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Proteases: A Very Important Player at a Critical Point of Cancer

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ABSTRACT

Proteases are one of the most common enzyme families in the world. Proteases have been used more effectively in recent years in fighting cancer. There are numerous reviews in the literature about the interaction of proteases with cancer. They usually focus on the entire cancer rather than focusing on a part of the cancer. This review generally focuses on angiogenesis (clearest stage for intervention), which is the most critical stage of cancer in the scientific world. In this review, searching of literature on the interaction of protease enzymes with angiogenesis, a very critical stage of cancer has been made into a summary table. With this study, it is envisaged that researchers can access information more easily and comparatively.

Keywords: Cancer, Protease, Angiogenesis, Disease, Diagnosis

INTRODUCTION

Apoptosis is the name given to an expression that is used to remove the diseased, injured or end-of-life cells [1]. Apoptotic cell death is characterized by a series of morphological and biochemical properties, for example chromatin condensation, cell membrane blabbing and DNA cleavage [2].

Proteases are the basic components of vital forms in all living organisms and are a group of enzymes that provide protein synthesis, degradation and homeostasis for cellular components. In a different way, protease enzymes have proven to be significant catalysts for industrial processes, important tools for life saving drugs and proteomic analysis [3-6]. In addition to, proteases are important drug targets for diseases, including various infections, cardiovascular diseases, and cancer [7,8]. Rawlings show that counts of proteolytic enzymes in some model organisms [9]. According to this table; *Homo sapiens*: 600, *Mus musculus*: 660, *Drosophila melanogaster*: 477, *Caenorhabditis elegans*: 359, *Arabidopsis thaliana*: 678, *Saccharomyces cerevisiae*: 117, *Escherichia coli*: 405, *Bacillus subtilis*: 190 and *Thermoplasma volcanium*: 43.

Proteases perform a variety of key tasks in the development and prevention of cancer. In this review, not all known tasks of the proteases in the literature, only the role of angiogenesis, in which cancer is considered to be a very important key step, is emphasized as they play a crucial role in angiogenesis. Because these are very important regulators of tissue degradation and cell migration in angiogenesis, the inhibition of these proteases is expected to be beneficial in inhibiting tumor growth and vascularization and/or inhibiting [10].

During cell growth and division, accumulation of various genetic and epigenetic alterations leads to transformation of a normal cell into a cancer cell. Cancer is an uncontrolled growth of body cells, which can spread by circulation and affect other parts of the body. If they are detected early, an important part of the cancers can be cured, by surgery, radiotherapy or chemotherapy [11].

Results from GLOBOCAN [11], Ferlay showed that there were an estimated 14.1 million new cancer cases diagnosed worldwide in 2012 (excluding non-melanoma skin cancer) and 8.2 million estimated deaths from cancer. An important extra note about these figures: When the cancer is being treated, due to illnesses such as celebral hemorrhage, heart attack, circulatory system diseases, etc. patients can die. Maybe, therefore, the most death-causing circulatory system disorders in the world.

Carcinogenesis is a multi-step events chain including transformation, survival, proliferation, invasion, angiogenesis

and tumor metastasis [12]. The most important struggle phase of cancer is angiogenesis. Because during the proliferation phase, the cancer is trying to be newly formed and most importantly the immune system and some DNA enzymes can prevent it. The next stage of angiogenesis, invasion and metastasis, is unfortunately too late for a real intervention. That is why the role of proteases has been emphasized in this key phase of cancer. Angiogenesis also occurs in normal human physiological development, as well as pathological conditions such as inflammation, wound healing, ischemia and rheumatoid arthritis, hemangiomas, tumor growth [13,14]. Angiogenesis is a complex and difficult process including extensive interaction between cells, soluble factors, and the extracellular matrix (ECM). This is facilitated by the balanced interaction between the cell adhesives and the dissociation which allows the cell to propagate to the ECM [15,16]. There is a need for proteolytic activity of proteases in the movement and interaction of these cells. Angiogenesis is controlled by chemical signals in the body. These signals can repair damaged blood vessels and stimulate the formation of new blood vessels. Furthermore, other chemical signals, also called angiogenesis inhibitors, interfere with blood vessel formation.

