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MMP-7 marks severe pancreatic cancer and alters tumor cell signaling by proteolytic release of ectodomains

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Abstract

Pancreatic cancer incurs the worst survival rate of the major cancers. High levels of the protease matrix metalloproteinase-7 (MMP-7) in circulation correlate with poor prognosis and limited survival of patients. MMP-7 is required for a key path of pancreatic tumorigenesis in mice and is present throughout tumor progression. Enhancements to chemotherapies are needed for increasing the number of pancreatic tumors that can be removed and for preventing relapses after surgery. With these ends in mind, selective inhibition of MMP-7 may be worth investigation. An anti-MMP-7 monoclonal antibody was recently shown to increase the susceptibility of several pancreatic cancer cell lines to chemotherapeutics, increase their apoptosis, and decrease their migration. MMP-7 activities are most apparent at the surfaces of innate immune, epithelial, and tumor cells. Proteolytic shedding of multiple protein ectodomains by MMP-7 from such cell surfaces influence apoptosis, proliferation, migration, and invasion. These activities warrant targeting of MMP-7 selectively in pancreatic cancer and other tumors of mucosal epithelia. Competitive and non-competitive modes of MMP-7 inhibition are discussed.

Keywords

adjuvant therapy; neoadjuvant therapy; prognostic; apoptosis; resistance to chemotherapy; tumor cell invasion; proliferation; tumor cell signaling; proteolytic enzyme; ectodomain shedding; MMP; monoclonal antibody; competitive inhibitor; non-competitive inhibitor; allosteric inhibitor

Introduction

6 to 7 % of cancer deaths in Western countries are attributable to pancreatic cancer [1]. Pancreatic cancer could increase from fourth to second leading source of cancer deaths in the U.S. by 2030 [2]. Surgical resection of pancreatic ductal adenocarcinoma (PDAC) is regarded as “curative”, with a 5-year survival rate of 30% and median survival of 26 months [3,4]. However, the tumor can be resected in only 10 or 15% of patients [4]. Consequently, clinical goals are to shrink tumors enough for resection, use better prognostics before committing to surgery, and apply chemotherapy more successfully after surgery [3,5].

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Competing Interests

The author declares no competing interests with this manuscript.

In advanced pancreatic cancer and colon cancer, matrix metalloproteinase-7 (MMP-7 or matrilysin) was prominent at the invasive edges of the tumors [6–9]. In models of metaplastic conversion in the pancreas, MMP-7 is upregulated and increases tumor size and metastases [10,11]. In the key, early acinar-to-ductal switch, both MMP-7 and the cell death signal FasL were implicated in acinar metaplasia [12]. Proteolysis of FasL by MMP-7 is one of the strategic proteolytic activities of MMPs at plasma membranes that influence cell signaling [13,14].

Matrix metalloproteinases (MMPs) comprise about two dozen proteases [13]. MMP-1, −2, −3, −7, −8, −9, −10, −12, −19, −28 and MT1-MMP were each implicated in inflammation or its resolution [15,16]. Meta-analysis implicated MMP-9 most often in chronic wound healing, MMP-2 and −7 often in acute wound healing, and also MMP-1, −3, −8, −12 and −13 [17]. MMP-1, −2, −7, −9, and MT1-MMP were implicated in regulating angiogenesis [18,19]. MMPs depend upon zinc and calcium ions in their catalytic domain for structure and activity in the interstices and extracellular matrix. Activation requires that the pro-domain be removed, often by a proteolytic cascade, to uncover the zinc-containing catalytic cleft. Most MMPs have a C-terminal hemopexin-like domain that binds protein substrates. MMP-7 and −26, the matrilysins, lack this accessory domain [13,20]. The collagenases comprise MMP-1, −8, −13, and −18 [13,20,21]. Of the MMPs with a transmembrane helix, MT1-MMP, MT2-MMP, and MT3-MMP digest collagen, but not MT5-MMP [22]. MT4- and MT6-MMP are anchored to plasma membranes by glycosylphosphatidylinositol [22]. Gelatinases A and B, i.e. MMP-2 and −9, respectively, have fibronectin-like inserts that support their activity towards collagen IV of basement membranes and other collagens [21,23–26]. The stromelysins are MMP-3, −10, and −11 [27]. Other soluble enzymes are MMP-12, −19, −20, −21, −23, −27, and −28 [20].

Inhibitors of a broad range of MMPs failed in clinical trials, prompting the search for MMP-selective inhibitors [13,20,28–35]. Overall and Kleifeld argued that most MMPs are either protective in cancer or too little understood. They proposed that MMPs −1, −2, −7, and tentatively −11 (if its substrates are discovered) should be prioritized for selective inhibition [29]. For the brevity of focusing on MMP-7, these other key MMPs in tumor progression are neglected herein. This review considers MMP-7 as a marker of PDAC, influencer of pancreatic tumor progression and microenvironment through release of protein ectodomains (ECDs) from cell surfaces, resistance to apoptosis, needs for therapeutic agents, and avenues for inhibitor development. Specific topics addressed below are summarized in Figure 1.

Guardian of mucosal epithelia

MMP-7 regulates innate immunity, wound healing, and inflammation in epithelial mucosa [14,36–38]. In normal tissues and benign tumors, MMP-7 was detected on the luminal side of glands such as Paneth cells in the intestine, breast ducts, and prostate [6]. Bacterial infection induces expression and activation of MMP-7 in lung epithelia [39,40]. In intestinal crypts, MMP-7 activates bactericidal alpha-defensins [41]. MMP-7 governs wound healing in the lung [36,37,42]. In injured lung epithelia, MMP-7 localizes neutrophil activation to the site of need [43–45] and sheds the ectodomains of E-cadherin [46] and syndecan-1 [42]. Due to the influence on epithelia, the maturation of the zymogen to active MMP-7 is regulated by the

glycosaminoglycan (GAG) chains of heparan sulfate proteoglycans (HSPGs) that it binds on cell surfaces [47,48].

MMP-7 as prognostic of severe pancreatic cancer

Reliable markers of PDAC are needed to aid decisions about surgery [5]. MMP-7 appears valuable as a marker of poor survival of PDAC. Elevated MMP-7 is associated with *two- to three-fold shorter mean survival times* in patient cohorts in Japan, the UK, and the US [7,8,11,49]. The levels of MMP-7 positively correlated with severity of all categories of pathological tumor-node-metastasis staging, and tended to be abundant at the invasive edge of tumors [7,8]. MMP-7 was not detected in healthy pancreas but was detected in 31 of 32 cases of invasive PDAC, all of the tumor-associated metaplastic duct lesions, and most pancreatic intraepithelial neoplasia (PanIN) lesions studied [12]. (PanIN lesions can progress to PDAC [50]). Most differentiated, invasive tumor cells expressed MMP-7, in contrast to the poorly differentiated invasive tumor cells [12].

In one study, all PDAC patients without lymph node involvement had < 20 ng/ml of MMP-7 in their serum vs. the > 20 ng/ml in all patients with metastases [11]. The prognostic value of serum MMP-7 was proposed for use in assessing tsurvival benefit before undertaking the severe demands of tumor resection and recovery [11,51]. This assertion was tested by a surgical study that found that > 13.5 ng/ml of MMP-7 in serum (~15% of the cohort of PDAC patients) was very predictive of either unresectable tumors or nodal involvement [5]. Combined use of the levels of MMP-7 and the carbohydrate antigen 19–9 (CA19–9) in plasma or sera improved the predictive value and discrimination of pancreatic cancer [52,53]. Elevated levels of MMP-7 are also prognostic of poor survival of colorectal cancer [9,54–57], gastric cancer [58], prostate cancer [59], and other cancers [60].

In discrimination of pancreatic cancer that used immunohistochemical detection of protein, elevation of MMP-7 in tumor cells ($P < 0.0001$) held an advantage over elevation of MMP-11 in the stroma ($P < 0.004$) [49]. Using RT-PCR detection of RNA, however, elevation of MMP-11 transcripts is more diagnostic [49], with more reliability across RT-PCR databases for pancreatic cancer [61]. MMP-11 expression appears to be a stromal response that both fosters and suppresses tumor progression [62].

MMP-7 in development of pancreatic cancer in transgenic mice

In genetically engineered murine models (GEMMs) of PDAC, MMP-7 was distinctively expressed in epithelial tumor cells [63]. Tumor size, stage, spread, metastasis, and Kras mutations all strongly correlated with MMP-7 mRNA expression [8]. Knockout of MMP-7 in a GEMM of PDAC eliminated metastases to lymph nodes, dramatically decreased metastases to liver, and decreased the size of the tumors in the pancreas [11]. Acinar cells and acinar-to-ductal metaplasia are one potential source for the development of metaplastic ductal lesions (a replacement of acinar cells)[64–66], PanINs, and PDAC [67]. These observations imply MMP-7 involvement in early stages of progression toward PDAC [12,68], analogous to apparent MMP-7 involvement in tumor formation in other epithelial tissues [69–71].

In a GEMM featuring PanIN development driven by activated *Kras*^{G12D}, Stat3 promoted cell proliferation, inflammation, and MMP-7 expression [11]. The MMP-7 expression was associated with pancreatitis, tumor size, and metastases in the mice [11]. (Pancreatitis is a risk factor prior to PDAC in < 5% of patients [72]. The fibrosis of pancreatitis appears to be promoted by MMP-2 activities of digestion of the type IV collagen and activation of pancreatic stellate cells [73].) The importance of Stat3 and MMP-7 in initiation and progression of PDAC suggested them both to be therapeutic targets [11]. The impacts of several MMP-7 activities upon cell signaling appear relevant.

MMP-7 activation of Notch signaling in pancreatic tumorigenesis

The Notch pathway regulates cell fate decisions, including development of the pancreas [67,74]. In development of pancreatic cancer, individual Notch receptors have distinct, context-dependent, and opposing roles [67,74]. Juxtacrine Notch signaling transmits bidirectionally between stroma and tumor cells via ligands of the Delta and Jagged families binding large Notch receptors [74]. This triggers proteolytic activation of Notch by a metalloproteinase, and ensuing intramembrane cleavage by γ-secretase that releases the Notch intracellular domain to traffic to the nucleus. There it binds a CSL transcription factor to recruit transcriptional co-activators such as Mastermind-like [74].

