Critical Role of OGT-mediated Novel NF-κB O-GlcNAcylation in Pancreatic Cancer

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Abstract ID 13965 Poster Board 436

Pancreatic ductal adenocarcinoma (PDAC) has one of the highest mortalities of all malignancies, with a mere 5-year survival of ~10%. However, the current first-line treatments have poor patient outcomes, highlighting the urgent need for innovative therapeutics. The nuclear factor κB (NF-κB) is a crucial transcription factor frequently activated constitutively in PDAC. It mediates the transcription of oncogenic and inflammatory genes that facilitate multiple PDAC phenotypes. Thus, a better understanding of the mechanistic underpinnings of NF-κB activation holds substantial promise in PDAC diagnosis and new therapeutics. The purpose of this study is to identify novel regulation of NF-κB, with the aim of providing new diagnostic and therapeutic strategies for PDAC. Here, we report protein O-GlcNAc transferase (OGT) - mediated NF-κB activation through novel serine O-GlcNAcylation of its p65 subunit. We show that overexpression of serine-to-alanine (S-A) mutant at the O-GlcNAcylation site impaired NF-κB nuclear translocation and transcriptional activity in PDAC cells. Moreover, these S-A p65 mutants downregulate NF-κB-target genes important to major cancer hallmarks and inhibit cellular proliferation, migration, and anchorage-independent growth of PDAC cells compared to WT-p65. Interestingly, this modification happens downstream of the inhibitor of NF-κB (IκBa) degradation. Collectively, we have identified novel OGT-mediated serine O-GlcNAcylation of NF-κB and determined its mechanistic and cellular function in driving PDAC phenotypes. Thus, our study holds great significance as it uncovers a potential strategy for effective therapeutics development for PDAC patients.