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Proteases in TUMOR SUPPRESSION

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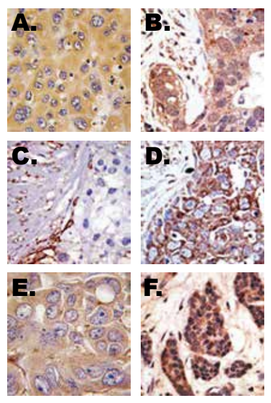
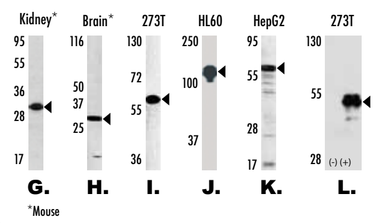
Selected Abgent Products

Figure	Target	Tissue/Cell line	Cat#
A.	APG4C	Human hepatocarcinoma	AP1810d
B.	SENP1	Human breast carcinoma	AP1230a
C.	USP7	Human breast carcinoma	AP2136a
D.	RCE1	Human breast carcinoma	AP2416b
E.	MMP12	Human breast carcinoma	AP6196a
F.	MMP19	Human breast carcinoma	AP6202a
G.	CASP6	Mouse kidney tissue lysate	AP1313d
H.	KLK3	Mouse brain tissue lysate	AP6322b
I.	MMP11	293T cell line lysate	AP6195a
J.	SENP6	HL60 cell lysate	AP1239a
K.	MMP20	HepG2 cell line lysate	AP6203a
L.	p53	293T cell line lysate	AP6266d





Proteases

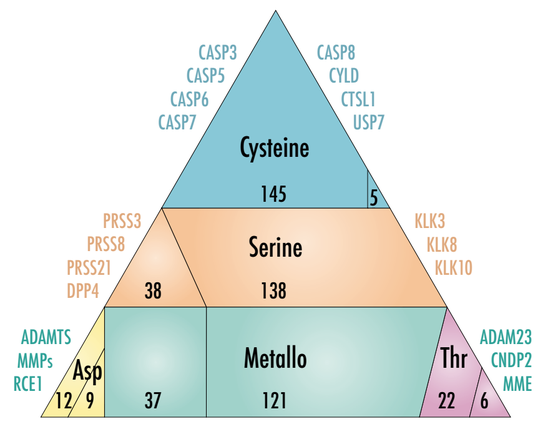


Fig. 1 Classification of human proteases. All identified human proteolytic enzymes are classified into five catalytic classes: metalloproteinases, serine, threonine, cysteine and aspartic proteases. Numbers at the left sections of each catalytic class correspond to intracellular or integral-membrane enzymes, whereas numbers at the right sections refer to extracellular or pericellular enzymes. The pyramidal structure of the figure does not imply a hierarchical organization of proteolytic systems (1). Indicated in red are the protein targets for ABGENT's antibody products.

Examples of human proteases with antitumor properties

Gene	Protease name	Antitumor mechanism	Type of cancer
ATG4C	Autophagin 3	Activation of autophagy	Fibrosarcoma
CASP3, -5, -6, -7, -8	Caspase	Induction of apoptosis	Neuroblastoma, lung, colorectal
CYLD	CYLD	Negative regulation of NF-κB pathway	Skin
SENP1	Sentrin protease 1	Induction of CDB2 tumor suppressor	Prostate
USP7	HAUSP	Stabilization of p53	Prostate
CNDP2	Glu-carboxypeptidase like B	Inhibition of proliferation and invasion	Hepatocarcinoma
CTSL1	Cathepsin L	Inhibition of proliferation	Skin
RCE1	Ras-converting enzyme 1	Inhibition of proliferation	Myeloproliferative
ADAM23	ADAM23	ND	Breast, gastric
ADAMTS1, -8, -9, -15, -18	ADAMTS1, -8, -9, -15, -18	Inhibition of angiogenesis	Breast, esophageal, colorectal
DPP4	Dipeptidyl peptidase 4	Inhibition of invasion	Ovarian
FOLH1	Folate hydrolase	Inhibition of invasion	Prostate
KLK3, -8, -10	Kallikrein	Activation of TGFβ	Prostate, breast
MME	Neprilysin	Inhibition of proliferation and angiogenesis	Prostate
MMP3, -8, -9, -11, -12, -19, -26	Metallopeptidase	Metastasis suppression	Breast, ovarian, lung, colorectal
PRSS3, -8, -21	Serine proteases	Inhibition of proliferation and invasion	Gastric, bladder, lung