In GEMMs driven by the activity of *Kras*^{G12D}, MMP-7 proved necessary and sufficient to induce Notch-dependent transdifferentiation of acinar cells into metaplastic ductal cells, which is an early precursor to PanINs [68]. In acinar cells, TGF-α induced expression of MMP-7 which digested the extracellular domain of Notch1 or Notch2 to activate them, with the downstream transcriptional effects of dedifferentiation of the cells *en route* to formation of a duct-like phenotype [68].

Release of cell surface members of death receptor pathways by MMP-7

Death receptors on the surface of tumor cells comprise the members of the tissue necrosis factor superfamily known as TNFR, Fas (CD95), and TNF-related apoptosis inducing ligand receptors. These respond to TNF-α, FasL, and TRAIL, respectively [75]. Binding of these protein ligands to their respective death receptors recruits the Fas-associated death domain and procaspase-8 and −10 into the death-inducing signaling complex (DISC) that activates caspase-8 to initiate proteolytic cascade in the cells [76]. PDAC cells require mitochondrial activity in order to activate caspase-8 and carry out apoptosis [76,77].

MMPs were implicated in proteolytic processing of membrane-bound mFasL to its soluble ectodomain sFasL (Fig. 2). This processing is known as ectodomain shedding. Inhibition of shedding accumulated mFasL and depleted sFasL [78–80]. MMP-7 was identified as the MMP that generates sFasL from mFasL [81]. In a GEMM of acinar-to-ductal metaplasia, MMP-7 generated sFasL [12].This is analogous to the shedding of TNF-α from the surfaces of macrophages by MMP-7 [82]. As soluble TNF-α can be elevated in the serum of pancreatic cancer patients with cachexia [83], it is possible that MMP-7 had shed part of this circulating TNF-α.

Important and less discussed in the literature is the shedding of the ectodomain of the Fas receptor (CD95) by MMP-7 [84] (Fig. 2). The shedding of Fas inhibits apoptosis, and can be impeded by an MMP inhibitor [84]. The site of proteolysis of Fas in its “pre-ligand assembly domain” is likely to interfere in the pre-oligomerization of Fas needed for ligand binding that is functional in apoptosis [84].

MMP-7 support of tumor cell survival and resistance to chemotherapy

Increased tumor cell survival due to MMP-7 activity is widely accepted. Its mechanisms may be varied. Importantly, the competence of sFasL (shed by MMP-7) to induce apoptosis has been controversial, as discussed [19,85]. MMP-7 generated sFasL that was more active than mFasL in inducing apoptosis of HEK 293 epithelial cells work done in found to be *more active* in inducing apoptosis [81]. This also appeared true of murine prostate [81] and early tumor cell lines with short exposures to MMP-7 [85]. However, lymphoma, lymphoblastoma, and carcinoma cell lines resisted apoptosis upon treatment with sFasL but underwent apoptosis in response to mFasL [86–88]. Fas-resistance is normal in cancer cells and can develop in cell transformation by many types of defects in the apoptosis pathway [89]. Oligomerizaton or cross-linking of the sFasL restored apoptosis of the cancer cell lines, apparently by restoring formation of DISC complexes [88]. More reconciliation of disparate sFasL activities came from evidence that constitutive MMP-7 exposure caused early cancer cells to undergo less apoptosis in response to sFasL [85]. (Recall that high MMP-7 can be a characteristic of aggressive tumor cells [19,60]). Ideas offered for the development of resistance to sFasL were that (i) MMP-7 expression by tumor cells should stifle immune infiltration and (ii) FasL expression by tumor cells could induce apoptosis in cytotoxic T cells (the “Fas counterattack”) [85,89,90]. The subsequent report of MMP-7 shedding the Fas receptor [84] should nonetheless be a major consideration in MMP-7-dependent resistance to apoptosis.

MMP-7 expression partly protected tumor cells from the toxicity of DNA-damaging agents such as chemotherapeutics [85,91]. Broad-spectrum MMP inhibitors increased the apoptosis induced in Fas-sensitive cell lines by the chemotherapeutic agent doxorubicin [79]. The pertinent target of this inhibition was identified as MMP-7 [91]. The chemotherapeutic oxaliplatin increased expression of MMP-7, depleted Fas due to proteolysis by MMP-7, and shifted Fas signaling from apoptosis to MAP kinase signaling which promotes survival [92]. Consequently, inhibition of MMP-7 for enhancing the therapeutic potential of standard chemotherapy was proposed [91,93,94], and tested very recently [95].

Proteoglycan of PDAC growth shed by MMP-7

Heparan sulfate proteoglycans are important in cell proliferation, migration, and cellular interactions. Expression of the heparan sulfate proteoglycan syndecan-1 in pancreatic tissues from patients increased with progression to pancreatic cancer [96]. Transgenic mice models of PDAC, driven by oncogenic KRAS expression, prominently expressed syndecan-1, employed it in tumor maintenance, and required syndecan-1 for micropinocytosis to feed tumor growth [97]. MMP-7 was demonstrated to shed syndecan-1 complexes with CXC chemokine from cell surfaces (murine CXCL1/KC or primate CXCL8/IL-8) [43,44]. Since

syndecan-1 ectodomain was reported in human pancreatic cancer tissues [96], it is possible that MMP-7 shed part of the syndecan-1 in these patient specimens. The MMP-7 - syndecan-1 axis is established in spatially localizing neutrophil activation to epithelia [43–45]. The potential effect of MMP-7 shedding of syndecan-1 on micropinocytosis in PDAC remains to be tested, however.

Proteolysis at cell surfaces by MMP-7 that promotes cell proliferation

Independent studies of human pancreatic surgical specimens found that loss of epithelial cadherin (E-cadherin) correlated with stage of pancreatic tumor progression, with lost E-cadherin even being prognostic of poor outcome [98–100]. Loss of E-cadherin is important in epithelial-to-mesenchymal transition in cancer [98,101]. Proteolytic shedding of E-cadherin by metalloproteinases is one of several mechanisms that can deplete E-cadherin from cell-cell junctions [98,102]. MMP-7 processing of E-cadherin increased epithelial cell migration of transformed MDCK canine kidney cells [103], A549 human lung adenocarcinoma cells, and non-transformed MDCK and C57MG cells [104]. The processing disrupted tight cell adherens junctions, and importantly increased cell proliferation with enhanced RhoA GTPase activity and increased cyclin D1 in non-transformed epithelial cells [104]. Proteolytic fragmentation of E-cadherin is likely to alter cell signaling [104]. Indeed, MMP-7 processing of E-cadherin cell promotes proliferation and migration of epithelial cells *in vitro* [46,103,104].

At adherens junctions, small proportions of E-cadherin and the EGF receptor (EGFR) associate in complexes, requiring the ECD of E-cadherin [105–108]. Association with E-cadherin activated EGFR signaling in an immortalized keratinocyte epithelial cell line (HaCat) [106] and a mammary epithelial cell line (MCF10A)[107], but inhibited activation of EGFR and other receptor tyrosine kinases (RTKs) in the MDCK line [108]. Since interference in E-cadherin-dependent cell adhesion disrupted regulation of an RTK [108], proteolytic shedding of E-cadherin by MMP-7 [103,104] may analogously interfere in regulation of RTKs such as EGFR.

EGFR activated by HB-EGF stimulates the proliferation of pancreatic stellate cells [109]. MMP-7 activated the related ErbB4 receptor by processing pro-HB-EGF to HB-EGF, not only in promoting the cell survival of uterine and mammary epithelia [110], but also in tumorigenesis in mammary epithelia [111].

Key strategies of colocalization of MMP-7 with substrates at cell surfaces

The glycosaminoglycan (GAG) chains radiating from heparin sulfate proteoglycans (HSPGs) anchored in plasma membranes recruit MMP-7 to substrates on cell surfaces that modulate cancer progression [19,48], as well to substrates for antibacterial defenses [41,47,48]. For example, the GAG chains of the HSPGs syndecan-1 and syndecan-2 recruit MMP-7, resulting in shedding of the syndecans [44,48,112]. The negative charges of the GAG chains are attracted to the cationic patch on the back of the catalytic domain (Fig. 3) and nearly encircling proMMP-7 [113,114]. HSPGs recruit MMP-7 to process proHB-EGF and release ErbB4 receptor from cells, thereby modulating the EGFR pathway [110,111,115].

Not only do anionic GAGs recruit MMP-7, but so also do membranes that contain sterols, anionic lipids, or especially anionic sterols [116,117]. Cholesterol sulfate recruitment of MMP-7 promotes homotypic cell adhesion and cleavage of laminin-332 and fibronectin [117–119]. The binding site of MMP-7 for anionic bilayers lies on the catalytic domain remote from the active site [120] and overlaps the chief binding site for GAG chains [114]. That mode of binding is rotated 80° and deeper than the association with zwitterionic bilayers [120] shown for better clarity in Fig. 3.

Maturation of proMMP-7 to active MMP-7

Endometrial cells harbored active MMP-7 rather than the proMMP-7 zymogen [116]. The recruitment of MMP-7 can be mediated both by the GAG chains of HSPGs [48,110,113] and by cholesterol sulfate [116,117]. GAG chains trigger activation of the zymogen by bridging them together into aggregates in which activation occurs *in trans*, i.e., with one enzyme proteolytically removing the pro-domain from a neighbor [121]. This or allosteric activation upon binding a lipid bilayer [120] are potential mechanisms of activation of MMP-7 at apical surfaces of epithelial cells; see ref [19].

Therapeutic priorities

Surgical resection is the centerpiece to treatment, but often becomes infeasible with advanced tumor progression impinging on blood vessels [3]. Neoadjuvant therapy has been proposed to shrink tumors to dimensions suitable for resection, in order to increase the number of PDAC patients who can be treated successfully [3]. The resistance of pancreatic cancer to chemotherapy poses an ongoing need for improvement of adjuvant therapy after surgery [3]. Immunotherapies have failed and therapeutic agents have been unable to penetrate the desmoplastic pancreatic tumor microenvironment [3,122]. To overcome barriers to entry, a chemotherapeutic was delivered to hepatocellular carcinoma tumors by localized heating of liposomes using focused ultrasound. Though this failed to increase progression-free survival in clinical trials, it increased overall survival by 2.1 years over radiofrequency ablation only [123,124]. This promising new delivery strategy [125] entered a phase I clinical trial in 2021 for non-resectable PDAC [126].

