ABSTRACT

THESIS TITLE: Studying the role of matrix metalloproteinases (MMPs) and their tissue inhibitors in gastric carcinoma under hyperglycemic condition

Submitted by: ABHISHEK CHATTERJEE **Index No.: 29/22/Life Sc./27**

Gastric cancer (GC) and diabetes are deleterious diseases, with hyperglycemia (HG) significantly contributing to cancer metastasis. HG dysregulates cancer cell metabolism, increases reactive oxygen species (ROS) production, and fosters a more aggressive cancer phenotype by affecting molecular pathways related to cell proliferation and metastasis. A major factor in metastasis is the upregulation of matrix metalloproteinase-9 (MMP-9) and subsequent downregulation of the tissue inhibitor of metalloproteinase-1 (TIMP-1). Therefore, targeting the MMP-9/TIMP-1 axis may serve as an effective treatment strategy for GC under hyperglycemia.

This thesis work is primarily focused on uncovering the signaling pathway responsible for HG-induced excess MMP-9 transcription. It has been observed that the AP-1 transcription factor produced by the MAPK signaling pathway plays a major role in regulating HG-induced excess MMP-9 transcription, while NF-κB signaling plays a basal role. The distal AP-1 binding site on the MMP-9 promoter is specifically responsible for HG-induced excess MMP-9 transcription. Targeting this AP-1 interaction could be a potential therapeutic strategy for GC-HG co-morbidity. In the quest for effective treatments, the potential of natural compounds such as melatonin and Shatavarin-IV are explored in mitigating HG-induced GC aggressiveness. Melatonin has been found to inhibit AGS cell proliferation in a dose-dependent manner by modulating MMP-9 and TIMP-1 expression. Additionally, it induced cell cycle arrest at the G0/G1 phase by inhibiting CDK-2 kinase activity, leading to reduced GC cell proliferation. Similarly, Shatavarin-IV, a steroidal saponin from *Asparagus racemosus*, exhibited strong anti-cancer properties under HG conditions. It significantly reduced AGS cell proliferation (IC_{50} = 2.463 μM), induced G0/G1 phase arrest, and promoted apoptotic cell death. Moreover, Shatavarin-IV also altered epithelial-mesenchymal transition (EMT) markers, downregulated MMP-9 expression, and enhanced TIMP-1 activity, effectively reducing cancer cell metastasis.

Altogether, the above findings highlight HG-induced MMP-9 activation as a key driver of GC progression and underscore the potential of natural compounds like melatonin and Shatavarin-IV as promising therapeutic agents. The ability of these compounds to regulate cell proliferation and metastasis under HG conditions provides a new avenue for the development of novel treatment for GC-HG co-morbidity.

02/04/25

DR. SNEHASIKTA SWARNAKAR
Ex. Chief Scientist, Ph.D. FNASc., FAScT
Head, Infectious Diseases & Immunology
Head, P&I Division, Professor, AcSIR
CSIR - India Institute of Chemical Biology
Jadavpur, Kolkata - 700 032, India

2/4/25

Dr. Sujoy K. Das, PhD
Principal Scientist
CSIR-Indian Institute of Chemical Biology
Jadavpur, Kolkata 700 032, India

Abhishek Chatterjee 02/04/25