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Bioinformatic analysis of bacterial DNA-dependent RNA polymerase identifies new targets for selective inhibition

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Tuberculosis, an infection caused by *Mycobacterium tuberculosis*, was declared a re-emerging infectious disease by the World Health Organization with 1.7 million deaths in 2009. Rifampicins are key components of anti-tuberculosis therapy that selectively bind to RNA polymerase subunit beta (RNAPbeta) and block the path of elongating RNA. However, the clinical efficiency of rifamycins is threatened by the emergence of drug-resistant strains with mutations in the corresponding binding site that decrease binding affinity. Therefore, it is necessary to search for new drug-targets and more efficient antibacterial agents to combat the emergence of drug resistance.

Bioinformatic analysis was used to study bacterial RNAPbeta to identify new target sites for selective inhibition. PSI-BLAST was used to collect sequences homologous to RNAPbeta of *Mycobacterium tuberculosis*. A non-redundant set of 156 sequences of bacterial RNAPbeta was identified together with 43 sequences referring to eukaryote subunits RPA2/B2/C2 of RNAPs I, II and III. Structural alignment of available PDBs representing different taxonomic groups was built with Matt and used to create a final structure-guided sequence alignment with T-Coffee. Bioinformatic analysis was used to identify subfamily-specific positions (SSPs) – conserved within bacterial and eukaryotic RNAPs, but different between them. 55 positions were identified as highly significant SSPs while 96 positions were highly conserved in the entire RNAP family. CASTp server was used to identify pockets and cavities within the structure of RNAPbeta. 58 pockets that could potentially bind xenobiotic substrates were identified to contain SSP residues and ranked according to their specificity. Two highly ranked pockets were previously known as binding targets for selective inhibitors. One of them selectively binds rifampicins in bacteria but shows no affinity in corresponding human enzymes. Another pocket contains specific positions that form a so called “switch region” responsible for opening and closing of the RNAP active center cleft during transcription initiation. It has been recently identified as specific target of antibacterial drugs myxopyronin, corallopyronin, and ripostatin.

Bioinformatic analysis was used to identify perspective inhibitor binding sites within RNAP beta subunits that are highly conserved within bacteria and different compared to human homologs, permitting for both broad-spectrum activity and therapeutic selectivity. Based on these results we suggest that patterns of subfamily-specific positions should be further explored to identify novel binding targets in pathogenic strains.