Multiple studies have suggested MMP-7 to be a promising target for therapeutic development to treat PDAC [7,8,11,12,19,49,68]. Inhibition of MMP-7 to enhance chemotherapy is a longstanding idea for improving adjuvant therapy [11,91,93,94]. The most effective time for inhibition of MMPs was asserted to be early in tumor progression, before or during metastasis, i.e., the neoadjuvant stage [33]. This proposal attributed the failures of clinical trials of MMP inhibitors largely to their testing at stages of cancer that were too advanced [33]. Earlier critiques attributed the failures to lack of selectivity for MMPs that foster cancer progression [28–30,127].

Allosteric inhibitors

High conservation of MMP active sites resulted in broad spectrum inhibition by the competitive inhibitors developed [35]. This limitation and the need for selectivity has

motivated searches for compounds that inhibit non-competitively by binding remotely to less conserved sites [20,32,34,128]. Targeting of remote exosites that distinguish among MMPs has been expected to provide selectivity [20,32,34,35,129,130]. Doxycycline was the first inhibitor demonstrated to bind remotely from the MMP-7 active site and to cause conformation adjustment [131]. While doxycycline inhibition of a broad spectrum of MMPs and other proteins could be a concern, it is the sole MMP inhibitor in clinical use [32], not to mention the use of closely related tetracycline for decades. Doxycycline is used for periodontal disease, promising in clinical trials for multiple sclerosis, and investigated in neuronal disease [132]. Doxycycline binds two sites, probably on the β-sheet where it slows deuterium exchange [131] (Fig. 3). One site is near the structural zinc ion [131], while the other adjoins the site of binding of a GAG chain (Fig. 3).

It was hypothesized that selective inhibition of MMP-7 in cancer could be accomplished if its GAG-triggered maturation could be blocked to prevent activity [48]. The GAG chains can be targeted, but without specificity [133]. We located the principal GAG binding sites on the back side of the catalytic domain (Fig. 3) and spanning from the pro-domain to the catalytic domain [114] (not shown). We also noticed allosteric, remote influences on MMP-7 activation [120] and catalytic velocity [121], confirming the zymogen and activated forms to be allosteric indeed. Preliminary evidence suggests that compounds can be found that bind remotely and modulate or inhibit GAG-triggered activation [134].

Selective inhibition at the active site

Selective inhibition of some MMPs other than MMP-7 has been achieved by engineering of tissue inhibitors of metalloproteinases [31,33,135]. Monoclonal antibodies (mAbs) have provided selective inhibition of several MMPs [20,31–33,35,136]. An inhibitory mAb selective for MMP-7 looks promising indeed [95]. This mAb, GSM-192, binds with high affinity epitopes around the active site of MMP-7 (Fig. 2), probably covering the active site [95]. Low micromolar concentrations of GSM-192 exhibited characteristics sought in MMP inhibitors. It clearly selects MMP-7 over its close homologues of MMP-9, MMP-12, MMP-13, and MMP-14 [95]. GSM-192 decreased the motility of an MMP-7-expressing pancreatic cancer cell line to half in a scratch assay [95]. This mAb markedly increased the apoptosis of MMP-7-expressing pancreatic cancer cell lines, apparently by protecting an active form of FasL from loss, presumably by preventing proteolytic attack by MMP-7 [95]. As proposed by Mitsiades and coworkers [91,93,94], GSM-192 enhanced the sensitivity of MMP-7-expressing pancreatic cancer cell lines to the DNA-damaging chemotherapeutics gemcitabine and oxaliplatin (standard for PDAC [3]), in some cases halving their IC_{50} values [95]. This synergism could result from GSM-192 partly overcoming the elevation of MMP-7, shedding of Fas, and resistance to apoptosis that results from chemotherapy; see refs [84,91,92].

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Abbreviations

CSL	CBF-1/Su(H)/LAG1
DISC	death-inducing signaling complex
E-cadherin	epidermal cadherin
ECD	ectodomain
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
GAG	glycosaminoglycan
GEMM	genetically engineered murine model
HB-EGF	heparin-binding epidermal growth factor
HEK	human embryonic kidney cells
HSPG	heparan sulfate proteoglycan
MMP	matrix metalloproteinase
mAb	monoclonal antibody
NMR	nuclear magnetic resonance
PanIN	pancreatic intraepithelial neoplasia
PDAC	pancreatic ductal adenocarcinoma
RTK	receptor tyrosine kinase
TMD	transmembrane domain
TNF	tissue necrosis factor
TNFR	tissue necrosis factor receptor

References

[1]. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. (2018) Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur. J. Cancer [Internet]. 103, 356–387. Available from: https://www.sciencedirect.com/science/article/pii/S0959804918309559 [PubMed: 30100160]

[2]. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. (2014) Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 74, 2913–2921. [PubMed: 24840647]

[3]. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. (2018) Therapeutic developments in pancreatic cancer: current and future perspectives. Nat. Rev. Gastroenterol Hepatol. [Internet]. 15, 333–348. Available from: 10.1038/s41575-018-0005-x [PubMed: 29717230]

[4]. Mas L, Schwarz L, Bachet J-B. (2020) Adjuvant chemotherapy in pancreatic cancer: state of the art and future perspectives. Curr. Opin. Oncol [Internet]. 32. Available from: https://journals.lww.com/co-oncology/Fulltext/2020/07000/Adjuvant_chemotherapy_in_pancreatic_cancer__state.18.aspx

[5]. Wang SC, Parekh JR, Porembka MR, Nathan H, D'Angelica MI, DeMatteo RP, et al. (2016) A Pilot Study Evaluating Serum MMP7 as a Preoperative Prognostic Marker for Pancreatic Ductal Adenocarcinoma Patients. J. Gastrointest. Surg [Internet]. 20, 899–904. Available from: 10.1007/s11605-015-3057-z [PubMed: 26921028]

[6]. Fingleton B, Powell WC, Crawford HC, Couchman JR, Matrisian LM. (2007) A rat monoclonal antibody that recognizes pro- and active MMP-7 indicates polarized expression in vivo. Hybrid. [Internet]. 26, 22–27. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17316082

[7]. Yamamoto H, Itoh F, Iku S, Adachi Y, Fukushima H, Sasaki S, et al. (2001) Expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human pancreatic adenocarcinomas: clinicopathologic and prognostic significance of matrilysin expression. J. Clin. Oncol [Internet]. 19, 1118–27. Available from: http://ascopubs.org/doi/10.1200/JCO.2001.19.4.1118 [PubMed: 11181677]

[8]. Fukushima H, Yamamoto H, Itoh F, Nakamura H, Min Y, Horiuchi S, et al. (2001) Association of matrilysin mRNA expression with K-ras mutations and progression in pancreatic ductal adenocarcinomas. Carcinogenesis [Internet]. 22, 1049–1052. Available from: https://academic.oup.com/carcin/article-lookup/doi/10.1093/carcin/22.7.1049 [PubMed: 11408348]

[9]. Adachi Y, Yamamoto H, Itoh F, Arimura Y, Nishi M, Endo T, et al. (2001) Clinicopathologic and prognostic significance of matrilysin expression at the invasive front in human colorectal cancers. Int. J. Cancer [Internet]. 95, 290–294. Available from: 10.1002/1097-0215(20010920)95:5<290::AID-IJC1050>3.0.CO [PubMed: 11494227]

[10]. Schmid RM. (2002) Acinar-to-ductal metaplasia in pancreatic cancer development. J. Clin. Invest [Internet]. 109, 1403–1404. Available from: https://pubmed.ncbi.nlm.nih.gov/12045253 [PubMed: 12045253]

[11]. Fukuda A, Wang SC, Morris JPI V, Folias AE, Liou A, Kim GE, et al. (2011) Stat3 and MMP7 Contribute to Pancreatic Ductal Adenocarcinoma Initiation and Progression. Cancer Cell [Internet]. 19, 441–455. Available from: http://www.cell.com/cancer-cell/abstract/S1535-6108(11)00091-2 [PubMed: 21481787]

[12]. Crawford HC, Scoggins CR, Washington MK, Matrisian LM, Leach SD. (2002) Matrix metalloproteinase-7 is expressed by pancreatic cancer precursors and regulates acinar-to-ductal metaplasia in exocrine pancreas. J Clin Invest [Internet]. 109, 1437–1444. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12045257 [PubMed: 12045257]

[13]. Egeblad M, Werb Z. (2002) New functions for the matrix metalloproteinases in cancer progression. Nat. Rev Cancer [Internet]. 2, 161–74. Available from: http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11990853 [PubMed: 11990853]

[14]. Rohani MG, Parks WC. (2015) Matrix remodeling by MMPs during wound repair. Matrix Biol [Internet]. 44–46, 113–121. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25770908 [PubMed: 25770908]

[15]. Khokha R, Murthy A, Weiss A. (2013) Metalloproteinases and their natural inhibitors in inflammation and immunity. Nat Rev Immunol [Internet]. 13, 649–665. Available from: 10.1038/nri3499 [PubMed: 23969736]

[16]. Fingleton B (2017) Matrix metalloproteinases as regulators of inflammatory processes. Biochim. Biophys. Acta - Mol. Cell Res [Internet]. 1864, 2036–2042. Available from: https://www.sciencedirect.com/science/article/pii/S0167488917301210 [PubMed: 28502592]

[17]. Tardáguila-García A, García-Morales E, García-Alamino JM, Álvaro-Afonso FJ, Molines-Barroso RJ, Lázaro-Martínez JL. (2019) Metalloproteinases in chronic and acute wounds: A systematic review and meta-analysis. Wound Repair Regen. [Internet]. 27, 415–420. Available from: 10.1111/wrr.12717 [PubMed: 30873727]

[18]. van Hinsbergh VW, Engelse MA, Quax PH. (2006) Pericellular proteases in angiogenesis and vasculogenesis. Arter. Thromb Vasc Biol [Internet]. 26, 716–728. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16469948

[19]. Ii M, Yamamoto H, Adachi Y, Maruyama Y, Shinomura Y. (2006) Role of matrix metalloproteinase-7 (matrilysin) in human cancer invasion, apoptosis, growth, and angiogenesis. Exp Biol Med [Internet]. 231, 20–27. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16380641

