Gauri Garg Dhingra, J Appl Bioinforma Comput Biol 2019, Volume: 8
DOI: 10.4172/2329-9533-C1-007

International Conference on
BIOINFORMATICS & SYSTEM BIOLOGY
&
3rd International Conference on
SURGERY & ANAESTHESIA
March 20-21, 2019 | Singapore City, Singapore

**Gauri Garg Dhingra**
Kirori Mal College, University of Delhi, India

## Comparative interactomic analysis to decipher the role of genes involved in rifamycin production in genetically modified Amycolatopsis mediterranei S699

The development of rifampicin-resistance strains of *Mycobacterium tuberculosis* (Mtb) has resulted in imperative need for development of analogs of rifamycin. The endless efforts by genetic manipulation of rifamycin biosynthetic gene cluster of *Amycolatopsis mediterranei* S699 has led to discovery of a new anti-tuberculosis drug, 24-desmethylrifamycin B, more effective against rifampicin-resistance strains of Mtb. The mutant strain *A. mediterranei* DCO#34 had undergone substitution of acyltransferase domain of module 6 of rifamycin polyketide synthase with that of module 2 of rapamycin polyketide synthase. Genetic manipulation resulted in reduced yield of analog ~20mg/litre as compared to 50mg/l yield by the wild type strain. In order to decipher the impact of domain swapping on rifamycin/analog production, and the intricate make-up and clinical importance of rifamycin brought up the idea to study the regulation of rifamycin biosynthesis, state-of-the-art protein expression methodologies were carried out. Whole cell proteins were extracted and digested with trypsin. The resulting peptides were analysed by nLC-MS/MS (Thermo Scientific Q Exactive HF Mass Spectrometer in conjunction with Dionex Ultimate 3000 UPLC). The emerging technique of protein-protein interaction approach was employed to determine the relation and interaction between various structural and regulatory genes involved in Rifamycin biosynthetic gene cluster. Comparing the relative abundance expression values for the wild type and mutant strain revealed the altered expression of structural genes, rifC-I (down-regulated), rifR, rifZ and other regulatory genes (up-regulated), that might have resulted from modified rifamycin polyketide backbone by domain swapping. Reduced yield of analog by the mutant strain is the outcome of subsequent down-regulation of structural genes due to absence of rifP transport gene. The repressed rifamycin transportation outside the cell further activated negative feedback mechanism. Complete protein profile of the rifamycin B producer *A. mediterranei* S699 revealed intricate mechanisms of rifamycin biosynthesis and its regulation.

### Biography

Gauri Garg Dhingra is currently working as Assistant Professor Zoology since 2006 at Kirori Mal College, University of Delhi, India. She completed her PhD on the topic "Manipulations of Rifamycin Gene Cluster in *A. mediterranei* and its partial characterization in *A. rifamycinica* and Post-Doctorate on "Comparative Genomics" under the supervision of Prof. Rup Lal, Department of Zoology, and University of Delhi, India.

gaurigargdhingra@gmail.com

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