Targets of antitumor proteases

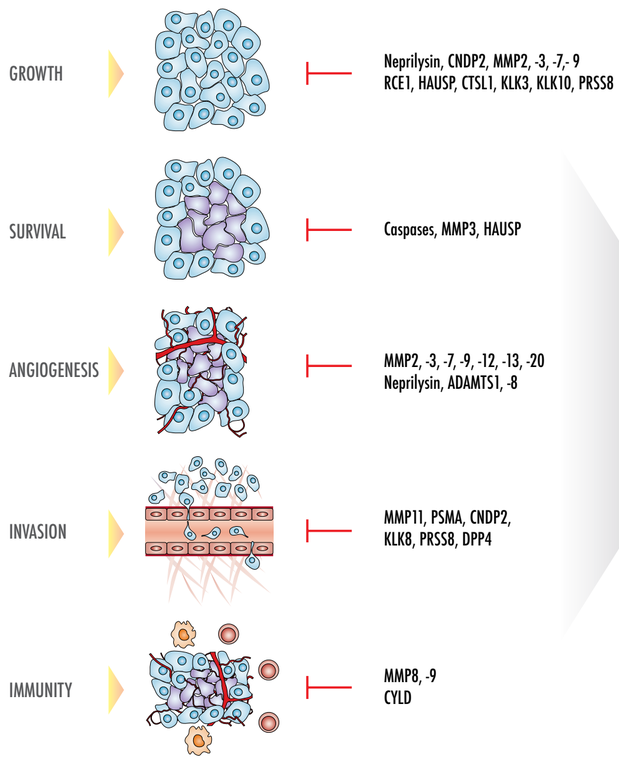


Fig.2

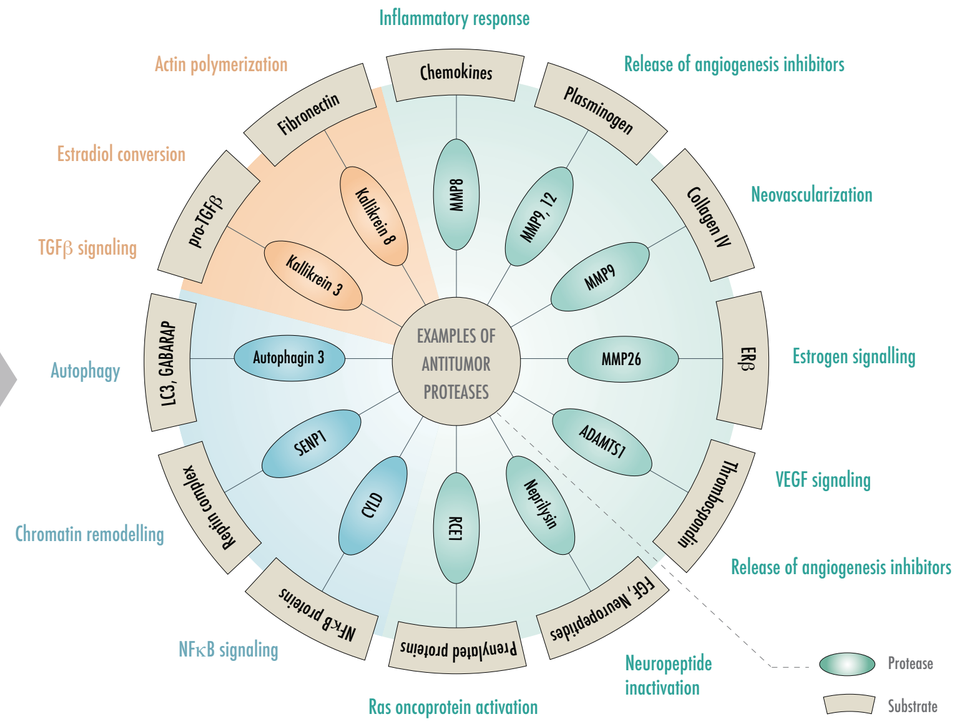


Fig.3

Fig. 2 Functional roles of antitumor proteases at different stages of cancer progression. Proteases belonging to different catalytic classes show tumor-defying functions by inhibiting stages of cancer progression, such as angiogenesis or invasion, or by their ability to modulate the inflammatory responses that are elicited by cancer cells (1, 2, 4).