[20]. Li K, Tay FR, Yiu CKY. (2020) The past, present and future perspectives of matrix metalloproteinase inhibitors. Pharmacol. Ther [Internet]. 207, 107465. Available from: https://www.sciencedirect.com/science/article/pii/S0163725819302177

[21]. Nagase H, Murphy G. (2013) Metalloproteinases, Matrix [Internet]. In: Lennarz WJ, Lane MD, editors. Encyclopedia of Biological Chemistry (Second Edition). Waltham: Academic Press; 2013. p. 90–97. Available from: https://www.sciencedirect.com/science/article/pii/B9780123786302004758

[22]. Itoh Y (2015) Membrane-type matrix metalloproteinases: Their functions and regulations. Matrix Biol [Internet]. 44–46, 207–223. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25794647 [PubMed: 25794647]

[23]. Collier IE, Krasnov PA, Strongin AY, Birkedal-Hansen H, Goldberg GI. (1992) Alanine scanning mutagenesis and functional analysis of the fibronectin-like collagen-binding domain from human 92-kDa type IV collagenase. J Biol Chem [Internet]. 267, 6776–6781. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1313021 [PubMed: 1313021]

[24]. O'Farrell TJ, Pourmotabbed T. (1998) The fibronectin-like domain is required for the type V and XI collagenolytic activity of gelatinase B. Arch Biochem Biophys [Internet]. 354, 24–30. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9633594 [PubMed: 9633594]

[25]. Tam EM, Moore TR, Butler GS, Overall CM. (2004) Characterization of the distinct collagen binding, helicase and cleavage mechanisms of matrix metalloproteinase 2 and 14 (gelatinase A and MT1-MMP): the differential roles of the MMP hemopexin c domains and the MMP-2 fibronectin type II modules in collage. J Biol Chem [Internet]. 279, 43336–43344. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15292230 [PubMed: 15292230]

[26]. Doren Van SR (2011) Structural Basis of Extracellular Matrix Interactions with Matrix Metalloproteinases. In: Parks WC, Mecham RP, editors. Extracellular Matrix Degradation. Berlin: Springer-Verlag; 2011. p. 123–144.

[27]. Jackson BC, Nebert DW, Vasiliou V. (2010) Update of human and mouse matrix metalloproteinase families. Hum. Genomics [Internet]. 4, 194. Available from: 10.1186/1479-7364-4-3-194 [PubMed: 20368140]

[28]. Coussens LM, Fingleton B, Matrisian LM. (2002) Matrix metalloproteinase inhibitors and cancer: trials and tribulations. Science (80-.) [Internet]. 295, 2387–2392. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11923519

[29]. Overall CM, Kleifeld O. (2006) Tumour microenvironment - opinion: validating matrix metalloproteinases as drug targets and anti-targets for cancer therapy. Nat Rev Cancer [Internet]. 6, 227–239. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16498445 [PubMed: 16498445]

[30]. Overall CM, Kleifeld O. (2006) Towards third generation matrix metalloproteinase inhibitors for cancer therapy. Br J Cancer [Internet]. 94, 941–946. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16538215 [PubMed: 16538215]

[31]. Radisky ES, Raeeszadeh-Sarmazdeh M, Radisky DC. (2017) Therapeutic Potential of Matrix Metalloproteinase Inhibition in Breast Cancer. J. Cell. Biochem [Internet]. 118, 3531–3548. Available from: 10.1002/jcb.26185 [PubMed: 28585723]

[32]. Fields GB. (2019) The Rebirth of Matrix Metalloproteinase Inhibitors: Moving Beyond the Dogma. Cells. 8.

[33]. Winer A, Adams S, Mignatti P. (2018) Matrix Metalloproteinase Inhibitors in Cancer Therapy: Turning Past Failures Into Future Successes. Mol. Cancer Ther 17, 1147–1155. [PubMed: 29735645]

[34]. Overall CM, Lopez-Otin C. (2002) Strategies for MMP inhibition in cancer: innovations for the post-trial era. Nat Rev Cancer [Internet]. 2, 657–672. Available from: internal-pdf://239.43.112.161/Overall-2002-Strategies for MMP i.pdf [PubMed: 12209155]

[35]. Levin M, Udi Y, Solomonov I, Sagi I. (2017) Next generation matrix metalloproteinase inhibitors — Novel strategies bring new prospects. Biochim. Biophys. Acta - Mol. Cell Res. [Internet]. 1864, 1927–1939. Available from: https://www.sciencedirect.com/science/article/pii/S0167488917301611 [PubMed: 28636874]

[36]. Parks WC, Wilson CL, Lopez-Boado YS. (2004) Matrix metalloproteinases as modulators of inflammation and innate immunity. Nat Rev Immunol [Internet]. 4, 617–629. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15286728 [PubMed: 15286728]

[37]. Gill SE, Parks WC. (2008) Metalloproteinases and their inhibitors: Regulators of wound healing. Int. J. Biochem. Cell Biol [Internet]. 40, 1334–1347. Available from: http://www.sciencedirect.com/science/article/pii/S1357272507003433 [PubMed: 18083622]

[38]. Smigiel KS, Parks WC. (2017) Chapter Five - Matrix Metalloproteinases and Leukocyte Activation [Internet]. In: Khalil RA, editor. Matrix Metalloproteinases and Tissue Remodeling in Health and Disease: Cardiovascular Remodeling. Academic Press; 2017. p. 167–195. Available from: https://www.sciencedirect.com/science/article/pii/S1877117317300145

[39]. Kassim SY, Gharib SA, Mecham BH, Birkland TP, Parks WC, McGuire JK. (2007) Individual matrix metalloproteinases control distinct transcriptional responses in airway epithelial cells infected with Pseudomonas aeruginosa. Infect Immun [Internet]. 75, 5640–5650. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17923522 [PubMed: 17923522]

[40]. López-Boado YS, Wilson CL, Parks WC. (2001) Regulation of Matrilysin Expression in Airway Epithelial Cells by Pseudomonas aeruginosa Flagellin*. J. Biol. Chem [Internet]. 276, 41417–41423. Available from: https://www.sciencedirect.com/science/article/pii/S0021925820780051 [PubMed: 11527977]

[41]. Wilson CL, Ouellette AJ, Satchell DP, Ayabe T, Lopez-Boado YS, Stratman JL, et al. (1999) Regulation of intestinal alpha-defensin activation by the metalloproteinase matrilysin in innate host defense. Science (80-.) [Internet]. 286, 113–117. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10506557

[42]. Chen P, Abacherli LE, Nadler ST, Wang Y, Li Q, Parks WC. (2009) MMP7 shedding of syndecan-1 facilitates re-epithelialization by affecting alpha(2)beta(1) integrin activation. PLoS One [Internet]. 4, e6565. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19668337 [PubMed: 19668337]

[43]. Gill SE, Nadler ST, Li Q, Frevert CW, Park PW, Chen P, et al. (2016) Shedding of Syndecan-1/CXCL1 Complexes by Matrix Metalloproteinase 7 Functions as an Epithelial Checkpoint of Neutrophil Activation. Am J Respir Cell Mol Biol [Internet]. 55, 243–251. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26934670 [PubMed: 26934670]

[44]. Li Q, Park PW, Wilson CL, Parks WC. (2002) Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. Cell [Internet]. 111, 635–646. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12464176 [PubMed: 12464176]

[45]. Swee M, Wilson CL, Wang Y, McGuire JK, Parks WC. (2008) Matrix metalloproteinase-7 (matrilysin) controls neutrophil egress by generating chemokine gradients. J Leukoc Biol [Internet]. 83, 1404–1412. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18334539 [PubMed: 18334539]

[46]. McGuire JK, Li Q, Parks WC. (2003) Matrilysin (matrix metalloproteinase-7) mediates E-cadherin ectodomain shedding in injured lung epithelium. Am J Pathol

[Internet]. 162, 1831–1843. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12759241 [PubMed: 12759241]

[47]. Ra HJ, Harju-Baker S, Zhang F, Linhardt RJ, Wilson CL, Parks WC. (2009) Control of promatrilysin (MMP7) activation and substrate-specific activity by sulfated glycosaminoglycans. J Biol Chem [Internet]. 284, 27924–27932. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19654318 [PubMed: 19654318]

[48]. Tocchi A, Parks WC. (2013) Functional interactions between matrix metalloproteinases and glycosaminoglycans. FEBS J [Internet]. 280, 2332–2341. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23421805 [PubMed: 23421805]

[49]. Jones LE, Humphreys MJ, Campbell F, Neoptolemos JP, Boyd MT. (2004) Comprehensive Analysis of Matrix Metalloproteinase and Tissue Inhibitor Expression in Pancreatic Cancer. Clin. Cancer Res [Internet]. 10, 2832–2845. Available from: http://clincancerres.aacrjournals.org/content/10/8/2832 [PubMed: 15102692]

[50]. Klein WM, Hruban RH, Klein-Szanto AJP, Wilentz RE. (2002) Direct Correlation between Proliferative Activity and Dysplasia in Pancreatic Intraepithelial Neoplasia (PanIN): Additional Evidence for a Recently Proposed Model of Progression. Mod. Pathol [Internet]. 15, 441–447. Available from: 10.1038/modpathol.3880544 [PubMed: 11950919]

[51]. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, et al. (2006) 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J. Gastrointest. Surg. Off. J. Soc. Surg. Aliment. Tract 10, 1191–1199.

[52]. Kuhlmann KFD, van Till JWO, Boermeester MA, de Reuver PR, Tzvetanova ID, Offerhaus GJA, et al. (2007) Evaluation of matrix metalloproteinase 7 in plasma and pancreatic juice as a biomarker for pancreatic cancer. Cancer Epidemiol. biomarkers Prev. a Publ. Am. Assoc. Cancer Res. cosponsored by Am. Soc. Prev. Oncol 16, 886–891.

