



## Mucins and mucin binding proteins in colon cancer metastasis

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### Abstract

**AIM:** To establish more directly the roles of the MUC2 mucin gene and the mucin binding protein galectin-3 in colon cancer metastasis.

**METHODS:** MUC2 levels were manipulated in highly metastatic human colon cancer cells using eukaryotic expression constructs designed to express a portion of MUC2 cDNA in the antisense orientation. Galectin-3 levels were also manipulated in human cancer cells using constructs designed to express the complete galectin-3 complementary DNA (cDNA) in either the sense or antisense orientation. Stable transfection was confirmed by a PCR-based approach and by Southern Analysis. Alterations in mRNA were determined by competitive RT-PCR and Northern Analysis. MUC2 apoprotein and galectin-3 protein levels were determined by Western Analysis. Liver colonization was assessed in athymic mice after splenic-portal inoculation or after spontaneous metastasis during cecal growth.

**RESULTS:** Stable integration of the MUC2 antisense construct into metastatic colon cancer cells (LS Lim6) resulted in an 80% reduction in MUC2-specific mRNA and a concomitant decrease in MUC2 apomucin protein. This was associated with a 50% reduction in synthesis of mature glucosamine labeled mucin, almost complete inhibition of secretion of sialyl Le-X and sialyl Tn antigens, and a 40% decrease in

binding of colon cancer cells to endothelial E-selectin. Reduction in MUC2 levels was associated with a marked decrease in liver colonization.

Introduction of galectin-3 antisense into metastatic Lim6 colon cancer cells resulted in an 80% reduction in galectin-3 specific mRNA by quantitative dot blot analysis (normalized to actin). Northern Analysis confirmed a decrease in the 1 kb product in these cells. There was a 13-fold reduction in galectin-3 protein by Western Analysis compared to parental cell line or vector-transfected controls. Similar results were obtained for another metastatic colon cancer cell line for HM7. Both total cellular and cell surface (FACS analysis) galectin-3 were reduced. Transfection of galectin-3 (sense) into low metastatic LS174 T cells resulted in a 4.5-fold increase in mRNA and a 10-fold increase in galectin-3 protein. Down-regulation of galectin-3 by antisense transformation resulted in a significant ( $P < 0.001$ ) decrease in liver colonization (liver weight, number of tumor nodules and percentage of parenchyma replaced by tumor) by Lim6 and HM7, while introduction of galectin-3 (sense) into LS174T resulted in a significant increase in liver colonization after both splenic-portal and cecal injection. Tumor tissue levels of galectin-3 in metastatic foci correlated with levels in injected cells. Manipulation of galectin in these cell lines resulted in coordinately decreased (or increased) levels of MUC2 mucin, a major ligand for this lectin. Galectin-3 was also detected in the serum of 11/13 patients with colonic adenocarcinoma, with highest levels in those with distant metastatic disease.

**CONCLUSION:** These studies provide direct evidence that the MUC2 mucin gene and mucin binding protein galectin-3 play an important role in colon cancer metastasis.

**Key words:** Colonic neoplasms; Neoplasm metastasis; Mucins; Mucin binding proteins; MUC2 mucin gene; Galectin-3

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