Fig. 3 Substrates and biological processes targeted by antitumor proteases (1-13). The indicated proteases develop their tumor-protective functions by targeting diverse substrates and a wide variety of signaling cascades, shown in the outer rings. Additional substrates include:

Kallikrein 3:
plasminogen, fibronectin, urokinase plasminogen activator, kallikrein 2; secretory leukocyte peptidase inhibitor, insulin-like growth factor binding protein, semenogelin, parathyroid hormone-like hormone, protease inhibitors 1 and 2 (anti-elastase)

Kallikrein 8:
casein, gelatin, collagen, fibrinogen, high-molecular-weight kininogen, tissue plasminogen activator

ADAMTS1:
aggrecan, versican, tissue factor pathway inhibitor 2

Neprilysin:
caspase 9, cholecystokinin A receptor, insulin B chain

RCE1:
lamin B1, farnesyl-Ki-Ras, -N-Ras, -Ha-Ras, farnesylated heterotrimeric protein G gamma 1 subunit, geranylgeranyl-Ki-Ras, geranylgeranyl-Rap1b

SENP1:
homeodomain-interacting protein kinase 2

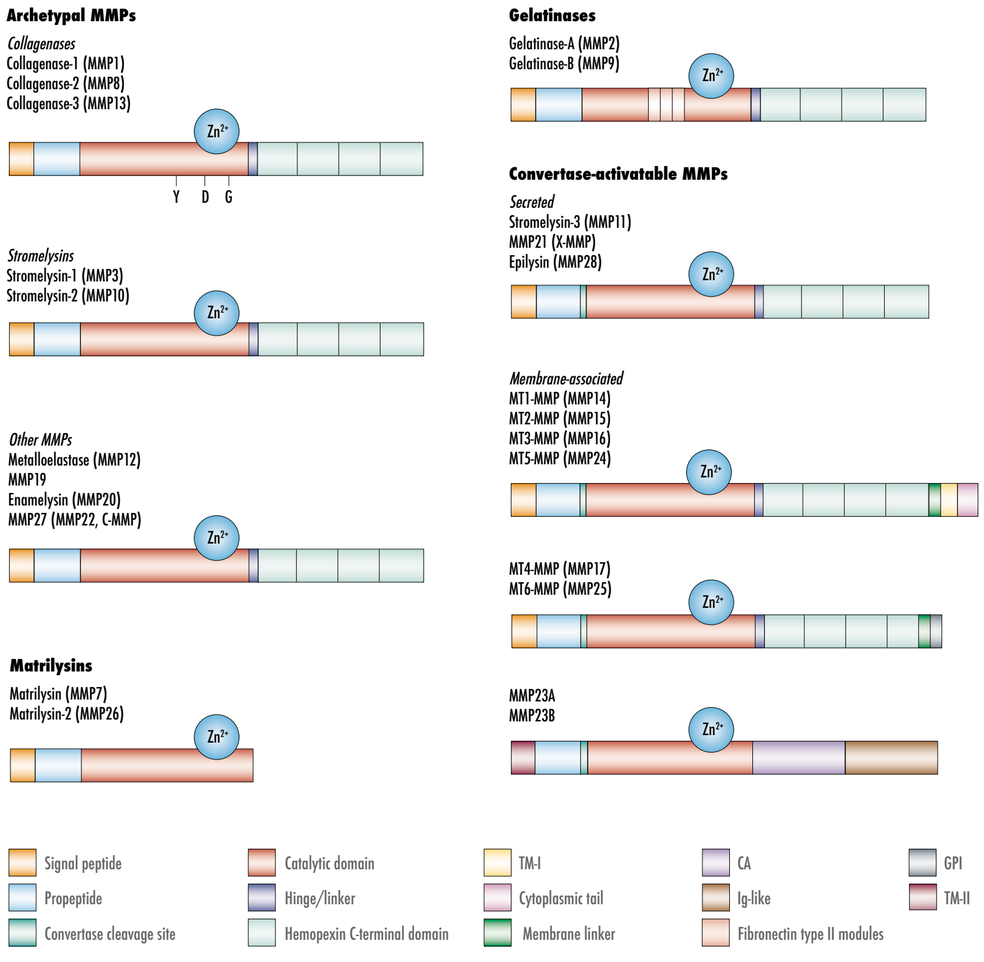
MMP8:
TNF, insulin-like growth factor binding protein, L-selectin, protease inhibitor 1 (anti-elastase), macroglobulin, antiplasmin