[53]. Park H-D, Kang E-S, Kim J-W, Lee K-T, Lee KH, Park YS, et al. (2012) Serum CA19–9, cathepsin D, and matrix metalloproteinase-7 as a diagnostic panel for pancreatic ductal adenocarcinoma. Proteomics [Internet]. 12, 3590–3597. Available from: https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/abs/10.1002/pmic.201200101 [PubMed: 23065739]

[54]. Klupp F, Neumann L, Kahlert C, Diers J, Halama N, Franz C, et al. (2016) Serum MMP7, MMP10 and MMP12 level as negative prognostic markers in colon cancer patients. BMC Cancer [Internet]. 16, 494. Available from: 10.1186/s12885-016-2515-7 [PubMed: 27431388]

[55]. Koskensalo S, Louhimo J, Nordling S, Hagström J, Haglund C. (2011) MMP-7 as a prognostic marker in colorectal cancer. Tumor Biol. [Internet]. 32, 259–264. Available from: 10.1007/s13277-010-0080-2

[56]. Sun D, Zhang Y, Qi Y, Zhou X, Lv G. (2015) Prognostic significance of MMP-7 expression in colorectal cancer: A meta-analysis. Cancer Epidemiol. [Internet]. 39, 135–142. Available from: https://www.sciencedirect.com/science/article/pii/S1877782115000284 [PubMed: 25677090]

[57]. Whatley AS, Ditzler MA, Lange MJ, Biondi E, Sawyer AW, Chang JL, et al. (2013) Potent Inhibition of HIV-1 Reverse Transcriptase and Replication by Nonpseudoknot, “UCAA-motif” RNA Aptamers. Mol Ther Nucleic Acids [Internet]. 2, e71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23385524 [PubMed: 23385524]

[58]. Koskensalo S, Mrena J, Wiksten J-P, Nordling S, Kokkola A, Hagström J, et al. (2010) MMP-7 overexpression is an independent prognostic marker in gastric cancer. Tumor Biol [Internet]. 31, 149–155. Available from: 10.1007/s13277-010-0020-1

[59]. Szarvas T, Csizmarik A, Váradi M, Fazekas T, Hüttl A, Nyirády P, et al. (2021) The prognostic value of serum MMP-7 levels in prostate cancer patients who received docetaxel, abiraterone, or enzalutamide therapy. Urol. Oncol 39, 296.e11–296.e19.

[60]. Liao H-Y, Da C-M, Liao B, Zhang H-H. (2021) Roles of matrix metalloproteinase-7 (MMP-7) in cancer. Clin. Biochem [Internet]. 92, 9–18. Available from: https://www.sciencedirect.com/science/article/pii/S0009912021000722 [PubMed: 33713636]

[61]. LEE J, LEE J, KIM JAEH. (2019) Identification of Matrix Metalloproteinase 11 as a Prognostic Biomarker in Pancreatic Cancer. Anticancer Res. [Internet]. 39, 5963–5971. Available from: https://ar.iiarjournals.org/content/39/11/5963 [PubMed: 31704821]

[62]. Zhang X, Huang S, Guo J, Zhou L, You L, Zhang T, et al. (2016) Insights into the distinct roles of MMP-11 in tumor biology and future therapeutics (Review). Int J Oncol [Internet]. 48, 1783–1793. Available from: 10.3892/ijo.2016.3400 [PubMed: 26892540]

[63]. Hosein AN, Huang H, Wang Z, Parmar K, Du W, Huang J, et al. (2019) Cellular heterogeneity during mouse pancreatic ductal adenocarcinoma progression at single-cell resolution. JCI Insight [Internet]. Available from: https://insight.jci.org/articles/view/129212

[64]. Giroux V, Rustgi AK. (2017) Metaplasia: tissue injury adaptation and a precursor to the dysplasia-cancer sequence. Nat. Rev. Cancer 17, 594–604. [PubMed: 28860646]

[65]. Parsa I, Longnecker DS, Scarpelli DG, Pour P, Reddy JK, Lefkowitz M. (1985) Ductal Metaplasia of Human Exocrine Pancreas and Its Association with Carcinoma. Cancer Res. [Internet]. 45, 1285–1290. Available from: https://cancerres.aacrjournals.org/content/45/3/1285 [PubMed: 2982487]

[66]. Wagner M, Lührs H, Klöppel G, Adler G, Schmid RM. (1998) Malignant transformation of duct-like cells originating from acini in transforming growth factor α transgenic mice. Gastroenterology [Internet]. 115, 1254–1262. Available from: https://www.sciencedirect.com/science/article/pii/S0016508598700988 [PubMed: 9797382]

[67]. Avila JL, Kissil JL. (2013) Notch signaling in pancreatic cancer: oncogene or tumor suppressor? Trends Mol. Med [Internet]. 19, 320–327. Available from: https://www.sciencedirect.com/science/article/pii/S1471491413000439 [PubMed: 23545339]

[68]. Sawey ET, Johnson JA, Crawford HC. (2007) Matrix metalloproteinase 7 controls pancreatic acinar cell transdifferentiation by activating the Notch signaling pathway. Proc Natl Acad Sci U S A [Internet]. 104, 19327–19332. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18042722 [PubMed: 18042722]

[69]. McDonnell S, Navre M, Coffey RJ Jr, Matrisian LM (1991) Expression and localization of the matrix metalloproteinase pump-1 (MMP-7) in human gastric and colon carcinomas. Mol Carcinog [Internet]. 4, 527–533. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1793490 [PubMed: 1793490]

[70]. Wilson CL, Heppner KJ, Labosky PA, Hogan BL, Matrisian LM. (1997) Intestinal tumorigenesis is suppressed in mice lacking the metalloproteinase matrilysin. Proc Natl Acad Sci U S A [Internet]. 94, 1402–1407. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9037065 [PubMed: 9037065]

[71]. Rudolph-Owen LA, Chan R, Muller WJ, Matrisian LM. (1998) The matrix metalloproteinase matrilysin influences early-stage mammary tumorigenesis. Cancer Res [Internet]. 58, 5500–5506. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9850086 [PubMed: 9850086]

[72]. Singhi AD, Koay EJ, Chari ST, Maitra A. (2019) Early Detection of Pancreatic Cancer: Opportunities and Challenges. Gastroenterology [Internet]. 156, 2024–2040. Available from: https://www.sciencedirect.com/science/article/pii/S0016508519303580 [PubMed: 30721664]

[73]. Sri Manjari K, Nallari P, Venkateshwari A. (2017) Matrix metalloproteinases in pancreatitis: current insights. Met. Med [Internet]. 4, 15–23. Available from: 10.2147/MNM.S105774

[74]. Meurette O, Mehlen P. (2018) Notch Signaling in the Tumor Microenvironment. Cancer Cell [Internet]. 34, 536–548. 5: https://www.sciencedirect.com/science/article/pii/S1535610818303155 [PubMed: 30146333]

[75]. Hamacher R, Schmid RM, Saur D, Schneider G. (2008) Apoptotic pathways in pancreatic ductal adenocarcinoma. Mol. Cancer [Internet]. 7, 64. Available from: 10.1186/1476-4598-7-64 [PubMed: 18652674]

[76]. Walczak H, Krammer PH. (2000) The CD95 (APO-1/Fas) and the TRAIL (APO-2L) Apoptosis Systems. Exp. Cell Res [Internet]. 256, 58–66. Available from: https://www.sciencedirect.com/science/article/pii/S0014482700948407 [PubMed: 10739652]

[77]. Hinz S, Trauzold A, Boenicke L, Sandberg C, Beckmann S, Bayer E, et al. (2000) Bcl-XL protects pancreatic adenocarcinoma cells against CD95- and TRAIL-receptor-mediated apoptosis. Oncogene [Internet]. 19, 5477–5486. Available from: 10.1038/sj.onc.1203936 [PubMed: 11114725]

[78]. Kayagaki N, Kawasaki A, Ebata T, Ohmoto H, Ikeda S, Inoue S, et al. (1995) Metalloproteinase-mediated release of human Fas ligand. J Exp Med [Internet]. 182, 1777–1783. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7500022 [PubMed: 7500022]

[79]. Mitsiades N, Poulaki V, Leone A, Tsokos M. (1999) Fas-Mediated Apoptosis in Ewing's Sarcoma Cell Lines by Metalloproteinase Inhibitors. JNCI J. Natl. Cancer Inst [Internet]. 91, 1678–1684. Available from: 10.1093/jnci/91.19.1678 [PubMed: 10511596]

[80]. Mitsiades N, Poulaki V, Kotoula V, Leone A, Tsokos M. (1998) Fas Ligand Is Present in Tumors of the Ewing's Sarcoma Family and Is Cleaved into a Soluble Form by a Metalloproteinase. Am. J. Pathol [Internet]. 153, 1947–1956. Available from: https://www.sciencedirect.com/science/article/pii/S0002944010657082 [PubMed: 9846984]

[81]. Powell WC, Fingleton B, Wilson CL, Boothby M, Matrisian LM. (1999) The metalloproteinase matrilysin proteolytically generates active soluble Fas ligand and potentiates epithelial cell apoptosis. Curr Biol [Internet]. 9, 1441–1447. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10607586 [PubMed: 10607586]

[82]. Haro H, Crawford HC, Fingleton B, MacDougall JR, Shinomiya K, Spengler DM, et al. (2000) Matrix metalloproteinase-3-dependent generation of a macrophage chemoattractant in a model of herniated disc resorption. J Clin Invest [Internet]. 105, 133–141. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10642591 [PubMed: 10642591]

[83]. Karayiannakis AJ, Syrigos KN, Polychronidis A, Pitiakoudis M, Bounovas A, Simopoulos K. (2001) Serum levels of tumor necrosis factor-alpha and nutritional status in pancreatic cancer patients. Anticancer Res. 21, 1355–1358. [PubMed: 11396212]

[84]. Strand S, Vollmer P, van den Abeelen L, Gottfried D, Alla V, Heid H, et al. (2004) Cleavage of CD95 by matrix metalloproteinase-7 induces apoptosis resistance in tumour cells. Oncogene [Internet]. 23, 3732–3736. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15077180 [PubMed: 15077180]

[85]. Fingleton B, Vargo-Gogola T, Crawford HC, Matrisian LM. (2001) Matrilysin [MMP-7] expression selects for cells with reduced sensitivity to apoptosis. Neoplasia [Internet]. 3, 459–468. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11774028 [PubMed: 11774028]

[86]. Tanaka M, Itai T, Adachi M, Nagata S. (1998) Downregulation of Fas ligand by shedding. Nat. Med [Internet]. 4, 31–36. Available from: 10.1038/nm0198-031 [PubMed: 9427603]

