Abstract

Deciphering Anti-caries and Immunological Protective Effect of ComA Inhibitors in *Streptococcus mutans*

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*Streptococcus mutans* a Gram-positive facultative anaerobic bacterium is one among the 700 bacterial species, to exist in the human buccal cavity and cause dental caries. Quorum Sensing (QS), a cell-density dependent communication process that respond to the inter/intra-species signals and elicit responses to show behavioural changes in the bacteria to an aggressive forms. In accordance to this phenomenon, the *S. mutans* also harbors a Competence Stimulating Peptide (CSP)-mediated quorum-sensing, ComCDE (Two-component regulatory system) to regulate several virulence-associated traits that includes the formation of the oral biofilm (dental plaque), genetic competence and acidogenicity. The QS-mediated response of *S. mutans* adherence on tooth surface (dental plaque) imparts antibiotic resistance to the bacterium and further progresses to lead a chronic state, known as periodontitis. The QS signal, CSP, is known to be processed and matured by ComA eliciting QS response controlling various virulence factors such as genetic competence and biofilm formation. The key involvement of ComA in maturation and secretion of CSP made it as a favourable target for QS inhibition of *S. mutans*. In the present study, we have chosen ComA as QS target and used in silico docking analysis of ligand libraries with the PEP domain of ComA. 1,3-disubstituted ureas (ComAI inhibitors) were selected in terms of various parameters considered during the in silico analysis and thus synthesized and
evaluated for antibiofilm effect. Although, fluoride possess a good anti-caries activity but presence of high concentration (upto 1000 ppm) of fluoride in formulations and its inappropriate use has led to the development of fluorosis, especially in children and also development of fluoride resistant strains of *S. mutans*. Our results indicate the synergistic effect of ComAI inhibitors, in particular ComAI (3.75 μM) along with fluoride at a lower concentration of 31.25 ppm. The *in vivo* Wistar rat model corroborated with our *in vitro* data resulting in prevention of caries in rats. We also demonstrated the target specific mechanism of ComAI through qRT-PCR analysis of various genes under the QS circuit of *S. mutans*. To the best of our knowledge, this is the first report of target specific drug synthesis against ComA in QS system of *S. mutans*.