

Abstract:

The mucin 1 (MUC1) oncoprotein is aberrantly overexpressed by approximately 90% of human breast cancers. However, there are no effective agents that directly inhibit MUC1 and induce death of breast cancer cells. We have synthesized a MUC1 inhibitor (called GO-201) that binds to the MUC1 cytoplasmic domain and blocks the formation of MUC1 oligomers in cells. GO-201, and not an altered version, attenuates targeting of MUC1 to the nucleus of human breast cancer cells, disrupts redox balance, and activates the DNA damage response. GO-201 also arrests growth and induces necrotic death. By contrast, the MUC1 inhibitor has no effect on cells null for MUC1 expression or nonmalignant mammary epithelial cells. Administration of GO-201 to nude mice bearing human breast tumor xenografts was associated with loss of tumorigenicity and extensive necrosis, which results in prolonged regression of tumor growth. These findings show that targeting the MUC1 oncoprotein is effective in inducing death of human breast cancer cells in vitro and in tumor models.