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REVIEW

Cathepsins mediate tumor metastasis

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Abstract

Cathepsins are highly expressed in various human cancers, associated with tumor metastasis. It is superfamily, concluding A, B, C, D, E, F, G, H, L, K, O, S, V, and W family members. As a group of lysosomal proteinases or endopeptidases, each member has a different function, playing different roles in distinct tumorigenic processes such as proliferation, angiogenesis, metastasis, and invasion. Cathepsins belong to a diverse number of enzyme subtypes, including cysteine proteases, serine proteases and aspartic proteases. The contribution of cathepsins to invasion in human cancers is well documented, although the precise mechanisms by which cathepsins exert their effects are still not clear. In the present review, the role of cathepsin family members in cancer is discussed.

Key words: Cathepsin; Tumor; Metastasis; Mechanism

Core tip: Cathepsins play an important role in tumor metastasis, as a superfamily, each member experts different function in tumor metastatic process. In the present, we summarized the roles of cathepsin family members and analyzed their mechanism in tumor metastasis. These provide a novel insight in tumor metastasis.

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INTRODUCTION

A multitude of processes are involved in cellular invasion and migration, including loss of cell-cell and cell-matrix adhesion and degradation of extracellular matrix (ECM) components[1]. When the expression of cell-cell and cell-matrix adhesion molecules is reduced or absent, cells lose contact with their microenvironment and are predisposed to invade and migrate into surrounding tissue. Malignant cells show increased proteolytic activity, which helps them digest the ECM. This digestion is required for cancer cells to invade and migrate through the basal lamina, which is the hallmark of malignancy[2]. In the past two decades, many researchers have focused on proteases and their role in cancer in the quest for new anticancer therapies. Proteases are a large group of enzymes that catalyze the cleavage of peptide bonds in proteins. They are subdivided into five categories: metalloproteases, including matrix metalloproteases (MMPs), cysteine proteases, serine proteases, aspartic proteases and threonine proteases[3].

Cathepsins are a class of globular proteases that were initially described as intracellular peptide hydrolases, although several cathepsins also have extracellular functions. The cathepsin family includes cathepsin A, B, C, D, E, F, G, H, L, K, O, S, V and W. Cathepsin B, C, F, H, L, K, O, S, V, W and X are cysteine proteases of the papain

Table 1 Characters of human cathepsin familymembers

Cathepsin	Subtype	Endo/exopeptidase	Expressed tissue	Function
A	Serine	Exopeptidase	Platelets, primary human antigen presenting cell, testis and epididymis	Autophagy, elastic fiber formation, platelet activation
B	Cysteine	Exo and endo	Widely distributed in macrophages, hepatocytes, renal tubules, all endocrine organs	Protein catabolism, processing of antigens hormone activation and bone turnover
C	Cysteine	Exo	Broadly distributed in tissues	Hydrolyze dipeptide esters,amides, anilides and beta-naphtylamides
D	Aspartic	Endo	Eccrine sweat, extracellular matrix and synovial fluid of cartilage	Protein degradation in an acidic milieu of lysosomes
E	Aspartic	Endo	Immune system	Antigen presentation
F	Cysteine	Endo	Antigen presenting cells	Antigen presenting
G	Serine	Endo	Polymorphonuclear leukocyte	Immune complex mediated inflammation production of angiotensin Ⅱ, degradation of extracellular matrix
H	Cysteine	Endo	Ubiquitous in cells and tissues	Endopeptidase activity
L	Cysteine	Endo	Ubiquitously expressed	Keratinocyte differentiation, protein turnover, antigen presentation
K	Cysteine	Endo	Bone, ovary, heart, placenta, lung, skeletal muscle, colon and small intestine	Bone remodeling
O	Cysteine	Endo	Broadly distributed in tissues	Protein degradation and turnover
S	Cysteine	Endo	Spleen and professional antigen-presenting cells	Ii chain proteolysis
V	Cysteine	Endo	Thymus and testis, corneal epithelium	Production of enkephalin and neuropeptide Y
W	Cysteine	Endo	T-lymphocytes	Cell-mediated cytotoxicity
X	Cysteine	Endo	Immune system	Phagocytosis, regulation of immune responses
Z	Cysteine	Exo	Widely expressed in human tissues	Protein degradation

