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Genetic Manipulation of Rifamycin Polyketide Biosynthetic Gene Cluster of *Amycolatopsis mediterranei* S699 for production of Rifamycin B analogs

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Rifamycin B is produced by an actinobacterium *Amycolatopsis mediterranei* S699. Semi synthetic derivatives of rifamycin B (rifampicin or rifampin, rifabutin, rifaximine, rifapentine and rifalazil) are used for the treatment of tuberculosis (TB), leprosy and AIDS related mycobacterial infections. But none of these is effective against Multi Drug Resistant-TB (MDR-TB). This raised the need to develop novel rifamycin B analogs and corresponding derivatives to combat MDR infections. However, due to the chemical complexity of the rifamycin B further chemical modifications are not possible. An alternative approach to modify the rifamycin B backbone is combinatorial biosynthesis by manipulation of the Rifamycin Polyketide Synthase (*rif*PKS) gene cluster in the producer strain itself. Thus acyltransferase (AT) domain of the sixth module (AT6) of *rif*PKS (which adds propionate unit to the growing polyketide chain) was swapped with AT domain of the second module (AT2) of rapamycin PKS (*rap*PKS) (adds acetate unit) in *A. mediterranei* S699. The resulting mutant produced 24-desmethylrifamycin B lacking pendant methyl group at C-33 of the rifamycin skeletal structure. It was confirmed using NMR and LC-MS studies. The analog was further converted to 24-desmethylrifamycin S & 24-desmethylrifampicin that showed better antibacterial activity than rifampicin against MDR strains of *M. tuberculosis*. Based on this proof of concept further manipulations of other domains (AT5, AT7, AT8, DH9 & DH10) are being carried out for production of more rifamycin analogs for biological and pharmaceutical applications.

Biography

Priya Singh has obtained her Master's Degree in Zoology from Department of Zoology, University of Delhi. Presently working as a Junior Research Fellow in Molecular Biology Laboratory, Department of Zoology. Her doctoral research focusses on "Genetic manipulation of *Amycolatopsis mediterranei* S699 for production of Rifamycin analogs".

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