

Abstract:

MUC1 is a heterodimeric glycoprotein that is overexpressed in breast cancers. The present studies demonstrate that the oncogenic MUC1 C-terminal subunit (MUC1-C) associates with the TCF7L2 transcription factor. The MUC1-C cytoplasmic domain (MUC1-CD) binds directly to the TCF7L2 C-terminal region. MUC1-C blocks the interaction between TCF7L2 and the C-terminal-binding protein (CtBP), a suppressor of TCF7L2-mediated transcription. TCF7L2 and MUC1-C form a complex on the cyclin D1 gene promoter and MUC1-C promotes TCF7L2-mediated transcription by the recruitment of β -catenin and p300. Silencing MUC1-C in human breast cancer cells down-regulated activation of the cyclin D1 promoter and decreased cyclin D1 expression. In addition, a MUC1-C inhibitor blocked the interaction with TCF7L2 and suppressed cyclin D1 levels. These findings indicate that the MUC1-C oncoprotein contributes to TCF7L2 activation and thereby promotes cyclin D1 expression in breast cancer cells.