

Abstract:

Human prostate cancers are dependent on the androgen receptor for their progression. The MUC1 heterodimeric oncoprotein is aberrantly overexpressed in prostate cancers; however, it is not known if MUC1 is of functional importance to these tumors. To assess dependence on MUC1, we synthesized an inhibitor, designated GO-201, which interacts directly with the MUC1-C subunit at its oligomerization domain. Treatment of MUC1-positive DU145 and PC3 prostate cancer cells with GO-201, and not an altered version, resulted in inhibition of proliferation. GO-201 also induced necrotic cell death that was associated with increases in reactive oxygen species, loss of mitochondrial transmembrane potential, and depletion of ATP. By contrast, GO-201 had no effect against MUC1-negative LNCaP, CWR22Rv1, and MDA-PCa-2b prostate cancer cells. Significantly, GO-201 treatment of DU145 and PC3 xenografts growing in nude mice resulted in complete tumor regression and prolonged lack of recurrence. These findings indicate that certain prostate cancer cells are dependent on MUC1-C for growth and survival and that directly targeting MUC1-C results in their death in vitro and in tumor models.