

Abstract:

BACKGROUND: The mucin 1 (MUC1) heterodimeric oncoprotein is overexpressed in human prostate cancers with aggressive pathologic and clinical features. However, few insights are available regarding the functional role of MUC1 in prostate cancer. **METHODS:** Effects of MUC1-C on androgen receptor (AR) expression were determined by RT-PCR, immunoblotting and AR promoter activation. Coimmunoprecipitations, direct binding assays, and chromatin immunoprecipitation (ChIP) studies were performed to assess the interaction between MUC1-C and AR. Cells were analyzed for invasion, growth in androgen-depleted medium, and sensitivity to MUC1-C inhibitors. **RESULTS:** The present studies in androgen-dependent LNCaP and LAPC4 prostate cancer cells demonstrate that the oncogenic MUC1-C subunit suppresses AR expression. The results show that MUC1-C activates a posttranscriptional mechanism involving miR-135b-mediated downregulation of AR mRNA levels. The results further demonstrate that MUC1-C forms a complex with AR through a direct interaction between the MUC1-C cytoplasmic domain and the AR DNA-binding domain (DBD). In addition, MUC1-C associates with AR in a complex that occupies the PSA promoter. The interaction between MUC1-C and AR is associated with induction of the epithelial-mesenchymal transition (EMT) and increased invasion. MUC1-C also conferred growth in androgen-depleted medium and resistance to bicalutamide treatment. Moreover, expression of MUC1-C resulted in sensitivity to the MUC1-C inhibitor GO-203 with inhibition of growth in vitro. GO-203 treatment also inhibited growth of established tumor xenografts in nude mice. **CONCLUSIONS:** These findings indicate that MUC1-C suppresses AR expression in prostate cancer cells and confers a more aggressive androgen-independent phenotype that is sensitive to MUC1-C inhibition.