Proteases are important in many processes such as cell proliferation, differentiation and remodeling of the ECM, vascularization and cell migration. Moreover in the angiogenesis process, proteases are also involved in modulating cell-matrix interactions, activating angiogenic growth factors and cytokines briefly discussed in Table 1 [17,18]. Muthukkaruppan et al. [19] examined how the cancer cells passed into the vascular process. Cancer cells without blood circulation went up to 1-2 mm^3 in diameter and then stopped, but grew over 2 mm^3 when placed in an area where angiogenesis was possible. Tumors may become necrotic or apoptotic if they are not integrated with the vasculature [20,21]. In a broader sense, the formation of the blood vessels needed during the cancer process is called neovascularization. Neovascularization is a four-step process which occurs in the following order; the basal membrane in the tissues is wounded then the endothelial cells get activated by angiogenic factors began to migrate. Afterwards these migrated endothelial cells multiply. In this process, vascular endothelial cells averagely divide in every 1000 days [22].

The ability of cancer to spread to adjacent or distant organs is called metastasis, which ultimately threatens human life [23]. For the metastatic spread of cancer tissues growth of vascular tissue is very important. The process by which new blood and lymphatic vessels are formed is called angiogenesis and lymphangiogenesis, respectively. These two formations have an important role in providing nutrients, oxygen and immune cells and also in removing waste products [23,24].

Vascular endothelial growth factor (VEGF) and other endothelial growth factors bind to their receptors in endothelial cells, initiating signals that allow new blood vessels to grow. Angiogenic activators have been shown to play an important role in the growth and spread of tumors [25]. Various studies have shown that levels of angiogenic factors in the tissue reflect the spreading aggressiveness of tumor cells and therefore predictive value in identifying high-risk patients with poor prognosis. The relationship between angiogenesis and tumor metastasis is evident in experiments in which identified primary tumors are treated with angiogenesis inhibitors [26].

Meprins are glycosylated tetrameric endopeptidase which contributes to the destruction of the stromal structure and thus increases the number of cancer cells by migrating to the ECM [27]. MMP proteases are involved in a wide range of study fields in preventing angiogenesis because they degrade a various ECM molecules and cell invasion are facilitated by MMP9 (matrix-metalloprotease9) [28,29].

Type I collagen is one of the most abundant proteins in humans and it strongly stimulates angiogenesis. Matrix metallo-protease enzymes are involved in the interaction of ECM matrix and type 1 collagens and MMP12, which is excreted by bone-growing prostate cancer cells, has been associated with increased invasion through type I collagen [30].

NF-kappa B (nuclear factor-kappa B) is the primary transcription factor found in all cell types. It participates in a variety of cellular responses and plays an important role in regulating immunological responses to infections. IKKε (inhibitor of kB kinase epsilon) is active in breast cancer cells and regulates NF-kB activity and invasive phenotype [31]. Ubiquitin-specific proteases (USP) are a class of enzymes with protein secretion activity and are used for treatment strategies in various diseases. USP21 has been associated with NF-κB metastatic urothelial carcinoma [32,33]. USP4 is targeted for deubiquitination and inhibits TNFα-induced cancer cell migration [34], in addition to: stimulates the TGFβ-mediated epithelial-mesenchymal transition EMT invasion [35]. de la Vega et al. performed a

study on the USP about 17 cell invasion and metastasis where USP17 has a critical role in cell motility and G1-S cell cycle control in terms of breast cancer and may also be a useful drug target for distal metastases [36].

