burning issues, Multidrug resistance and HIV-coinfection. Crit Rev Microbiol 38: 267-275.
5. Mdluli K, Takushi K, Anna U (2015) The tuberculosis drug discovery and development pipeline and emerging drug targets. Cold Spring Harbor perspectives in medicine.
6. Wenk MR (2005) The emerging field of lipidomics. Nat Rev Drug Discov 4: 594-610.
7. Cotes K, Bakala N'goma JC, Dhouib R, Douchet I, Maurin D, et al. (2008) Lipolytic ezymes in Mycobacterium tuberculosis. Appl Microbiol Biotechnol 78: 741-749.
8. Singh G, Jadeja D, Kaur J (2010) Lipid hydrolizing enzymes in virulence, Mycobacterium tuberculosis as a model system Crit Rev Microbiol 36: 259-269.
9. Parker SK, Barkley RM, Rino JG, Vasil ML (2009) Mycobacterium tuberculosis Rv3802c encodes a phospholipase/thioesterase and Is inhibited by the antimycobacterial agent tetrahydrolipstatin. PLoS One 4: e4281.
10. Crellin PK, Vivian JP, Scoble J, Chow FM, West NP, et al. (2010) Tetrahydrolipstatin inhibition, functional analyses, and three-dimensional structure of a lipase essential for mycobacterial viability. J Biol Chem 285: 30050– 30060.
11. West NP, Cergol KM, Xue M, Randall EJ, Britton WJ, et al. (2011) Inhibitors of an essential mycobacterial cell wall lipase Rv3802c as tuberculosis drug leads. Chem Commun Camb 47: 5166-5168.
12. Côtes K, Dhouib R, Douchet I, Chahinian H, de Caro A, et al. (2011) Characterization of an exported monoglyceride lipase from Mycobacterium tuberculosis possibly involved in the metabolism of host cell membrane lipids. Biochem J 408: 417-427.
13. Dhouib R, Laval F, Carrière F, Daffé M, Canaan S (2010) A monoacylglycerol lipase from Mycobacterium smegmatis involved in bacterial cell interaction. J Bacteriol 192: 4776-4785.
14. Saravanan P, Dubey VK, Patra S (2012) Potential selective inhibitors against rv0183 of mycobacterium tuberculosis targeting host lipid metabolism. Chem Biol Drug Des 79: 1056-1062.
15. Saravanan P, Avinash H, Dubey VK, Patra S (2012) Targeting essential cell wall lipase Rv3802c for potential therapeutics against tuberculosis. J Mol Graph Model 38: 235-242.
16. West NP, Chow FM, Randall EJ, Wu J, Chen J, et al. (2009) Cutinase-like proteins of Mycobacterium tuberculosis, characterization of their variable enzymatic functions and active site identification. FASEB J 23: 1694-1704.
17. Adindla S, Guruprasad L (2003) Sequence analysis corresponding to the PPE and PE proteins in Mycobacterium tuberculosis and other genomes. J Biosci 28: 169-179.
18. Frieden TR, Munsiff SS (2005) The DOTS strategy for controlling the global tuberculosis epidemic. Clin Chest Med 26: 197-205.