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Gene Section
Review

MMP26 (matrix metallopeptidase 26)

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Identity

HGNC (Hugo): MMP26
Location: 11p15.4

DNA/RNA

Description

This gene can be found at chromosome 11p15.4, and contains 6 exons spanning 4,24 kb.

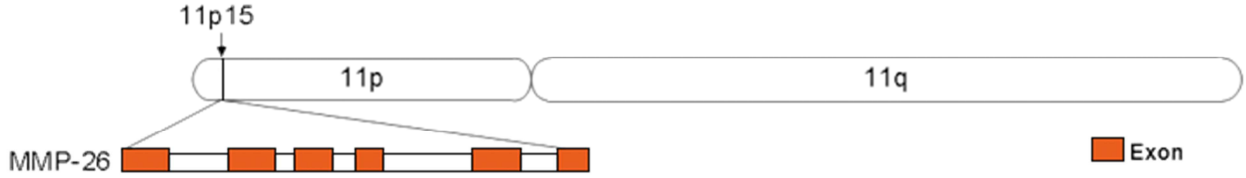
Transcription

MMP-26 has 998 mRNA nucleotides and no transcript variant. The transcription of this gene is regulated by three elements, estrogen-responsive element (ERE), T-cell factor-4 (TCF-4), and activator protein-1 (AP-1), due to the highly unusual poly (A) site located upstream of its promoter. Further regulation of TCF-4 is accomplished by the β-catenin/epithelial-cadherin (E-cadherin) pathway and suggests that MMP-26 is specifically expressed in cells of epithelial origin. The gene for MMP-26 has one transcriptional start site and a consensus TATA-box, located 35 and 60 nucleotides upstream of the translational start site respectively.

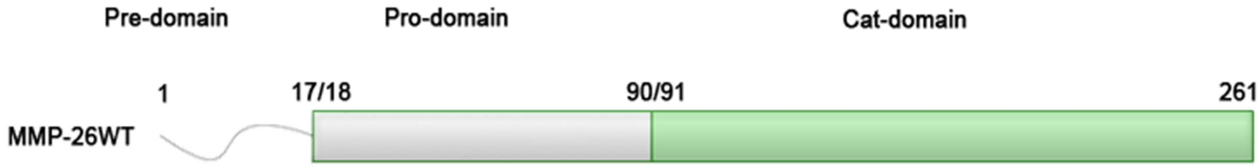
Protein

Description

MMP-26 is the smallest member of the matrix metalloproteinase (MMP) family of zinc-dependent endopeptidases. Synthesized as a zymogen, the nascent form is composed of three domains: (1) "pre" domain, N-terminal signal sequence, which directs the protein into the endoplasmic reticulum; (2) an unconventional "pro" domain, which maintains enzyme-latency; and (3) a catalytic domain, which contains the conserved zinc-binding region for proteolysis.
The MMP-26 pro-enzyme starts at residue 18, with the full length of the protein spanning 261 amino acids.
The full-length enzyme has a theoretical molecular weight of 28 kDa that is truncated to 19 kDa upon activation (cleavage of the pro-domain).



Containing 6 exons spanning 4,24 kb, MMP-26 is found at chromosome 11p15.4.



Schematic of MMP-26 (wild type). Pre-, signal peptide of MMP-26 (residues 1-17); Pro-, pro-peptide of MMP-26 (residues 18-90); and Cat-, catalytic domain of MMP-26 (residues 91-261).

Among the MMPs, only MMP-26 has a "cysteine-switch" sequence that contains a histidine residue instead of the usual arginine residue ($PH^{81}CGVPDGSD$) in the pro-peptide domain and has a zinc-binding motif ($V^{205}ATHEIGHSLGLQH$) in the catalytic domain. Additionally, MMP-26 lacks the hinge region and hemopexin-like domain that is common to other family members. MMP-26 has two calcium binding sites: (1) a high-affinity site required for enzymatic activity, protein stability, and protection from denaturation; and (2) a low-affinity site primarily important for protein folding, tertiary structure, and native conformation. The protein also contains three possible N-linked glycosylation sites (N64, N133, N221).

