Proteome scale comparative modeling for conserved drug and vaccine targets identification in Salmonella serovers

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Abstract

Despite extensive surveillance, foodborne Salmonella enterica infections continue to cause a significant burden on public health systems worldwide. Salmonella is a food-borne pathogen that leads to substantial illness worldwide. The clinical syndromes associated with Salmonella infection are enteric (typhoid) fever and gastroenteritis, in healthy humans. Typhoid fever is caused by host-adapted S. Typhi and S. Paratyphi. Gastroenteritis is caused by serovars usually referred to as non-typhoidal Salmonellae (NTS). In this work, we used a Modelome approach for the proteome of Salmonella Typhi species. This served to bridge the gap between raw genomic information and the identification of good therapeutic targets based on the three-dimensional structures. The novelty of this strategy relies in using the structural information from high-throughput comparative modeling for large-scale proteomics data for inhibitor identification, potentially leading to the discovery of compounds able to prevent bacterial growth. The proteomes of 3 Salmonella typhimurium strains were modeled (pan-modelome) using the MHOLline workflow. Intra-species conserved proteome (core-modelome) with adequate 3D models was further filtered for their essential nature for the bacteria, using the database of essential genes (DEG). This led to the identification of essential bacterial proteins without homologs in the host proteomes. Furthermore, we investigated a set of essential host homologs proteins. We observed residues of the predicted bacterial protein cavities that are completely different from the ones found in the homologous domains, and therefore could be specifically targeted. By applying this computational strategy, we provide a final list of predicted putative targets in Salmonella typhimurium which were common to all the three serovars. They could provide an insight into designing of peptide vaccines, and identification of lead, natural and drug-like compounds that bind to these proteins. We propose that some of these proteins can be selectively targeted using structure-based drug design approaches (SBDD). Our results facilitate

the selection of Salmoenlla tyhpimurium putative proteins for developing broad-spectrum novel drugs and vaccines. A few of the targets identified here have been validated in other microorganisms, suggesting that our modelome strategy is effective and can also be applicable to other pathogens.

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