Cancer cells spread to different parts of the body in the metastatic stage, and unfortunately at this stage the chances of combating the disease are greatly reduced. Protease enzymes play critical roles in the metastases phase as well as in every step of the cancer which is briefly discussed in Table 1. Cathepsins are a family of proteases that play a role in many diseases. Cathepsin X enzyme plays a role in lymph node metastases and liver metastases in lung adenocarcinoma [37,38]. The urokinase-type plasminogen activator (uPA) is a kind of serine protease found in humans and other animals. uPA activity is involved in cancer spread and pathological tissue remodeling [39]. ADAMTS1 (a disintegrin and metalloproteinase with thrombospondin motif)1 is a protease commonly up-regulated in metastatic carcinoma, increased ADAMTS1 expression in progression of metastasis [40,41] and diminished ADAMTS1 expression generally occurs with at the beginning of many primary cancers [42,43]. ADAM 9 enzyme promotes tumor cell invasion by regulating several types of integrins and E-cadherin [44,45]. Kallikrein is a serine protease consisting of a light chain and a heavy chain linked by disulfide bridges. hK7 (human kallikrein 7) has been extensively increased in pancreatic adenocarcinomas and enhances pancreatic cancer cell invasion by shedding E-cadherin [46]. hK15 is increase in aggressive prostate tumors [47,48]. hK14, is down-regulated by androgen receptor signalling is associated with elevated aggressive prostate tumors [49-51].

Matriptase is an integral membrane trypsin-like serine protease that is a member of the type II transmembrane serine protease family. Matriptase play a vital role in growth, invasion of breast cancer [52]. Matriptase stimulates pro-HGF, which results in initiation of the c-Met-mTOR signaling pathway to induce proliferation and migration in primary epithelial cells [53].

Transmembrane protease serine 4(TMPRSS4) a group of serine proteases, is involved in the process of tumor invasion and its expression depends on the metastatic potential [54] besides TMPRSS4 enzymes facilitate the epithelial mesenchymal transition facilitating the invasive potential of cancer cells [55,56]. Legumain is a member of the cysteine protease group. Legumain expression increases and this situation enhance the migration and invasive activity of tumor cells [57]. MMP enzymes family plays an important role in signal generation in the metastatic process and in spreading the cells to other tissues. MMP2 increases invasion and uptake of bone marrow-derived cells and metastatic tumor cells [58]. MM3/MMP10 is involved in impairing the integrity of the blood vessel, reducing the infiltration of myeloid cells and reducing the ability of human breast cancer cells to metastasize to the lung [59]. MMP7 acts on VEGF [60], destroying pre-metastatic niches [61], PACE4 (Paired basic Amino acid Cleaving Enzyme) is one of the neuroendocrine-specific mammalian subtilis in-related endoproteases and it plays a role in the regulation of MMP-9/ TIMP-1 mediated cell motility and invasion [62].

Table 1: Roles of proteases in proliferation, angiogenesis, and metastasis

Protease	Mission critical stage of cancer
Cathepsin B	- Destruction of ECM [63,64]
Cathepsin C	- Found in leukocytes played in the regulation of both squamous and mammary carcinogenesis [65-68]
Cathepsin K	- Included in tumour progression in Bone cancer [69,70]
	- Promoting ECM degradation and angiogenesis in Breast cancer [71,72]
	- Lung Lymph node metastases, and Liver metastases in lung adenocarcinoma [37,38]
	- Release of growth factors Bone metastasis [73,74]
	- Show correlation with coronin 3 expression which promotes gastric cancer metastasis
	with MMP-9 in Gastric cancer [75]
Cathepsin X	- Higher Cat X levels to progression of cancer and shorter overall survival of Colorectal Cancer patients [76,77]
ADAMTS1	- Diminished ADAMTS1 expression generally occurs with at the beginning of many primary cancers [42,43]
	- Increased ADAMTS1 expression in progression of metastasis [40,41]
	- Enhance tumor vascular development in a fibrosarcoma [78,79]
	- Acts as an inhibitor of angiogenesis by sequestering pro-angioigenic stimuli [80,81]
ADAMTS4/	- Have an influence on ECM-degrading enzymes and so pivotal importance in tissue
ADAMTS5	degradation/remodeling and cell infiltration [82,83]

