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Expressions of CAVEOLIN 1 in Human Uterine Mesenchymal Tumors and Normal Myometrium

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ABSTRACT

Although most smooth muscle neoplasms detected in the human uterus are benign, uterine leiomyosarcoma (Ut-LMS) is extremely malignant with high rates of recurrence and metastasis. CAVEOLIN 1 (CAV1) levels in the epithelial cells of some carcinomas have been reported to increase during tumor progression. We herein evaluated the relationship between CAV1 expression and the pathological features of patients diagnosed with uterine mesenchymal tumors at several clinical facilities. No clinical link was observed between CAV1 expression and the malignancy of human uterine mesenchymal tumors. CAV1 expression was decreased in the normal myometrium, whereas it was markedly expressed in uterine mesenchymal tumors. However, the expression of CAV1 was not a potential biomarker to distinguish human Ut-LMS from other types of uterine mesenchymal tumors. The perivascular expression of CAV1 was clearly observed in myometria and all types of uterine mesenchymal tumors. Therefore, the results of the present study suggest that CAV1 may not act as a potential biomarker of uterine malignant mesenchymal tumors. However expression of CAV1 may do biological effects in the development of uterine mesenchymal tumors.

KEYWORDS : CAVEOLIN 1, myometrium, leiomyosarcoma, leiomyoma

Introduction

CAVEOLIN 1 (CAV1) is a protein that is encoded by the *CAV1* gene in humans.[1] The scaffolding protein encoded by this gene is the main component of the caveolae plasma membranes found in most cell types. This protein links integrin subunits to the tyrosine kinase FYN, an initiating step in coupling integrins to the RAS-ERK pathway and promoting cell cycle progression. CAV1 is a tumor suppressor gene candidate or a negative regulator of the RAS-MAP kinase cascade. *CAV1* and *CAV2* genes are located next to each other on chromosome 7 and express co-localizing proteins that form a stable hetero-oligomeric complex. Using alternative initiation codons in the same reading frame, two isoforms were found to be encoded by a single transcript from the *CAV* gene.[2] CAV1 and CAV2 are widely co-expressed in fully differentiated mesenchymal and endothelial normal tissues as well as in many solid tumors, whereas CAV3 is primarily expressed in muscle cells.[2,3] Numerous disease processes have recently been suspected of being affected by the ablation or mutation of CAVs that regulate many signaling molecules and signaling cascades.[1]

Previous studies revealed that CAV1 levels in the epithelial cells of some carcinomas increased during tumor progression. Conversely, CAV1 expression in peritumoral stromal cells was found to decrease in advanced and metastatic cancers, which may also occur in sarcomas.[3,4] Human uterine leiomyomas (LMA) are the most frequently detected mesenchymal tumors in the uterus. Most human uterine mesenchymal tumors are readily classifiable as uterine LMA or uterine leiomyosarcoma (Ut-LMS) based on their gross and microscopic appearances. Uterine mesenchymal tumors that cannot be histologically diagnosed as unequivocally benign or malignant are currently termed cellular LMA, Bizarre LMA, mitotically active LMA, and smooth muscle tumor of uncertain malignant potential (STUMP).[5,6] Recent studies have suggested that immunohistochemical (IHC) staining for some proliferation markers such as ki-67, Proteasome subunit beta (PSMB)9/b1i, CYCLIN B, and CALPONIN h1 may useful for differentially diagnosing uterine mesenchymal tumors.[5,6] CAV1 has been shown to act as either a tumor suppressor or tumor promoter in different tumors.[7,8] However, few studies have examined the function of CAV1 in uterine mesenchymal tumors.[9,10] The aim of the present study was to investigate IHC for CAV1 expression in uterine mesenchymal tumors and evaluate the relationship between CAV1 expression and many prognostic findings such as tumor size, stage of the disease, histological features, age, survival rate, and overall and event-free survival.

