MOLECULAR MODELING OF THE STRUCTURAL BASIS OF SAL-B AS CYCLOOXYGENASE-2 INHIBITOR

Yayin Fang¹, Xinbin Gu² and William M. Southerland¹,³

¹Department of Biochemistry & Molecular Biology, ²Howard University College of Medicine, ³Department of Oral Diagnostics, Howard University College of Dentistry, Washington, D. C. 20059

Abstract: Every year, more than 55,000 Americans will develop cancer of the head and neck and expected 13,000 will die from the head and neck cancer. In addition, African-Americans suffer the highest incidence of head and neck cancer and have the lowest survival rate of any racial/ethnic group. Overexpression of cyclooxygenase-2 (COX-2) in oral mucosa has been associated with increased risk of head and neck squamous cell carcinoma (HNSCC). Despite overall survival rates of head and neck cancer have briefly improved in recent years, it remains an appealing strategy to develop effective, non-toxic and affordable novel pharmacological agents for preventing development of HNSCC and second primary HNSCC. Celecoxib is a nonsteroidal anti-inflammatory drug, which inhibits COX-2 but not COX-1. This selective COX-2 inhibitor holds promise as a cancer preventive agent. However the cardiotoxicity of celecoxib greatly limits its use in long-term chemoprevention and therapy. Recent studies have demonstrated that the Salvianolic acid B (Sal-B), a leading bioactive component of a well-known Chinese herbal medicine *Salvia miltiorrhiza* Bge, significantly decreased COX-2 expression in cultured HNSCC cells and in HNSCC cells isolated from tumor xenografts as well as Celecoxib did, showing promise as a COX-2 targeted anticancer agent for HNSCC prevention and treatment. In addition Sal-B and celecoxib combination shows promise on enhancing anticancer efficacy and reducing cardio-toxicity of celecoxib for HNSCC treatment and prevention. Molecular modeling has been carried out on 3D structures of COX-2 protein bound with substrate, arachidonic acid and inhibitor celecoxib. The comparison of protein complexes shown that celecoxib occupies the same binding site in the COX-2 as the substrate arachidonic acid does, indicating a competitive inhibition. Based on the fact that Sal-B inhibits Cox-2 similar to celecoxib, the possible binding Sal-B into COX-2 has been proposed. Structural analysis of the proposed structure shown that Sal-B not only is able to fit into the binding site of celecoxib but also can form more h-bonds with the protein, which often indicate a stronger interaction. These results match the experimental results of Sal-B as potential COX-2 targeted anticancer agent and are expected to lead to the modification of Sal-B and to develop more efficient COX-2 targeted therapy for drug resistant head and neck cancer.

Keywords: Salvianolic acid B; COX-2 targeted therapy, head and neck cancer therapy