Abstract:

Signal transducer and activator of transcription 3 (STAT3) is activated in human breast cancer and other malignancies. Mucin 1 (MUC1) is a heterodimeric cell surface glycoprotein that is overexpressed in human carcinomas and, like STAT3, promotes cell survival and induces transformation. We found that in breast cancer cells, the MUC1 carboxyl-terminal receptor subunit (MUC1-C) associates with the gp130-Janus-activated kinase 1 (JAK1)-STAT3 complex. The MUC1-C cytoplasmic domain interacted directly with JAK1 and STAT3, and MUC1-C was necessary for JAK1-mediated STAT3 activation. In turn, MUC1-C and activated STAT3 occupied the promoter of MUC1, and MUC1-C contributed to STAT3-mediated activation of MUC1 transcription. The MUC1-C inhibitor GO-201 blocked the MUC1-C interaction with STAT3, thereby decreasing MUC1-C and STAT3 occupancy on the MUC1 and STAT3 promoters and activation of STAT3 target genes, including MUC1 itself. These findings indicate that MUC1-C promotes STAT3 activation and that MUC1-C and STAT3 function in an autoinductive loop that may play a role in cancer cell survival.