[87]. Schneider P, Holler N, Bodmer J-L, Hahne M, Frei K, Fontana A, et al. (1998) Conversion of Membrane-bound Fas(CD95) Ligand to Its Soluble Form Is Associated with Downregulation of Its Proapoptotic Activity and Loss of Liver Toxicity . J. Exp. Med [Internet]. 187, 1205–1213. Available from: 10.1084/jem.187.8.1205 [PubMed: 9547332]

[88]. Nils H, Aubry T, Magdalena K-B, Sylvie H, Olivier G, Fabio M, et al. (2003) Two Adjacent Trimeric Fas Ligands Are Required for Fas Signaling and Formation of a Death-Inducing Signaling Complex. Mol. Cell. Biol [Internet]. 23, 1428–1440. Available from: 10.1128/MCB.23.4.1428-1440.2003 [PubMed: 12556501]

[89]. O'Connell J, Bennett MW, O'Sullivan GC, Collins JK, Shanahan F. (1997) The Fas Counterattack: A Molecular Mechanism of Tumor Immune Privilege. Mol. Med [Internet]. 3, 294–300. Available from: 10.1007/BF03401808 [PubMed: 9205945]

[90]. Walker PR, Saas P, Dietrich PY. (1997) Role of Fas ligand (CD95L) in immune escape: the tumor cell strikes back. J. Immunol [Internet]. 158, 4521–4524. Available from: https://www.jimmunol.org/content/158/10/4521 [PubMed: 9144461]

[91]. Mitsiades N, Yu WH, Poulaki V, Tsokos M, Stamenkovic I. (2001) Matrix metalloproteinase-7-mediated cleavage of Fas ligand protects tumor cells from chemotherapeutic drug cytotoxicity. Cancer Res [Internet]. 61, 577–581. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11212252 [PubMed: 11212252]

[92]. Almendro V, Ametller E, García-Recio S, Collazo O, Casas I, Augé JM, et al. (2009) The Role of MMP7 and Its Cross-Talk with the FAS/FASL System during the Acquisition

of Chemoresistance to Oxaliplatin. PLoS One [Internet]. 4, 1–12. Available from: 10.1371/journal.pone.0004728

[93]. Mitsiades N, Poulaki V, Mitsiades CS, Anderson KC. (2001) Induction of tumour cell apoptosis by matrix metalloproteinase inhibitors: new tricks from a (not so) old drug. Expert Opin Investig Drugs [Internet]. 10, 1075–1084. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11772236

[94]. Poulaki V, Mitsiades CS, Mitsiades N. (2001) The role of Fas and FasL as mediators of anticancer chemotherapy. Drug Resist Updat [Internet]. 4, 233–242. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11991678 [PubMed: 11991678]

[95]. Mohan V, Gaffney JP, Solomonov I, Levin M, Klepfish M, Akbareian S, et al. (2021) Conformation-Specific Inhibitory Anti-MMP-7 Monoclonal Antibody Sensitizes Pancreatic Ductal Adenocarcinoma Cells to Chemotherapeutic Cell Kill. Cancers (Basel). [Internet]. 13. Available from: https://www.mdpi.com/2072-6694/13/7/1679

[96]. Conejo JR, Kleeff J, Koliopanos A, Matsuda K, Zhu ZW, Goecke H, et al. (2000) Syndecan-1 expression is up-regulated in pancreatic but not in other gastrointestinal cancers. Int. J. Cancer [Internet]. 88, 12–20. Available from: 10.1002/1097-0215(20001001)88:1<12::AID-IJC3>3.0.CO [PubMed: 10962434]

[97]. Yao W, Rose JL, Wang W, Seth S, Jiang H, Taguchi A, et al. (2019) Syndecan 1 is a critical mediator of macropinocytosis in pancreatic cancer. Nature [Internet]. 568, 410–414. Available from: http://www.nature.com/articles/s41586-019-1062-1 [PubMed: 30918400]

[98]. Sommariva M, Gagliano N. (2020) E-Cadherin in Pancreatic Ductal Adenocarcinoma: A Multifaceted Actor during EMT. Cells [Internet]. 9. Available from: https://www.mdpi.com/2073-4409/9/4/1040

[99]. Hong S-M, Li A, Olino K, Wolfgang CL, Herman JM, Schulick RD, et al. (2011) Loss of E-cadherin expression and outcome among patients with resectable pancreatic adenocarcinomas. Mod. Pathol [Internet]. 24, 1237–1247. Available from: 10.1038/modpathol.2011.74 [PubMed: 21552209]

[100]. Al-Aynati MM, Radulovich N, Riddell RH, Tsao M-S. (2004) Epithelial-Cadherin and β-Catenin Expression Changes in Pancreatic Intraepithelial Neoplasia. Clin. Cancer Res [Internet]. 10, 1235–1240. Available from: https://clincancerres.aacrjournals.org/content/10/4/1235 [PubMed: 14977820]

[101]. Huang H, Wright S, Zhang J, Brekken RA. (2019) Getting a grip on adhesion: Cadherin switching and collagen signaling. Biochim. Biophys. Acta - Mol. Cell Res. [Internet]. 1866, 118472. Available from: https://www.sciencedirect.com/science/article/pii/S0167488919300734

[102]. Beavon IRG. (2000) The E-cadherin–catenin complex in tumour metastasis: structure, function and regulation. Eur. J. Cancer [Internet]. 36, 1607–1620. Available from: https://www.sciencedirect.com/science/article/pii/S0959804900001581 [PubMed: 10959047]

[103]. Noe V, Fingleton B, Jacobs K, Crawford HC, Vermeulen S, Steelant W, et al. (2001) Release of an invasion promoter E-cadherin fragment by matrilysin and stromelysin-1. J. Cell Sci [Internet]. 114, 111–118. Available from: http://jcs.biologists.org/content/114/1/111.abstract [PubMed: 11112695]

[104]. Lynch CC, Vargo-Gogola T, Matrisian LM, Fingleton B. (2010) Cleavage of E-Cadherin by Matrix Metalloproteinase-7 Promotes Cellular Proliferation in Nontransformed Cell Lines via Activation of RhoA. J. Oncol [Internet]. 2010, 530745. Available from: 10.1155/2010/530745

[105]. Hoschuetzky H, Aberle H, Kemler R. (1994) Beta-catenin mediates the interaction of the cadherin-catenin complex with epidermal growth factor receptor. J. Cell Biol [Internet]. 127, 1375–1380. Available from: 10.1083/jcb.127.5.1375 [PubMed: 7962096]

[106]. Pece S, Gutkind JS. (2000) Signaling from E-cadherins to the MAPK Pathway by the Recruitment and Activation of Epidermal Growth Factor Receptors upon Cell-Cell Contact Formation *. J. Biol. Chem [Internet]. 275, 41227–41233. Available from: 10.1074/jbc.M006578200 [PubMed: 10969083]

[107]. Fedor-Chaiken M, Hein PW, Stewart JC, Brackenbury R, Kinch MS. (2003) E-Cadherin Binding Modulates EGF Receptor Activation. Cell Commun. Adhes [Internet]. 10, 105–118. Available from: 10.1080/cac.10.2.105.118 [PubMed: 14681060]

[108]. Qian X, Karpova T, Sheppard AM, McNally J, Lowy DR. (2004) E-cadherin-mediated adhesion inhibits ligand-dependent activation of diverse receptor tyrosine kinases. EMBO J. [Internet]. 23, 1739–1748. Available from: https://pubmed.ncbi.nlm.nih.gov/15057284 [PubMed: 15057284]

[109]. Blaine SA, Ray KC, Branch KM, Robinson PS, Whitehead RH, Means AL. (2009) Epidermal growth factor receptor regulates pancreatic fibrosis. Am. J. Physiol. Liver Physiol [Internet]. 297, G434–G441. Available from: 10.1152/ajpgi.00152.2009

[110]. Yu WH, Woessner JF Jr, McNeish JD, Stamenkovic I (2002) CD44 anchors the assembly of matrilysin/MMP-7 with heparin-binding epidermal growth factor precursor and ErbB4 and regulates female reproductive organ remodeling. Genes Dev [Internet]. 16, 307–323. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11825873 [PubMed: 11825873]

[111]. Lynch CC, Vargo-Gogola T, Martin MD, Fingleton B, Crawford HC, Matrisian LM. (2007) Matrix metalloproteinase 7 mediates mammary epithelial cell tumorigenesis through the ErbB4 receptor. Cancer Res [Internet]. 67, 6760–6767. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17638887 [PubMed: 17638887]

[112]. Ryu H-Y, Lee J, Yang S, Park H, Choi S, Jung K-C, et al. (2009) Syndecan-2 Functions as a Docking Receptor for Pro-matrix Metalloproteinase-7 in Human Colon Cancer Cells. J. Biol. Chem [Internet]. 284, 35692–35701. Available from: http://www.jbc.org/content/284/51/35692.abstract [PubMed: 19858218]

[113]. Yu WH, Woessner JF Jr (2000) Heparan sulfate proteoglycans as extracellular docking molecules for matrilysin (matrix metalloproteinase 7). J Biol Chem [Internet]. 275, 4183–4191. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10660581 [PubMed: 10660581]

[114]. Fulcher YG, Prior SH, Masuko S, Li L, Pu D, Zhang F, et al. (2017) Glycan Activation of a Sheddase: Electrostatic Recognition between Heparin and proMMP-7. Structure. 25.

[115]. Kivisaari AK, Kallajoki M, Ala-aho R, McGrath JA, Bauer JW, Königová R, et al. (2010) Matrix metalloproteinase-7 activates heparin-binding epidermal growth factor-like growth factor in cutaneous squamous cell carcinoma. Br. J. Dermatol [Internet]. 163, 726–735. Available from: 10.1111/j.1365-2133.2010.09924.x [PubMed: 20586780]

[116]. Berton A, Selvais C, Lemoine P, Henriet P, Courtoy PJ, Marbaix E, et al. (2007) Binding of matrilysin-1 to human epithelial cells promotes its activity. Cell Mol Life Sci [Internet]. 64, 610–620. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17310281 [PubMed: 17310281]

[117]. Yamamoto K, Higashi S, Kioi M, Tsunezumi J, Honke K, Miyazaki K. (2006) Binding of active matrilysin to cell surface cholesterol sulfate is essential for its membrane-associated proteolytic action and induction of homotypic cell adhesion. J Biol Chem [Internet]. 281, 9170–9180. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16476739 [PubMed: 16476739]

[118]. Yamamoto K, Miyazaki K, Higashi S. (2010) Cholesterol sulfate alters substrate preference of matrix metalloproteinase-7 and promotes degradations of pericellular laminin-332 and fibronectin. J Biol Chem [Internet]. 285, 28862–28873. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20605794 [PubMed: 20605794]

[119]. Yamamoto K, Miyazaki K, Higashi S. (2014) Pericellular proteolysis by matrix metalloproteinase-7 is differentially modulated by cholesterol sulfate, sulfatide, and cardiolipin. FEBS J [Internet]. 281, 3346–3356. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24903600 [PubMed: 24903600]

[120]. Prior SH, Fulcher YG, Koppisetti RK, Jurkevich A, Van Doren SR. (2015) Charge-Triggered Membrane Insertion of Matrix Metalloproteinase-7, Supporter of Innate Immunity and Tumors. Structure. 23.