family, and represent the largest and best-known class of cathepsin[4]. Cathepsin A and G are serine carboxy peptidases, and cathepsin D and E are aspartic proteases. Cathepsins are synthesized as inactive proenzymes and processed to become mature and active enzymes[5]. Some cathepsins are ubiquitously expressed, such as cathepsin B, L, H, and C, whereas the newly found cathepsins K, W, and X are expressed by specific cells and tissues. Historically, cathepsins were described as a group of intracellular hydrolases that participate in general protein turnover in the lysosome. However, in the last 20 years, using gene knockout models, a number of discrete functions have been identified for the cathepsin family. Specifically, cathepsin S is important for major histocompatibility complex (MHC)-Ⅱ-mediated antigen presentation[6], cathepsin L is implicated in keratinocyte differentiation[7], heart functions and reproduction[8], cathepsin K is a major factor in bone remodeling[9], and cathepsin C activates granzymes and mast cell proteases. Mutations in the *cathepsin K* or *C* genes result in the hereditary disorders pycnodysostosis and Papillon-Lefevre syndrome, respectively[10-12]. Cathepsins can be expressed at the cell surface and secreted into the extracellular space, where they can degrade components of the ECM[13]. Cathepsins are proteolytically active when attached to other cell surface proteins[14]. This extracellular activity allows cancer cells to invade surrounding tissues, blood, and lymph vessels and metastasize to distant sites. All cathepsins are synthesized as inactive precursors. The endopeptidases are activated by autolysis at acidic pH in the lysosomes and the exopeptidases are activated by endopeptidases[15]. In the present review, the roles of each member of the cathepsin family in tumor metastasis are discussed.

CATHEPSIN FAMILY AND THEIR FUNCTION

The cathepsin family includes cathepsin A, B, C, D, E, F, G, H, L, K, O, S, V and W, and their characters are showed Table 1. Cathepsin B, C, F, H, L, K, O, S, V, W, and X are cysteine proteases of the papain family, and represent the largest and best-known class of cathepsins. Cathepsin B is a lysosomal cysteine protease of the papain family of enzymes that functions as an endopeptidase and an exopeptidase[16]. The human *cathepsin B* gene is located at 8p22-p23.1[17], and the protein is widely distributed in macrophages, hepatocytes, renal tubules, gastrointestinal epithelium and fibroblasts, stratified squamous epithelium, transitional epithelium, salivary glands, pancreas, central and peripheral neuronal cell bodies, trophoblasts, and all endocrine organs[18]. It functions in intracellular protein catabolism, and in certain situations may also be involved in other physiological processes, such as processing of antigens in the immune response, hormone activation and bone turnover[16]. Cathepsin C is a papain-like cysteine protease with dipeptidyl aminopeptidase activity that is thought to activate various granule-associated serine proteases[19]. It can hydrolyze dipeptide esters, amides, anilides, and beta-naphtylamides[20]. Cathepsin C also shows transpeptidase activity[21]. Cathepsin C is involved in normal neuronal function in certain brain regions, and also participates in inflammatory processes accompanying pathogenesis in the central nervous system (CNS)[22]. The *cathepsin F* gene localizes to the long arm of chromosome 11 at 11q13. This position is the same for the *cathepsin W* gene, thereby indicating that these genes are clustered in the human genome[23]. Cathepsin

