Original Article

Do mesothelin/MUC16 interactions facilitate adenocarcinoma metastases to intracranial meningiomas?

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Abstract

Background: Meningiomas have been shown to express mesothelin, a high affinity binding site for MUC16, a transmembrane protein on adenocarcinoma cells. The mechanisms underlying adenocarcinoma metastases to meningiomas may provide insight into tumor-to-tumor metastases and adenocarcinoma metastases to leptomeningeal cells.

Methods: Two meningiomas containing metastases from adenocarcinomas were identified and evaluated immunohistochemically for the expression and localization of mesothelin and MUC16.

Results: Both meningiomas show extensive mesothelin immunoreactivity, and the adenocarcinomas metastatic to the meningiomas show mesothelin and MUC16 immunoreactivity at the interface with meningioma.

Conclusions: Interactions between MUC16 and/or mesothelin on the cell membrane of adenocarcinoma cells with mesothelin on meningioma cells may facilitate adenocarcinoma metastases to meningiomas and possibly the leptomeninges.

Key Words: Meningioma, mesothelin, metastasis, MUC16, tumor-to-tumor

INTRODUCTION

Adenocarcinomas are one group of carcinomas known to metastasize to the leptomeninges.[24,25,28] Several reports suggest that they represent the majority of tumors metastasizing to extant meningiomas in the leptomeninges.[2,4,6,8,11,13,17,20,22,27] The mechanisms underlying this tumor-to-tumor metastases are not known. Identifying these factors may facilitate the development of therapies for these metastases.

Transmembrane mucins such as MUC1 and MUC16 are thought to facilitate the metastases of many carcinomas, including pulmonary adenocarcinomas.[7,10,21,30] These bind to a number of membrane proteins in recipient tissues.[7,10,21,30] Mesothelin is a 40kDa glycosyl-phosphatidylinositol-anchored cell surface protein that has been identified in low levels in mesothelial cells of the pleura, pericardium, and peritoneum.[7,27] Mesothelin is a potential adhesion molecule for itself and is a receptor for MUC16. It is commonly expressed by adenocarcinoma...
cells. Previously, we found widespread expression of mesothelin in leptomeninges and meningiomas.\(^{12,13}\) It is also overexpressed in mesotheliomas, pancreatic, and pulmonary adenocarcinomas and squamous cell carcinomas of the head, neck, lung, esophagus, cervix, and vulva.\(^{5,16,29}\) The functions of mesothelin are not established, however, it may function as a binding site for transmembrane mesothelin and mucins expressed by tumor cells.\(^{5,16}\)

Recently, it has been shown that mesothelin binds MUC16, a type I transmembrane protein that belongs to the mucin family of glycoproteins. It is also called CA125.\(^{10}\) In the peritoneum, mesothelin binds MUC16/CA125 with high affinity anchoring ovarian adenocarcinoma facilitating carcinomatous peritonitis.\(^ {7,21}\) In the present study, we evaluated whether two meningiomas with intratumoral metastasis from adenocarcinomas co-express mesothelin and MUC16/CA125 and whether this co-localized at the sites of metastasis.

**MATERIALS AND METHODS**

Two meningiomas with intratumoral adenocarcinoma were identified in the University of Rochester archives and consultative material after obtaining Institutional Review Board approval. The first was from a 74-year-old male with a right frontal transitional meningioma. He had a known lung mass. The second patient was a 66-year-old female with a left sphenoid wing meningioma and an adenocarcinoma identified 2 years earlier.

**Immunohistochemistry**

Each case was analyzed with a monoclonal antibody to human mesothelin.\(^ {18,19}\) The mesothelin antibody is made against 100 amino acid sequence present in the membrane-bound form of mesothelin (clone 5B2, Novo Castra, Newcastle upon Tyne, UK), which has been characterized previously.\(^ {18,19}\) MUC16 (OV185:1, Santa Cruz Biotechnology Inc. Santa Cruz, CA) was prepared with streptavidin-biotin immunohistochemistry, as described previously.\(^ {12,13}\)