[121]. Fulcher YG, Sanganna Gari RR, Frey NC, Zhang F, Linhardt RJ, King GM, et al. (2014) Heparinoids activate a protease, secreted by mucosa and tumors, via tethering supplemented by allostery. ACS Chem. Biol 9, 957–966. [PubMed: 24495220]

[122]. Olaoba OT, Ligali FC, Alabi ZO, Akinyemi AO, Ayinde KS. (2021) Of immune checkpoint maladies and remedies: The throwing of jabs in the oncogenic ring of PDAC. Biochim. Biophys. Acta - Rev. Cancer [Internet]. 1875, 188483. Available from: https://www.sciencedirect.com/science/article/pii/S0304419X2030202X

[123]. Dou Y, Hynynen K, Allen C. (2017) To heat or not to heat: Challenges with clinical translation of thermosensitive liposomes. J. Control. Release [Internet]. 249, 63–73. Available from: https://www.sciencedirect.com/science/article/pii/S0168365917300238 [PubMed: 28122204]

[124]. Lyon PC, Griffiths LF, Lee J, Chung D, Carlisle R, Wu F, et al. (2017) Clinical trial protocol for TARDOX: a phase I study to investigate the feasibility of targeted release of lyso-thermosensitive liposomal doxorubicin (ThermoDox®) using focused ultrasound in patients with liver tumours. J. Ther. Ultrasound [Internet]. 5, 28. Available from: 10.1186/s40349-017-0104-0 [PubMed: 29118984]

[125]. Boissenot T, Bordat A, Fattal E, Tsapis N. (2016) Ultrasound-triggered drug delivery for cancer treatment using drug delivery systems: From theoretical considerations to practical applications. J. Control. Release [Internet]. 241, 144–163. Available from: https://www.sciencedirect.com/science/article/pii/S0168365916308070 [PubMed: 27667179]

[126]. Coussios CC, Middleton MR. (2021) Focused Ultrasound for Pancreatic Cancer [Internet]. Available from: https://eng.ox.ac.uk/news/focused-ultrasound-for-pancreatic-cancer/

[127]. Fingleton B (2008) MMPs as therapeutic targets-Still a viable option? Semin Cell Dev Biol [Internet]. 19, 61–68. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17693104 [PubMed: 17693104]

[128]. Sela-Passwell N, Rosenblum G, Shoham T, Sagi I. (2010) Structural and functional bases for allosteric control of MMP activities: Can it pave the path for selective inhibition? Biochim. Biophys. Acta - Mol. Cell Res [Internet]. 1803, 29–38. Available from: http://www.sciencedirect.com/science/article/pii/S0167488909001062

[129]. Cathcart J, Pulkoski-Gross A, Cao J. (2015) Targeting matrix metalloproteinases in cancer: Bringing new life to old ideas. Genes Dis. [Internet]. 2, 26–34. Available from: https://www.sciencedirect.com/science/article/pii/S2352304215000021 [PubMed: 26097889]

[130]. Fulcher YG, Van Doren SR. (2011) Remote exosites of the catalytic domain of matrix metalloproteinase-12 enhance elastin degradation. Biochemistry. 50.

[131]. Garcia RA, Pantazatos DP, Gessner CR, Go KV, Woods VL Jr, Villarreal FJ (2005) Molecular interactions between matrilysin and the matrix metalloproteinase inhibitor doxycycline investigated by deuterium exchange mass spectrometry. Mol Pharmacol [Internet]. 67, 1128–1136. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15665254 [PubMed: 15665254]

[132]. Vandenbroucke RE, Libert C. (2014) Is there new hope for therapeutic matrix metalloproteinase inhibition? Nat Rev Drug Discov [Internet]. 13, 904–927. Available from: 10.1038/nrd4390 [PubMed: 25376097]

[133]. Weiss RJ, Esko JD, Tor Y. (2017) Targeting heparin and heparan sulfate protein interactions. Org. Biomol. Chem [Internet]. 15, 5656–5668. Available from: 10.1039/C7OB01058C [PubMed: 28653068]

[134]. Van Doren SR, Bernard D, Alcantar M, Troupe C, Breton H, McKay C, et al. (2020) Targeting invasion-promoting proteases MMP-7 and MMP-14 at remote exosites [Internet]. In: ACS Fall 2020 Virtual Meeting. San Francisco: American Chemical Society; 2020. Available from: 10.1021/scimeetings.0c06795

[135]. Zou H, Wu Y, Brew K. (2016) Thermodynamic Basis of Selectivity in the Interactions of Tissue Inhibitors of Metalloproteinases N-domains with Matrix Metalloproteinases-1, −3, and −14*. J. Biol. Chem [Internet]. 291, 11348–11358. Available from: https://www.sciencedirect.com/science/article/pii/S0021925820408737 [PubMed: 27033700]

[136]. Sela-Passwell N, Kikkeri R, Dym O, Rozenberg H, Margalit R, Arad-Yellin R, et al. (2012) Antibodies targeting the catalytic zinc complex of activated matrix metalloproteinases show therapeutic potential. Nat. Med [Internet]. 18, 143–147. Available from: 10.1038/nm.2582

[137]. Jo S, Lim JB, Klauda JB, Im W. (2009) CHARMM-GUI Membrane Builder for Mixed Bilayers and Its Application to Yeast Membranes. Biophys. J [Internet]. 97, 50–58. Available from: https://www.sciencedirect.com/science/article/pii/S0006349509007917 [PubMed: 19580743]

[138]. Liu W, Ramagopal U, Cheng H, Bonanno JB, Toro R, Bhosle R, et al. (2016) Crystal Structure of the Complex of Human FasL and Its Decoy Receptor DcR3. Structure [Internet]. 24, 2016–2023. Available from: https://www.sciencedirect.com/science/article/pii/S0969212616302994 [PubMed: 27806260]

[139]. Chodorge M, Züger S, Stirnimann C, Briand C, Jermutus L, Grütter MG, et al. (2012) A series of Fas receptor agonist antibodies that demonstrate an inverse correlation between affinity and potency. Cell Death Differ. [Internet]. 19, 1187–1195. Available from: 10.1038/cdd.2011.208 [PubMed: 22261618]

[140]. Fu Q, Fu T-M, Cruz AC, Sengupta P, Thomas SK, Wang S, et al. (2016) Structural Basis and Functional Role of Intramembrane Trimerization of the Fas/CD95 Death Receptor. Mol. Cell [Internet]. 61, 602–613. Available from: https://www.sciencedirect.com/science/article/pii/S1097276516000101 [PubMed: 26853147]

Perspectives

- Combining the circulating MMP-7 and CA19–9 levels of a patient increases prognostic accuracy for severe pancreatic cancer.
- Selective inhibition of MMP-7 offers a potential means of enhancing neoadjuvant and adjuvant therapy, in combination with chemotherapy, to increase apoptosis of tumor cells. This has potential to increase successful resection of pancreatic tumors.
- Promising MMP-7-selective mAbs await evaluation in genetically engineered mice models of PDAC. This may test the question of bioavailability in the tumors.

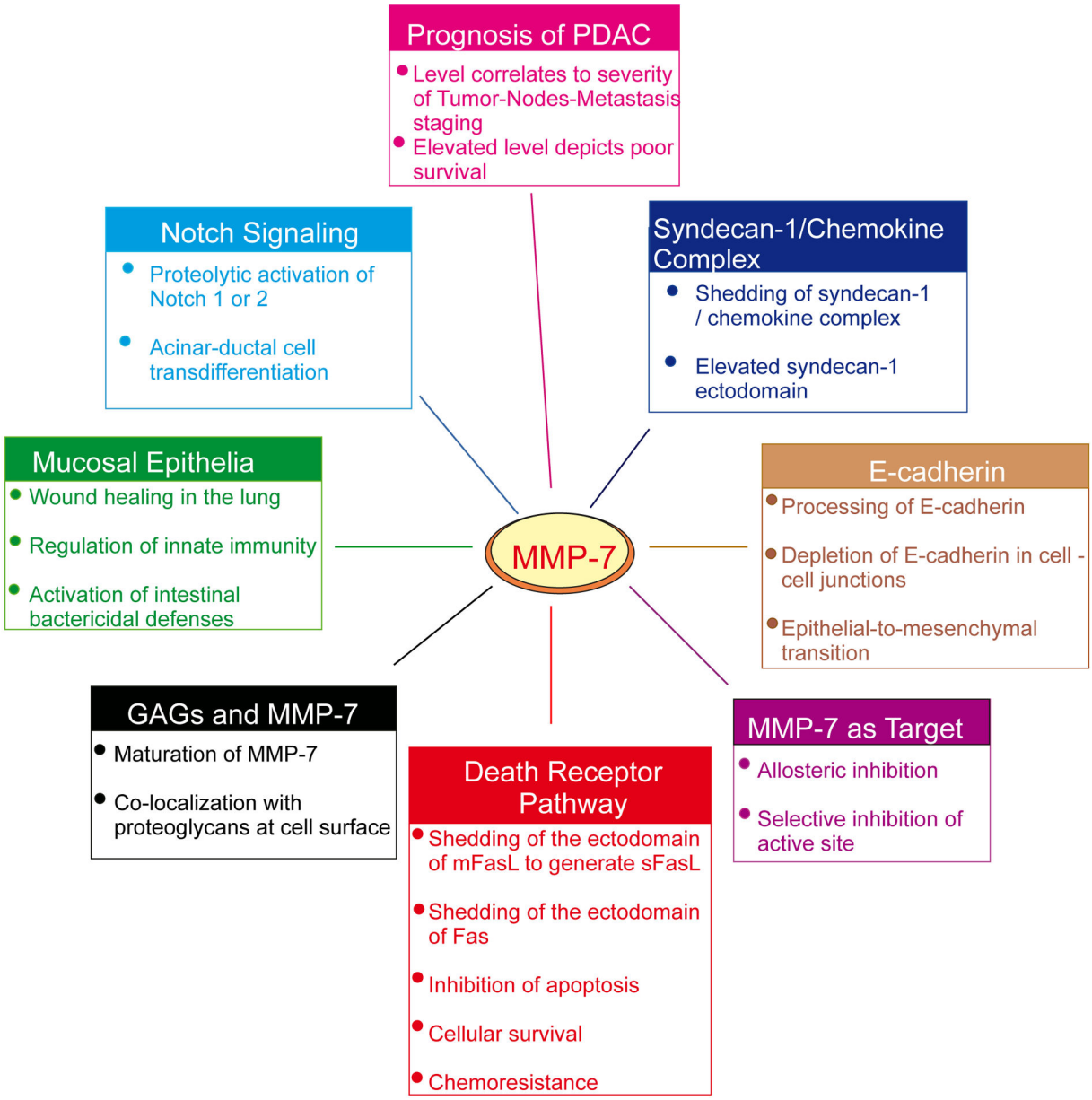

Figure 1.
MMP-7 roles, structure, function, and inhibition discussed herein.

