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GATA3 protein as a *MUC1* transcriptional regulator in breast cancer cells

Martín C Abba[1,2], María I Nunez[1], Andrea G Colussi[2], María V Croce[2], Amada Segal-Eiras[2] and C Marcelo Aldaz[1]

[1]Department of Carcinogenesis, The University of Texas MD Anderson Cancer Center, Science Park – Research Division, PO Box 389, Smithville, TX 78957, USA
[2]Centro de Investigaciones Inmunológicas Básicas y Aplicadas (CINIBA), Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Calle 60 y 120, La Plata, CP:1900, Argentina

Corresponding author: Martín C Abba, mabba777@hotmail.com

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Abstract

Introduction Recent studies have demonstrated that members of the GATA-binding protein (GATA) family (GATA4 and GATA5) might have pivotal roles in the transcriptional upregulation of mucin genes (*MUC2*, *MUC3* and *MUC4*) in gastrointestinal epithelium. The zinc-finger GATA3 transcription factor has been reported to be involved in the growth control and differentiation of breast epithelial cells. In SAGE (serial analysis of gene expression) studies we observed an intriguing significant correlation between *GATA3* and *MUC1* mRNA expression in breast carcinomas. We therefore designed the present study to elucidate whether *MUC1* expression is regulated by GATA3 in breast cancer cells.

Methods Promoter sequence analysis of the *MUC1* gene identified six GATA *cis* consensus elements in the 5' flanking region (GATA1, GATA3 and four GATA-like sequences). Chromatin immunoprecipitation and electrophoretic mobility-shift assays were employed to study the presence of a functional GATA3-binding site. *GATA3* and *MUC1* expression was analyzed *in vitro* with a GATA3 knockdown assay. Furthermore, expression of *GATA3* and *MUC1* genes was analyzed by real-time RT-PCR and immunohistochemistry on breast cancer-specific tissue microarrays.

Results We confirmed the presence of a functional GATA3-binding site on the *MUC1* promoter region in the MCF7 cell line. We determined that GATA3 knockdown assays led to a decrease in MUC1 protein expression in MCF7 and T47D cells. In addition, we detected a statistically significant correlation in expression between *GATA3* and *MUC1* genes at the mRNA and protein levels both in normal breast epithelium and in breast carcinomas ($p = 0.01$). GATA3 expression was also highly associated with estrogen receptor and progesterone receptor status ($p = 0.0001$) and tumor grade ($p = 0.004$) in breast carcinomas.

Conclusion Our study provides evidence indicating that GATA3 is probably a mediator for the transcriptional upregulation of *MUC1* expression in some breast cancers.

Introduction

GATA3 (GATA-binding protein 3) belongs to a family of transcription factors (GATA1 to GATA6) that bind with high affinity to the consensus sequence (A/T)GATA(A/G) and share a steroid-hormone-receptor superfamily C4 zinc-finger DNA-binding motif [1]. GATA factors are classified into two subfamilies on the basis of structural features and expression patterns. The expression of *GATA1*, *GATA2*, and *GATA3* has been detected predominantly in hematopoietic cells, whereas *GATA4*, *GATA5*, and *GATA6* are expressed mainly in the cardiovascular system and in endodermal-derived tissues including liver, lung, pancreas, and intestine [2]. The function of GATA factors is modulated by their interaction with other tran-

bp = base pairs; ChIP = chromatin immunoprecipitation; DAB = diaminobenzidine; DTT = dithiothreitol; ELISA = enzyme-linked immunosorbent assay; EMSA = electrophoretic mobility-shift assay; ER = estrogen receptor; *ESR1* = gene encoding estrogen receptor α; GATA3 = GATA-binding protein 3; HRP = horseradish peroxidase; IDC = invasive ductal carcinoma; MUC1 = mucin 1; PR = progesterone receptor; RT-PCR = reverse-transcriptase-mediated polymerase chain reaction; SAGE = serial analysis of gene expression; TMA = tissue microarray.