CAVEOLINs play a paradoxical role in the development of human disease. They have been implicated in both tumor suppression and oncogenesis. The strong expression of CAVs has been shown to inhibit cancer-related pathways, such as growth factor signaling pathways. However, certain cancer cells that express caveolins are more aggressive and metastatic because of a potential for anchorage-independent growth. CAV1 links integrin subunits to FYN, an initiating step in coupling integrins to the RAS-ERK pathway and promoting cell cycle progression. Previous studies demonstrated that CAV1 facilitated both ERK and AKT signaling in cancer cells from the kidney, colon, prostate, epidermis, muscle, and brain and promoted cell invasion, proliferation, angiogenesis, and multi-drug resistance.[7,8,13,14] A similar relationship has also been reported between CAV1 expression and B-RAF mutations in melanomas.[13] Previous studies have suggested that CAV1-positive tumor cells serve as tumor promoters by these signaling pathways.[3,14] We also detected the expression of CAV1 in a limited number of STUMPs and in most LMSs. Although tumors became more aggressive and invasive, they did not significantly change the expression of CAV1 or perivascular CAV1. The tumor microenvironment plays a crucial role in the initiation and progression of malignancies. It is now clear that tumors promote increases in microvessel density, recruit reactive stromal fibroblasts and different inflammatory cells, and release peptide-signaling molecules and proteases.[1,3] Tumor-associated fibroblasts (TAF) produce an altered extracellular matrix (ECM) that can induce epithelial-mesenchymal transition (EMT) or other types of behaviors associated with a more aggressive phenotype in neighboring epithelial cells. The exact mechanisms of this relationship remain largely unknown. A definition of the expression status in peritumoral stromal cells has been accepted as a better parameter. CAV1 has also been shown to play a role in integrin signaling. The tyrosine phosphorylated form of CAV1 co-localizes with focal adhesions, suggesting a role for CAV1 in migration. The up-regulation of CAV1 was previously reported to induce efficient migration *in vitro*. Many oncogenes such as SRC, RAS, and BCR-ABL are known to transcriptionally down-regulate CAV1 expression.[1] However, certain cancer cells that express CAVs are more aggressive and metastatic because of the potential for anchorage-independent growth. Recent studies suggested that stromal and tumoral CAV1 may play an important role in promoting tumor progression and metastasis.[15] In other words, stromal CAV1 expression in association with the strong tumoral expression of CAV1 is closely related with poor outcomes in different malignancies.[9,10,14,15] Knock-out animals develop abnormal, hypertrophic lungs, and cardiac myopathy, leading to a reduction in lifespan.[16] Mice lacking *Caveolins* also have impaired angiogenic responses as well as abnormal responses to vasoconstrictive stimuli.[17] CAVs are thought to be crucially involved in the development of the tumoral microvasculature.

İn the present study, we could not evaluate CAV1 expression in peritumoral uterine stroma, and perivascular CAV1 expression within tumors was not associated with the malignancy of uterine mesenchymal tumors. Although CAV1 expression has been extensively studied

in several carcinomas, there is little or no data on the expression and significance of CAV1 in uterine mesenchymal tumors.[9,10] Recent studies demonstrated that CAV1 was often expressed in LMAs, but was absent in normal myometrial cells.[10] We herein demonstrated that the expression status of tumoral and perivascular CAV1 was not significantly changed by tumor aggressiveness. In conclusion, the results of our studies revealed that the altered expression of the CAV1 protein in uterine mesenchymal tumors may be a component for tumor dedifferentiation. Although our results need to be confirmed in larger series, they still suggest that CAV1 plays an important role during the development of uterine mesenchymal tumors, but does not mediate tumoral malignancy. We previously demonstrated the abnormal expression of ovarian steroid receptors; however, TP53 and ki-67 and mutations in TP53 were frequently associated with human Ut-LMS, and defective PSMB9/b1i and CALPONIN h1 expression and marked CYCLIN B1 expression appeared to be more characteristic of human Ut-LMS than these factors.[6,18] Taken together, our results suggest that CAV1 does not act as a targeted molecule for a biomarker or clinical treatment like previously examined molecular candidates against uterine malignant mesenchymal tumors.

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