F, in a subset of antigen presenting cells (APCs), can efficiently degrade the MHC class Ⅱ-associated invariant (Ii) chain[24]. Cathepsin H, which is a cysteine protease, is ubiquitous in cells and tissues, and mainly functions as an aminopeptidase that exhibits limited endopeptidase activity. Cathepsin H is synthesized as a 41-kDa preproenzyme that is proteolytically activated through a multistep process initially resulting in a 30 kDa intermediate form and finally a single chain mature form of 28 kDa. This form can be further processed to a 22 kDa heavy chain and a 5-6 kDa light chain[25]. The human *cathepsin K* gene is encoded by approximately 12.1 kb of genomic DNA and is mapped to chromosome 1q21[26]. *Cathepsin K* mRNA has been detected in a variety of tissues including bone, ovary, heart, placenta, lung, skeletal muscle, colon and small intestine. High concentrations of cathepsin K have been found in osteoclasts and osteoclast-like cells (giant multinucleated cells)[27]. Cathepsin K is primarily responsible for the degradation of bone matrix by osteoclasts and plays a key role in osteoporosis[28]. Cathepsin L is produced as preprocathepsin L, transported *via* the Golgi apparatus as procathepsin L in secretory vesicles, and then stored as mature cathepsin L in lysosomes[29]. Intracellular protein turnover by cathepsin L is involved in several important processes, and regulation of the cell cycle may be affected by cathepsin L as it is able to degrade nuclear transcription factors[30]. In addition, cathepsin L plays a role in the immune system by degrading the Ii chain in MHC class Ⅱ processing, which is a critical step in antigen presentation. The expression of cathepsin L in the thymus was shown to be essential for the development of natural killer cells[31], cathepsin L plays a part in recycling processes during axon outgrowth and synapse formation in the developing postnatal central nervous system. When present in the acidic lysosomal compartment, cathepsin L is proteolytically active. Cathepsin O is a cysteine proteinase from the papain superfamily that is composed of 8 coding exons and 7 introns and spans more than 30 kb. The number and distribution of exons and introns differ from those reported for other human cysteine proteinases, thereby indicating that these genes are not closely related. *Cathepsin O* maps to the chromosome location 4q31-q32, which is a unique site for cysteine proteinases mapped to date[32]. Cathepsin O is expressed in all examined tissues, which is consistent with a putative role of this protein as a proteolytic enzyme involved in normal cellular protein degradation and turnover[33]. Cathepsin S, which is a cysteine protease originally cloned from human alveolar macrophages, is highly expressed in the spleen and professional antigen-presenting cells, including B lymphocytes, macrophages, and other class Ⅱ-positive cells[34,35]. Cathepsin S is essential in B cells for effective Ii chain proteolysis necessary to render class Ⅱ molecules competent to bind peptides[36] *Cathepsin V* was mapped to the chromosomal region 9q22.2, which is a site adjacent to the *cathepsin L* locus[37]. Cathepsin V shares 80% protein sequence identity with cathepsin L; however, in contrast to the ubiquitously expressed cathepsin L, its expression is restricted to the thymus and testis[38], and its uniquely high expression in corneal epithelium[39]. Human cathepsin V is involved in the production of enkephalin and neuropeptide Y, which are required for neurotransmission in health and neurological diseases[40]. The *cathepsin W* gene maps to 11q13.1 and contains 10 exons and 9 introns[41]. Cathepsin W is predominantly expressed in T-lymphocytes, specifically natural killer cells and $CD8^+$ cells, and may therefore, play a role in cell-mediated cytotoxicity[42,43]. Cathepsin X expression is restricted to various cells of the immune system, such as monocytes, macrophages and dendritic cells[44]. It is involved in phagocytosis and the regulation of immune responses, such as signal transduction, growth, maturation, adhesion, cell-cell communication, proliferation and migration of immune cells[45]. By proteolytic cleavage of C-terminal amino acids, cathepsin X regulates β2 integrin functions, impairs neurotrophic activity of gamma enolase, and the role of chemokine CXCL-12 in adhesion of hematopoietic stem and progenitor cells to osteoblasts[46].