ADAMTS9	- Suppres nasopharyngeal and esophageal tumor formation by inhibiting angiogenesis [84,85]
	- Acts as antitumor activity in nasopharyngeal carcinoma and esophageal squamous cell carcinoma [84,85]
ADAMTS12	- Reduce the proliferative properties of tumor cells [86,87]
ADAM9	- Promotes tumour cell invasion by regulating several types of integrins and E-cadherin [44,45]
	-Act in the ectodomain shedding of membrane-anchored proHB-EGF [88]
ADAM10	- A major protease for N-cadherin shedding in N-cadherin expression [89,90]
	- Lead to elevated Notch signaling and decreased B-cell development in hematopoietic cells [91] and shown to activate notch signalling to releasing EGFR ligands [92-94]
	- Considered a therapeutic target in cancer, largely due to its Notch cleavage ability as well as EGFR processing [95,96]
	- Contributes to E-cadherin shedding [97,98]
ADAM12	- Is the major sheddase for pro HBEGF [99,100]
	- Increase with tumor aggressiveness and progression [101,102]
ADAM17	- For the regulated cleavage of several important signaling molecules such as TNF-a, L-selectin and various epidermal growth factor (EGF) ligands [103,104]
	- Play role in EGFR ligand processing [105,106]
Testisin	- Promotes malignant transformation formation and induces colony in cancer cells [107]
matriptase	- Act in growth, invasion, and metastasis of breast cancer [52]
	reduced in prostate and endometrial carcinoma [108-110]
	- Increase process of pro-HGF, which results in initiation of the c-Met-mTOR signaling pathway to induce proliferation and migration in primary epithelial cells [53]
hepsin	- Regulation and/or activation of the HGF receptor c-met in ovarian cancer [111]
TMPRSS4	- Play role in the process of tumor invasion and metastasis formation, and its expression is linked the metastatic potential [54]
	- Making easy epithelial-mesenchymal transition moved invasive and metastatic potential of human cancer cells [55,56]
Legumain	- Up-regulation of legumain expression in tumor cells also increased their migratory and invasive activity [57]
Meprin	- Towards the ECM, where it can contribute to the destruction of stromal structure thus affecting proliferation and migration of cancer cells [27]
MMP1/MMP7	- Contributing to EMT by degrading E-cadherin [112]
MMP2	- Viewed as key regulators of pathological angiogenesis with MMP9 [113,114]
	- Play enhances the invasion and recruitment of additional bone marrow derived cells and metastasizing tumor cells [58]
	- Degrading a various of ECM molecules and facilitating cell invasion with MMP9 [28,29]
	- Shown to play critical roles in the "angiogenic switch" and stimulate angiogenesis and increase VEGF release (with MMP-9) [115]
MMP3/MMP10	- Plays an important role in corrupting the integrity of the blood vessel, reduces infiltration of myeloid cells, and the ability of human breast cancer cells metastasize to the lung [59]
MMP7	- Regulates cell proliferation and apoptosis by cleaving the ectodomain of heparin binding-epidermal growth factor (HB-EGF) precursor [116]
	- Influences cell-cell interaction and control cell migration by releasing soluble E-Cadherin [112]
MMP9	- Acted tumor differentiation, vessel permeation and lymph node metastasis in esophageal cancer [117]
	- Play restore vasculogenesis in tumors angiogenesis [118]
	- Acted tumor-promoting function and differentiate into tumor-associated endothelial cells [119]
	- Contributes to the development of melanoma by eliminating inflammation [120]
	- Play destroys the pre-metastatic niche [61] an effect attributed to VEGF [60]
	- Participates in the angiogenic switch [61,121,122]
	- Mobilizes VEGF sequestered in ECM [61]
	- Enables an angiogenic switch by making sequestered VEGF bioavailable in pancreatic tumors [61]

