NOVEL TARGET IN STAPHYLOCOCCUS AUREUS

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Staphylococcus aureus (S. aureus), a representative opportunistic pathogen, catabolizes mannitol using mannitol 1-phosphatede hydrogenase (M1PDH) that mediates the NAD(P)/NAD(P)H dependent reversible conversion of mannitol 1-phosphate to fructose 6-phosphate. M1PDH is indispensable for the survival of S. aureus under stress environment, and can be a potential target for antibiotics to combat infectious diseases caused by this pathogen. Therefore, studies of structure and reaction mechanism of M1PDH are expected to not only uncover its role in bacterial energy metabolism, but also facilitate the structure-based design of inhibitors for the development of new antibiotics. We solved the crystal structure of S. aureus M1PDH at 1.8Å resolution, and identified essential residues for the recognition of mannitol and phosphate moieties. In addition, we have discovered that the catalytic direction of mannitol 1-phosphate/fructose 6-phosphate by M1PDH potentially depends on the solute concentration in the environment, which might provide a clue to the mechanism of how M1PDH regulates osmotic stress response in this pathogen. Furthermore, we identified the virulent effect of M1PDH during infection and introduced a novel strategy to eliminate clinical methicillin resistant S. aureus on the understanding of reverting the mannitol-osmotic regulation. Our study provides the molecular basis for the substrate selectivity of M1PDH and a new opportunity for the development of antibiotics against S. aureus infection.

Keywords : Staphylococcus aureus, mannitol, mannitol 1-phosphate dehydrogenase, osmotic pressure