## Abstract:

Nuclear factor-kappaB (NF-kappaB) is constitutively activated in diverse human malignancies. The mucin 1 (MUC1) oncoprotein is overexpressed in human carcinomas and, like NF-kappaB, blocks cell death and induces transformation. The present studies show that MUC1 constitutively associates with NF-kappaB p65 in carcinoma cells. The MUC1 COOH-terminal subunit (MUC1-C) cytoplasmic domain binds directly to NF-kappaB p65 and, importantly, blocks the interaction between NF-kappaB p65 and its inhibitor IkappaBalpha. We show that NF-kappaB p65 and MUC1-C constitutively occupy the promoter of the Bcl-xL gene in carcinoma cells and that MUC1-C contributes to NF-kappaB-mediated transcriptional activation. Studies in nonmalignant epithelial cells show that MUC1-C interacts with NF-kappaB in the response to tumor necrosis factor-alpha stimulation. Moreover, tumor necrosis factor-alpha induces the recruitment of NF-kappaB p65-MUC1-C complexes to NF-kappaB target genes, including the promoter of the MUC1 gene itself. We also show that an inhibitor of MUC1-C oligomerization blocks the interaction with NF-kappaB p65 in vitro and in cells. The MUC1-C inhibitor decreases MUC1-C and NF-kappaB p65 promoter occupancy and expression of NF-kappaB target genes. These findings indicate that MUC1-C is a direct activator of NF-kappaB p65 and that an inhibitor of MUC1 function is effective in blocking activation of the NF-kappaB pathway.