Delving into the characteristic features of "menace" *Mycobacterium Tuberculosis* Homologs: A structural dynamics and proteomics perspectives

Adewumi T. A.[a], Ramharack P.[a], S. Soremekun O.[a], Soliman M. E. S.[a]

[a]Molecular Bio-computation and Drug Design Laboratory, School of Health Sciences, University of KwaZulu-Natal, Westville Campus, Durban 4001, South Africa

Abstract

The global increase in the morbidity/mortality rate of Mycobacterial infections, predominantly renascent tuberculosis, leprosy, and Buruli ulcers have become worrisome over the years. More challenging is the incidence of resistance mediated by mutant *Mycobacterium strains* against front-line antitubercular drugs. Homologous to all *Mycobacteria* species is the GlcNAc-6-phosphate deacetylase (NagA) which catalyzes essential amino sugars synthesis required for cell wall architecture, hence, metamorphosing into an important pharmacological target for curtailing virulence and drug-resistance. This study used integrated bioinformatics methods, MD simulations, and *DynaMut* and *PolyPhen2* to; explore unique features, monitor dynamics, and analyze the functional impact of non-synonymous single-nucleotide polymorphisms of the six NagA of most ruinous Mycobacterium species; *tuberculosis* (*Mtb*), *smegmatis* (*MS*), *marinum* (*MM*), *ulcerans*, *africanum*, and *microti respectively*. This approach is essential for multi-targeting and could result in the identification of potential polypharmacological antitubercular compounds. Comparative sequential analyses revealed ≤ 50% of the overall structure, including the catalytic Asp267 and reactive Cys131, remained conserved. Interestingly, *MS*-NagA and *MM*-NagA possess unique hydrophobic isoleucine (Ile) residues at their active sites in contrast to leucine (Leu) found in other variants. More so, unique to the active sites of the NagA is a 'subunit loop' that covers the active site; probably crucial in binding (entry and exit) mechanisms of targeted NagA inhibitors. Relatively, nsSNP mutations

exerted a destabilizing effect on the native NagA conformation. Structural and dynamical insights provided, basically pin-pointed the “Achilles’ heel” explorable for the rational drug design of target-specific ‘NagA’ inhibitors potent against a wide range of mycobacterial diseases.

Keywords: Mycobacterial infections, GlcNAc-6-phosphate deacetylase protein, bioinformatics tools, peptidoglycan, Molecular dynamics simulations, mutation