Expression

MMP-26 has been found strictly expressed in normal tissues of the placenta and moderately expressed in the uterus. However, MMP-26 expression is also associated with human cancer cells, especially in estrogen receptor (ER)-α positive breast cancer cells and cancerous cells of the ovary and endometrium. The expression of MMP-26 in cancerous breast, colon, lung, brain, head and neck, prostate, and melanoma tissues was significantly elevated when compared with parallel normal tissues, while not significantly elevated in kidney cancer, ovarian cancer, and non-Hodgkin's lymphoma.

Localisation

Intracellular (endoplasmic reticulum-retained), secreted, pericellular, and extracellular.

Function

MMP-26 cleaves many extracellular matrix and plasma proteins including: (1) amino terminus of estrogen receptor β; (2) α1-antitrypsin; (3) insulin-like growth factor-binding protein 1 (IGFBP-1); (4) fibronectin; (5) vitronectin; (6) fibrinogen; (7) gelatins of types I-IV; (8) gelatinase B (MMP-9); (9) α2-macroglobulin; and (10) type IV collagen. MMP-26 digests one peptide substrate of tumor necrosis factor-α converting enzyme (TACE/ADAM17) and four peptide substrates of MMPs. MMP-26 activates MMP-9 by cleavage of the pre-proenzyme (Ala93-Met94 site) and produces activated MMP-9 products that are more stable than those activated by MMP-7. MMP-26 also forms a complex with tissue inhibitors of metalloproteinases 4 (TIMP-4). MMP-26 is inhibited by GM6001 and TIMPs -2 (1,60 nM) and -4 (0,62 nM), exhibiting an inhibition profile most similar to those of MMPs with intermediate S1' pockets (His-233). MMP-26 can auto-digest itself during the folding process and is also capable of self-activation with its catalytic activity affected by detergents.

Homology

Belongs to matrix metalloproteinase (MMP) family and exhibits a similar domain structure to that of matrilysin (MMP-7) but is most homologous to metalloelastase (MMP-12) with ~52% identity.

Implicated in

Breast cancer

Note

MMP-26 is not expressed in normal mammary epithelium, is strongly upregulated in ductal carcinoma in situ (DCIS), and decreases throughout further disease progression (stages I to III). Co-expression of MMP-26 and TIMP-4 or MMP-9 has been detected in DCIS. Estrogen receptor-β (ER-β), not ER-α, is a substrate of MMP-26 in vivo and in vitro, indicating a novel regulation loop between estrogen and ER and modification of the ER-α/ER-β ratio. Additionally, silencing MMP-26 expression in the human breast cancer cell line MDA-MB-231 up-regulated the expression of five proteins (heat shock protein 90, glucose-regulated protein 78, annexin V, tropomyosin, peroxiredoxin II) and down-regulated the expression of four proteins (α-tubulin, cystatin SA-III, breast cancer metastasis suppressor 1 (BRMS1), and β-actin).

Prognosis

MMP-26 expression is associated with ER+ human breast cancer and has positive correlation with patient survival in DCIS.

Endometrial cancer, ovarian cancer

Note

MMP-26 mRNA is localized in the epithelial component of normal, hyperplastic, premalignant, and malignant samples of endometrial tissue and in situ hybridization indicates maximal levels in normal tissue (midcycle) and in endometrial hyperplasia (with and without atypia). Endometrial carcinomas

exhibit greater expression compared to benign endometrium from the postmenopausal period, but not from the secretory phase of the menstrual cycle. Expression progressively decreases with loss of histological differentiation in malignant samples. Increased staining intensity correlates with grade III tumors and with the depth of myometrial invasion in tumors histologically characterized as endometrioid adenocarcinoma. Relating to ovarian cancer, MMP-26 is expressed in normal tissue as well as ovarian tumors with expression increasing with increased tumor stage. Invading ovarian tumor cells display the strongest expression of MMP-26, and progression of ovarian cancer is correlated with MMP-26 co-expression with TIMP-3, and TIMP-4.

Prostate cancer, prostatitis, benign prostate hyperplasia (BPH), and high-grade prostatic intraepithelial neoplasia (HGPIN)

Note

Protein levels in human prostate carcinomas from multiple patients were significantly higher than those in prostatitis, benign prostate hyperplasia (BPH), and normal prostate glandular tissue.