Cathepsin A and G are serine carboxy peptidases. Cathepsin A is a serine carboxypeptidase that forms a complex with beta-galactosidase and neuraminidase. The enzyme is synthesized as a 54-kDa precursor/zymogen and processed into a catalytically active two-chain form composed of 32-kDa and 20-kDa peptides[47]. Cathepsin A is expressed in various tissues and cells such as primary human APC[48], platelets[49], testis and epididymis[50]. Cathepsin A is implicated in autophagy, which occurs after the digestion of lysosome-associated membrane protein type 2a (lamp2a)[51], and plays a crucial role in effective elastic fiber formation[52]. Cathepsin G is an endoprotease that belongs to the S1 class of serine proteases. The *cathepsin G* gene is located on chromosome 14q11.2 and has a genomic structure similar to that of neutrophil elastase. Specifically, the gene contains 5 exons and 4 introns, and spans 2.7 kb of genomic DNA. Exon 2 encodes the active site histidine, exon 3 the aspartic acid, and exon 5 the serine, which together form the catalytic triad of cathepsin G[53]. Cathepsin G, like other cathepsins, is differentially expressed within various APC types. Cathepsin G functions in primary human monocytes, B cells, mDC1, mDC2, pDC and murine microglia. In addition, purified cathepsin G can be internalized into endocytic compartments in non-expressing cells to expand their protease repertoire[54].

Cathepsin D and E are aspartic proteases. The human *cathepsin D* gene is located on the short arm of chromosome 11 in region p15 in the vicinity of the *H-ras* oncogene[55]. Three molecular forms of the proteolytic enzyme cathepsin D are found in the cell: the precursor (procathepsin D), the intermediate single-chain and the mature double-chain. Procathepsin D, which is found in the Golgi complex, is enzymatically inactive, while the intermediate and mature forms are enzymatically active and are found in the endosomes and lysosomes, respectively. The latter are involved in autophagy and apoptosis pathways, thus playing a crucial role in the control of cell and tissue homeostasis[56]. Cathepsin E is an intracellular aspartic protease of the pepsin superfamily. It is highly

Table 2 Cathepsin family members expressed in cancers

Cathepsin	Elevated in cancer	Location of cancer
A	Yes	Malignant melanoma
B	Yes	Breast carcinomas, melanoma, gastric cancer, lung cancer, colon cancer, ovarian cancer, cervical cancer pancreatic carcinomas, glioblastoma thyroid carcinoma,cholangiocarcinomas, hepatocellular carcinomas, bladder caner
C	Unclear	
D	Yes	Thyroid carcinomas, squamous cell carcinoma, renal cell, carcinoma, glioma brain tumors, laryngeal carcinoma, breast cancer, lung cancer, ovarian carcinoma
E	Yes	Pancreatic ductal adenocarcinoma, gastric cancer
F	Yes	cervical carcinoma
G	Yes	Breast cancer
H	Yes	Breast carcinoma, colorectal cancer, melanoma, head and neck carcinoma, glioma, prostate cancer
L	Yes	Breast cancer, lung cancer, gastric cancer, colon cancer, head and neck carcinomas, melanomas, gliomas, ovarian cancer, pancreatic cancer
K	Yes	Gastric cancer, squamous cell carcinoma, basal cell carcinoma, breast tumor, lung cancer, melanomas, prostate tumors, renal tumor
O	Unclear	
S	Yes	Astrocytoma, gastric cancer, hepatocellular carcinomas, glioblastomas, melanoma, gastric cancer, pancreatic islet cell cancer
V	Unclear	
W	Unclear	
X	Yes	Prostate cancer, gastric cancer, malignant melanomas, prostate cancer, lung tumors, breast cancer, colonrectal cancer
Z	Yes	Melanomas, gastric cancer, hepatocellular carcinomas, pancreatic carcinomas

homologous to the analogous aspartic protease cathepsin D. Early reports implicated the presence of an aspartic protease distinct from cathepsin D in vertebrate cells[57]. Cathepsin E is mainly present in cells of the immune system, including APC such as lymphocytes, microglia, DC, Langerhans cells, interdigitating reticulum cells and human M cells. Although cthepsin E is not present in resting B-lymphocytes, it is upregulated late in human B cell activation at both the mRNA and protein level. It has also been detected in gastric epithelial cells and osteoclasts[58].

The *cathepsin Z* gene maps to chromosome 20q13, and the protein is widely expressed in human tissues, thereby suggesting that this enzyme could be involved in normal intracellular protein degradation that occurs in all cell types[59].