MMP12	- Produces angiostatin by plasminogen cleavage in angiogenesis [123]
	- Expressed by prostate cancer cells growing in bone and expression was related enhance invasion through type I collagen [30]
MMP13	- Plays a key role in collagen remodelling in angiogenesis [116,124]
	- Increases VEGF and VEGFR-2 protein and thus promoted tumor angiogenesis [125,126]
	- Associated with more aggressive tumors [127,128] and high expression of it related to tumor behavior and prognosis [129]
MMP14	- Acted cleaving fibrillar collagens to ECM matrix in angiogenesis [130] and contributes to vascular regression [131]
	- Promoted tumor growth and angiogenesis accompanied by up-regulation of VEGF expression [132]
	- Play critical roles in orchestrating carcinoma cell behavior [133-135]
	- activates αvβ3 in cancer angiogenesis [136]
MMP15	- Involved in growth of colorectal cancer [137,138]
	- A regulator of intra-tumoral angiogenesis in growth of human esophageal cancer [139]
	involved in cancer cells behavior [133-135]
MMP26	- Degrading many extracellular matrix (ECM) components such as bronectin, collagen IV,
	vitronectin and brinogen [140-142]
MMP28	- Plays a role in the proteolytic activation of TGF-b and a forceful inducer of EMT in cancer growth [143,144]
USP1	- Tumor promoter FA pathway , overexpressed in melanoma, myeloma, gastric, cervical,
	brain, liver, lung and colorectal cancers [145,146]
USP3	- Acted transcription recovery after DNA damage in bladder, brain and prostate cancers [147]
USP4	- Targets for deubiquitination and inhibits TNFα-induced cancer cell migration [34], in
	addition to: stimulates the TGFβ-mediated EMT, invasion and metastasis [35]
	- An important determinant of crosstalk between TGFβ and AKT signaling in breast cancer [148,149]
USP 5	- Related p53, DNA damage response in Melanoma and glioblastoma [150-152]
	- Deubiquitinase inhibition by WP1130 molecule triggers aggresome formation and tumor cell apoptosis [151]
USP7	- Tumor promoter p53, PI3-K, PTEN, FOXO4 in myeloma, prostate cancer, neuroblastoma and gliomas [153,154]
	- Induces elevated p53 and apoptosis [155]
USP8	- Tumor promoter Wnt, hedgehog cytokine receptor signaling Non-small cell lung cancer [156]
USP10	- Tumor suppressor, tumor promoter cMyc in p53 [157,158]
USP11	- Tumor promoter DDR, NF-kB in breast cancer [36,159]
	- Together with USP15 regulates TGFβ signaling [159,160]
USP14	- Tumor promoter Wnt Colorectal cancer, non-small cell lung cancer [161]
	- Promotes proliferation through the accumulation of beta-catenin in lung adenocarcinoma [162]
	- Inducing I-kB degradation and increasing cytokine release in lung epithelial cells [163]
USP15	- Tumor promoter NF-kB Wnt is found amplified in human breast and ovarian tumors and in glioblastoma [164,165]
USP16	- Leading to decreased tumour cell viability and tumour growth [166]
USP17	- Tumor promoter GTPase subcellular localization and cell motility and G1-S cell-cycle
	checkpoint Breast cancer NSCLC distal metastases [36]
USP18	- Associated NF-kB in AML [167]
USP19	- Associated ERAD pathway Breast and prostate cancer [168]
USP21	- Associated NF-kB Metastatic urothelial carcinoma [32,33]
USP22	-Tumor promoter Implicated C-Myc signaling pathway papillary thyroid carcinoma,
	non-small cell lung carcinoma, oral squamous cell carcinoma and colorectal cancer [169,170]
USP42	- Regulation of p53 in AML [171]
USP47	- Regulate DNA base excision repair (BER) by controlling deubiquitylation of Polβ [172]
	- Reduce cancer cell proliferation and enhance the cytotoxic activity of chemotherapeutic Agents [173]
USP 50	- In G2-M checkpoint in AML [174]