MMP-26 and TIMP-4 expression was found higher in HGPIN and cancer when compared to non-neoplastic acini.

Prognosis

For the progression of high-grade prostatic intraepithelial neoplasia (HGPIN) to invasive adenocarcinoma, it is crucial to disrupt the continuity of the basal cell layer and basement membrane.

MMP-26 may play an integral role during this conversion and may serve as a marker for earlier diagnoses.

Oncogenesis

MMP-26, by cleaving basement membrane proteins and activating pro-MMP-9, promotes invasion of human prostate cancer cells.

Squamous cell carcinomas (SCC)

Note

Squamous cell cancers can be recognized as an uncontrolled wound healing process.

MMP-26 expression is present in migrating keratinocytes (KC) of healing wounds compared with normal intact skin cells.

Furthermore, expression was not found to be present in proliferating Ki-67-positive KC but co-localized with tumor suppressor p16. MMP-26 was also detected in squamous cell cancer (SCC) grades I and II, but was not present in grade III.

In another study, high-grade SCC shows a statistically significant higher expression of MMP-26 and is associated with morphological scores of malignancy.

MMP-26 is suggested to contribute to more aggressive behavior of SCCs in organ transplant recipients.

In SCC of the esophagus (ESCC), MMP-26 was upregulated in incipient invasion and its expression associated with regions of low differentiation being more sporadic at the invasive front. MMP-26, nuclear β-catenin, and active MMP-9 expression correlate in ESCC tissue, which was found significantly correlated with depth of invasion, lymph node and distant metastasis, advances in pTNM stage, and recurrence.

Disease

Oral squamous cell carcinomas, Esophageal squamous cell carcinoma.

Prognosis

Lack of MMP-26 in SCC could be a marker of aggressive growth. Another report questions the usefulness of MMP-26 as an indicator of the metastatic potential of SCCs of the tongue.

MMP-26 positive ESCC patients showed significantly shorter overall and disease-free survival periods than those did with MMP-26-negative cancers.

Lung cancer

Note

Expression of MMP-26 is significantly higher in non-small cell lung cancer (NSCLC) than in atypical hyperplasia and normal lung tissue and correlates with carcinogenesis, lymph node metastasis, clinical stage, and prognosis. Silencing of MMP-26 significantly reduced invasiveness of A549 cells in Transwell invasion assays, suggesting MMP-26 to play an important role in local invasion, at least in part through coordination with MMP-9.

Disease

Non-small Cell Lung Cancer (NSCLC).

Prognosis

MMP-26 may be used as a tumor marker in monitoring progression and predicting prognosis of NSCLC since disease-free and overall survival are shorter in NSCLC patients with high expression of MMP-26.

Glioblastoma multiforme (brain tumor)

Note

Overexpression of MMP-26 in U251 cells resulted in a significantly higher cell-spreading ratio when compared to parental U251 cells.

The relative migration distance on Matrigel was also significantly greater. Boyden Chamber assays further indicated an enhanced invasive ability of MMP-26 overexpressed U251 cells.

The microvessel density of tumor tissues derived from MMP-26 transfected cells was also greater when compared to the parental cell line.

Oncogenesis

MMP-26 contributes to U251 cell invasion and migration in vitro and plays an important role in local invasion and angiogenesis.

Merkel cell carcinoma (cutaneous tumor)

Note

MMP-26 expression was positive in stromal cells and was associated with tumors greater than or equal to 2-cm in diameter.

Prognosis

Stroma expression is associated with larger tumors with poor prognosis.

Pancreatic cancer, pancreatic adenocarcinoma

Note

Patients with metastatic cancer cells in lymph nodes had increased expression of MMP-26 in tumor samples. In a pancreatic cell line (PANC-1) MMP-26 was neither expressed basally nor induced by TNF-α, TGFβ1, EGF, or interferon γ.

Colon cancer

Note

Unlike classical MMPs, MMP-26 is expressed in the normal intestine and was detected in migrating enterocytes. Staining for MMP-26 revealed a meshwork-like pattern between cancer islets and suggested to be involved in enterocyte migration.

To be noted

Note

No intracellular substrates of MMP-26 identified in disease with its high expression except for ER-β in breast cancer. No homologous analog of MMP-26 found in rodents.

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