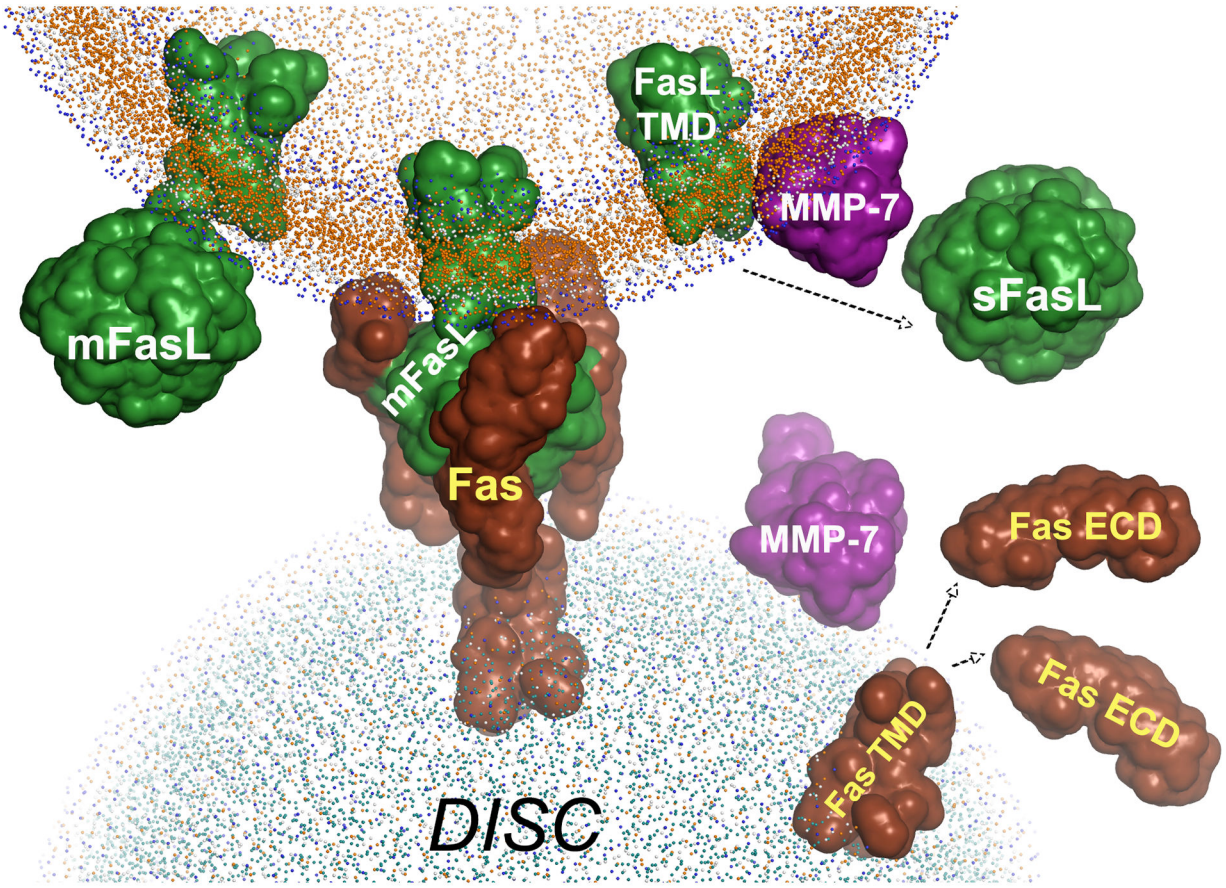

Figure 2. Ectodomains of FasL and Fas receptor are proteolytically shed by MMP-7 to interfere in apoptosis.

The upper sphere symbolizes the T cell or macrophage and the lower sphere the tumor cell or epithelial cell targeted. The spheres are vesicles of 12:0 phosphatidylcholine constructed at the CHARMM-GUI server [137]. The death domains of Fas and DISC complex are not pictured. PDB accession codes of the structural coordinates used are 4MSV for the FasL trimer and the FasL complex with Fas (by truncating the decoy DcR3 receptor present) [138]; 3TJE for the Fas ectodomain [139]; 2NA7 for the trimeric Fas transmembrane domain [140] and FasL transmembrane domain; and 2MZH for MMP-7 associated with a bilayer [120].

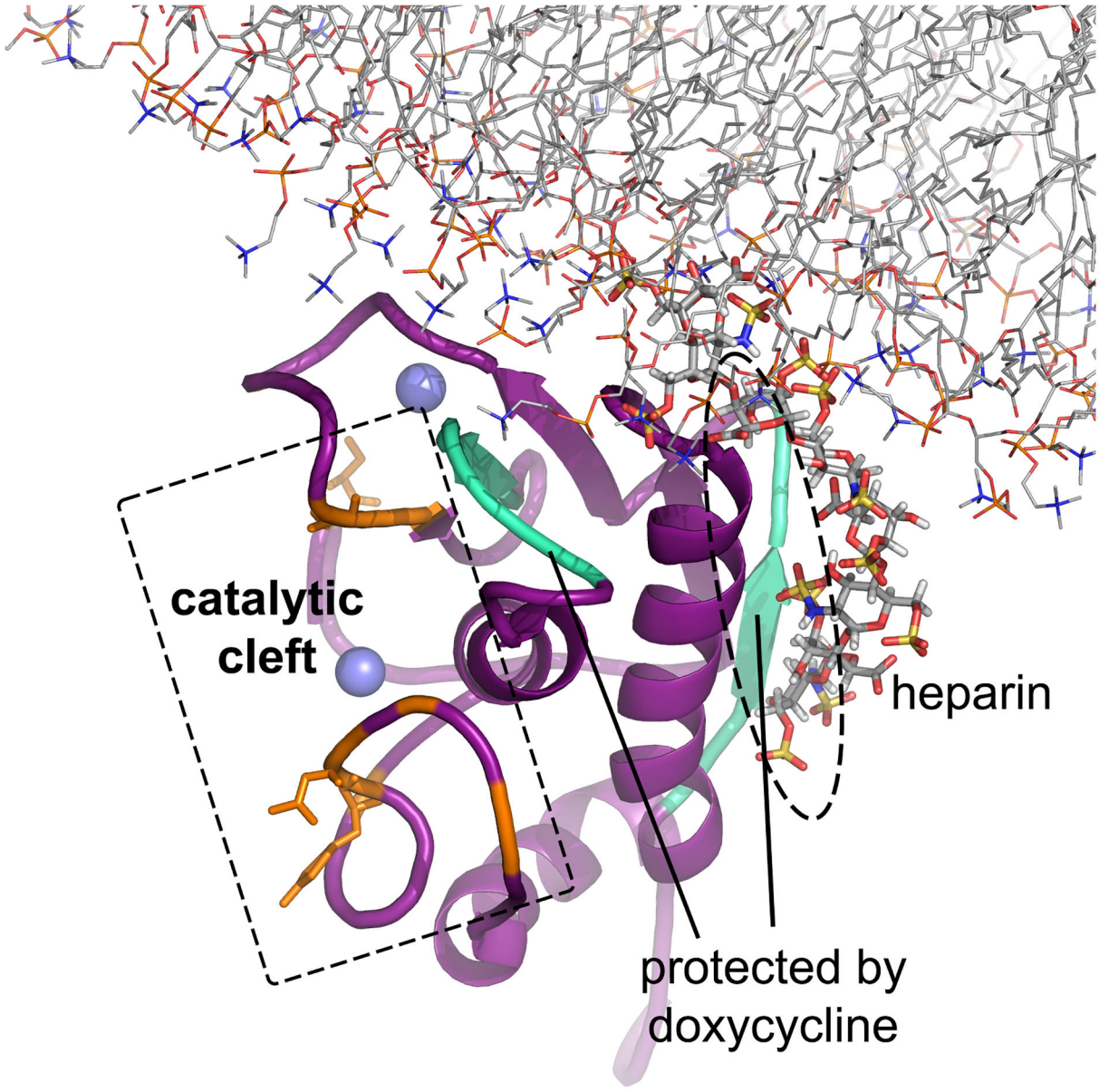

Figure 3. MMP-7 sites of binding of inhibitors and cell surface features.

The MMP-7 solution structure bound to a zwitterionic bilayer [120] (upper right, PDB: 2MZH) is plotted. Blue spheres mark the zinc ions. The mode of binding of an 8-residue heparin chain [114] (PDB: 5UE5) is superimposed and plotted with sticks at right. Sites that doxycycline slowed in deuterium exchange [131] are pointed out in light green. Predicted sites of contact with the mAb GSM-192 lie within the dashed rectangle with orange coloring [95]. Orange sidechains mark positions proposed to confer specificity [95]. To prevent GAG-induced activation of proMMP-7 as proposed [48], a potential region to target lies in the dashed ellipse, an area that might overlap a site of doxycycline binding.