**RESULTS**

**Pathology**

*Patient 1.* The sections revealed a transitional, meningioma containing a relatively circumscribed, poorly differentiated adenocarcinoma with clear cell features and necrosis. The metastasis exhibited vimentin, cytokeratin 7, TTF-1, and AE1/AE3, however, no cytokeratin 20 or S-100 immunoreactivity. The adenocarcinoma had clear periodic acid Schiff (PAS) and dPAS negative cytoplasm, large pleomorphic nuclei with prominent nucleoli, and focal glandular formation and necrosis. Ki-67 labeling was brisk in the metastasis and approximately 6% in the meningioma. The meningioma had numerous whorls and rare mitoses, but no loss of lobularity, with only modest cellularity and no definite small cell component. The PAS/PAS-D stain revealed no clear cell component.

*Patient 2.* The meningioma was transitional with atypical features, including hypercellularity, focal loss of lobular pattern, small cell change, and focal necrosis. The meningioma showed extensive epithelial membrane antigen (EMA) but no CAM 5.2, cytokeratin 7, TTF-1, napsyn, or PAS staining. The metastatic adenocarcinoma shows gland formation. The epithelioid cells had prominent nucleoli, high mitotic activity, and necrosis and Kreyberg staining. The carcinoma cells showed EMA, Cam 5.2, cytokeratin 7, napsyn, TTF-1, and Ki-67 labeling of 60%.

**Immunohistochemistry**

Mesothelin immunoreactivity was detected in both meningiomas and was extensive [Figure 1a and 2a]. High mesothelin expression was also seen in the adenocarcinoma metastases to the meningiomas [Figure 1c and 2c]. Muc16 immunoreactivity was not detected in either meningioma [Figure 1b and 2b], however, was variably detected in both adenocarcinomas, including focal areas with mesothelin in the carcinoma and interface with the meningioma immunoreactivity [Figure 1d and 2d].

**DISCUSSION**

Previously, we have demonstrated mesothelin expression in the majority of meningioma and 30% of human leptomeninges tested.\(^ {12}\) Several groups have suggested that adenocarcinomas may metastasize frequently to the peritoneum and pleura due to interactions between...
mesothelin and MUC16. High concentrations of mesothelin in these tissues as well as its high affinity for MUC16 have been noted;[12,23] we have also reported the same observation.[13] Some, but not all, MUC16 adenocarcinoma also metastasized to the leptomeninges, however, not in significantly higher numbers than MUC16 adenocarcinomas spreading to the peritoneum and pleura.[13] This may reflect the limited expression of mesothelin the leptomeninges, and thus limited binding sites.[12]

In contrast, meningiomas show widespread mesothelin expression and may have more favorable binding sites for MUC16-expressing carcinomas. Consistent with this is our finding of widespread mesothelin in both meningiomas as well as MUC16 in both carcinomas. Thus, these interactions may represent another mechanism by which tumors metastasize to remote tissues (and tumors). [1]

Mesothelin may also facilitate metastases by other mechanisms. Recent studies have shown that mesothelin induces expression of metalloproteinase MMP9, which has been implicated in tumor invasion.[13,23,24] Numerous other factors may also contribute to this tumor-to-tumor metastasis. For example, proportionately higher blood flow to the meningioma than to the leptomeninges or brain may influence the site of metastasis. In addition, changes in e-cadherin-catenin complex expression, expression of other adhesion molecules with receptors on endothelial cells, paracrine expression of various growth factors, and stromal proteases affecting transmigration across blood vessel/endothelial barriers likely have complex effects on this tumor-to-tumor metastases.[26,28] Nonetheless, analyses of these is beyond the scope of this study.

Targeting mesothelin with an anti-mesothelin immunotoxin SS1P binding has been shown to cause regression of mesothelin-expressing tumors in athymic mice. It also has exhibited tumoricidal effects on mesotheliomas and ovarian carcinomas.[5,14,31] Vaccines against mesothelin are also being developed.[5,18] Because of the low level of mesothelin expression in a limited number of normal tissues, as well as high levels of expression in some tumors, such as seen here, these therapies may prove to be relatively specific and are in phase I and II clinical trials.

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Conflicts of interest
There are no conflicts of interest.

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