MMP9:
TNF, TGF, tumstatin, endostatin, plasminogen, FGF receptor, macroglobulin, metastin

MMP12:
TNF, plasminogen, endostatin, protease inhibitor 1 (anti-elastase)

MMP26:
MMP9, MMP26, insulin-like growth factor binding protein 1, vitronectin, fibronectin, fibrinogen, protease inhibitor 1 (anti-elastase)

MMPs domain organization



Mouse model	Tumor development
MMP2$^{-/-}$	Reduced pancreatic carcinogenesis Decreased tumor growth
MMP7$^{-/-}$	Reduced intestinal adenoma formation
MMP8$^{-/-}$	Increased skin carcinogenesis in males
MMP9$^{-/-}$	Reduced skin carcinogenesis Reduced pancreatic carcinogenesis Reduced experimental metastasis
MMP11$^{-/-}$	Reduced mammary carcinogenesis Decreased tumor cell survival and growth Increased number of metastasis
MMP14$^{-/-}$	Defective angiogenesis

Table 2. Tumor development in MMP knock-out mice (4).

Fig.4 Diversity of human MMPs based on their domain organization. Schematic representation of the structure of the 24 human matrix metalloproteinases (MMPs), which are classified into four different groups on the basis of domain organiz ation. Archetypal MMPs contain a signal peptide necessary for secretion, propeptide, a **catalytic domain** that binds zinc (Zn^{2+}) and a **hemopexin** carboxy (C)-terminal domain. **Y**, **D**, and **G** represent tyrosine, aspartic acid and glycine amino acids that are present in the catalytic domain of all collagenases. Matrilysins contain the minimal domain organization that is required for secretion, latency and catalytic activity. Gelatinases contain **fibronectin** type II modules that improve collagen and gelatin degradation efficiency. Convertase-activatable MMPs contain a basic insert in the propeptide that is targeted by furin-like proteases (convertase cleavage site). MMPs that belong to this group can be secreted enzymes, or membrane-anchored via **GPI** (glycosylphosphatidylinositol), type I or type II transmembrane **(TM)** segments. MMP23A and MMP23B contain unique cysteine array **(CA)** and immunoglobulin **(Ig)-like** domains in their C-terminal region.

The evolution of the MMP family to generate this structural diversity reflects the number and complexity of biological processes in which these enzymes are involved (1, 2, 4, 6).

Product abbreviations

ATG4C: ATG4 autophagy related 4 homolog C; AUT-like 3 cysteine endopeptidase
SENP1: SUMO1/sentrin specific peptidase 1
USP7: ubiquitin specific peptidase 7; Herpes virus-associated ubiquitin-specific protease
RCE1: RCE1 homolog, prenyl protein peptidase; farnesylated protein-converting enzyme 2
MMP11, 12, 19, 20: matrix metallopeptidase 11, 12, 19, 20
CASP6: caspase 6, apoptosis-related cysteine peptidase; apoptotic protease MCH-2
KLK3: kallikrein-related peptidase 3; prostate specific antigen; P-30 antigen; gamma-seminoprotein
SENP6: SUMO1/sentrin specific peptidase 6
p53: tumor protein p53; p53 antigen; p53 transformation suppressor; p53 tumor suppressor; TP53

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