hK2	- Represent important regulators of the insulin-like growth factor (IGF) axis in prostate carcinogenesis (with hK3) [175]
	- Play in the activation of uPA/uPAR systems [176]
	- Together with KLK4 stimulates ECM destruction and CaP promotes the accumulation of uPA [175,177]
hK4	- Play in the activation of uPA/uPAR systems [176]
hK6	- Up-regulated in squamous skin tumors [178]
	- Inhibition of epithelial-to-mesenchymal transition in berast cancer [179]
hK7	- Play in the epithelial-mesenchymal transition of prostatic carcinoma cells [180]
	- Overexpressed in pancreatic adenocarcinomas and enhances pancreatic cancer cell invasion by shedding Ecadherin [46]
hK14	- Down-regulated by androgen receptor signalling is associated with prostate tumour
	aggressiveness [49] and elevated aggressive prostate tumors [50,51]
hK15	- Increases in aggressive prostate tumors [47,48]
DPPII	- A key enforcer in fibroblasts and lymphocytes [181]
	- Leads to pRb phosphorylation, ERK phosphorylation, decrease in p130 expression and an increase in p107 [181,182]
DPP IV	- Show inverse activity in prostate, thyroid and colorectal cancer [183-185]
Progastriscin	- Associated with the invasive breast cancer lesions [186,187]
	- Abnormal differentiation of colorectal cancer cells [188]
CYLD	- Tumor suppressor cycle of NF-kB JNK in hepatocellular carcinoma [189]
HtrA3	- Inducing mitochondria-mediated apoptosis [190,191]
ECE-1c	- Acted regulation by CK2 in colorectal cancer [192]
HGFA	- Involved in the activation of pro-HGF in several tumors [193-195]
IKKE	- Active in breast cancer cells and regulates NFkB activity and invasive phenotype [31]
	- Causes a significant increase in MMP-9 levels in kidney epithelial cells [196]
PACE4	- Play in the regulation of MMP- 9/TIMP-1-mediated cell motility and invasion [62]
	- Upregulated processing of growth factors in prostate cancer progression [197]
uPA	- Activity in the spread of cancer and pathological tissue remodeling [39]
	- Degrading or remodeling several ECM components such as laminin, fibronectin, tenascin
	C, and osteopontin [198,199]
Caspase3	- Lead to intrinsic and extrinsic pathways in apoptosis [200]
	- Plays critical role for induction of DNA fragmentation in apoptosis [201,202]

Abbreviations: TMPRSS: Transmembrane Protease Serine; MMP: Matrix Metallo Protease; USP: Ubiquitin Specific Protease; hK: Human Kallikrein; DPP: Dipeptidyl Peptidase; CYLD: Cylindromatosis Protein; HtrA: High Temperature Requirement A; ECE: Endothelin-Converting Enzyme; HGFA: Hepatocyte Growth Factor Activators; IKKε: IkappaB Kinase Epsilon; PACE: Paired Basic Amino Acid Cleaving Enzyme; uPA: Urokinase-Type Plasminogen Activator; DDR: DNA Damage Response

CONCLUSION

However, each person has its own unique structure and cancer progression and effects that may be seen in the treatment process may not be the same. While fighting cancer, the body's immune cells and immune cells can also suffer serious damage. Some triggers such as immunity, stress, morale, nutrition and environmental conditions are extremely important for cancer progression and treatment. Another important point is that cancer has a different status in every person. So, in recent years, Scientists focuses on special treatments for the person in the fight against cancer. As shown in the review, proteases play an important role in the critical stages of cancer. For example, new studies on proteases have been performed in some processes such as stabilization of mature blood vessels, regulation of cytokines and growth factors. In addition to, better understanding of the activities of proteases will help further tailored therapies for new cancer progressions and treatments. Better clarification of the roles of proteases at critical stages of cancer will lead to new approaches to diagnosis in the early stages and treatments.

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