CATHEPSINS MEDIATE CANCER METASTASIS

Cathepsins highly expressed in invasive tumor

Some members of the cathepsin family are highly expressed in metastatic tumors (Table 2). Cathepsin A activity in lysates of metastatic lesions of malignant melanoma was significantly higher than in primary focus lysates. Therefore, cathepsin A may play a role in metastatic dissemination of malignant melanoma[60]. Overexpression of *cathepsin B* mRNA, increased cathepsin B staining, and elevated cathepsin B activity have been found in the invasive edges of cancers, thereby suggesting that cathepsin B plays a role in tumor invasion. Cathepsin B activity is significantly elevated in a variant of the B16 melanoma with high metastatic potential tumor cells[61]. Lung cancer patients with upregulated cathepsin B tend to have higher rates of haematogenous and intrapulmonary metastases[62]. In addition, a significant increase in the cathepsin B activity in tumor-infiltrated lymph nodes was observed compared to non-infiltrated regional lymph nodes[63]. Non-small cell lung-cancer patients with high levels of cathepsin B had more frequent metastasis compared to patients with low levels of cathepsin B. This implies that cathepsin B plays an important role in tumor cell invasion and metastasis[64]. Cathepsin B enzyme activity levels are inversely correlated with the Dukes' stages. Specifically, the tumor-specific increase in *cathepsin B* mRNA content is almost 4 times greater in earlier stage (Dukes' A and B) tumors than in later stage (Dukes' C and D) tumors. Therefore, increased *cathepsin B* gene expression is a characteristic of tumors that are in the process of invading the bowel wall or local tissues, as distinct from tumors that have already spread to more distant sites[65,66]. In cervical cancer development and progression, cathepsin B expression in the invasive carcinomas was positively correlated to tumor invasion depth and lymphatic metastasis. When the *cathepsin B* gene is silenced in cervical cancer HeLa cells by siRNA, the cathepsin B expression levels of both the mRNA and protein were significantly reduced, and importantly the cell proliferation, migration, and invasion of the HeLa cells decreased significantly[67]. Cathepsin B expression increased throughout cancer progression, and gradually increased from 3- to 6-fold in low-grade astrocytoma to high-grade glioblastoma, and increased in protein abundance and enzyme activity. Therefore, cathepsin B may play an important role in human glioma progression and invasion[68]. In addition, cathepsin B directly binds to Hepatitis B spliced protein, which promotes hepatoma cell motility and invasion[69]. *Cathepsin B* knockouts retard cell proliferation and tumor growth and significantly reduce the tumor invasion[2]. Cathepsin D expressed in breast cancer cells seems to be involved in the local recurrence and metastasis formation[70]. In laryngeal cancers, neck node metastasis was significantly higher in the cathepsin D positive group

than the cathepsin D negative group[71]. High expression of lymphatic microvessel density and overexpression of cathepsin D could promote cervical lymph node metastasis in laryngeal carcinoma. Procathepsin D secreted by cancer cells, increases proliferation, metastasis, and progression of breast cancer and lung cancer[72-74]. Intense expression of cathepsin D in high-grade carcinomas may be a marker for invasive potential and aggressive behavior[75]. Among patients with positive lymph nodes, those with cathepsin D immunopositive tumor cells were at higher risk of relapsing[76]. Stromal cathepsin K expression levels were significantly higher in invasive squamous cell carcinomas (SCC) than in other epidermal tumors. Therefore, cathepsin K may play a crucial role in SCC progression by promoting extracellular matrix degradation, thereby facilitating SCC growth and invasion into surrounding tissue and vasculature[77]. Cathepsin K also was expressed in the tumour cells of all basal cell carcinoma cases and perivascular epithelioid cell neoplasms[78,79].

Cathepsins increase motility and invasion of cancer cells

In esophageal cancer invasion into the ECM, cathepsin B induction is necessary for fibroblast-mediated invasion[80]. In breast cancer, overexpression of cathepsin D results in increased fibroblast motility and invasion[81]. A matrigel invasion assay demonstrated that a cathepsin H antibody inhibited the invasion of glioblastoma cell lines[82]. Cathepsin L may increase the ability of ovarian cancer cells to invade and metastasize *in vitro*[83]. Cathepsin H affects cell migration by influencing the activity of integrins, a process that could be regulated by talin cleavage[84]. Coronin 3 has been suggested to promote the invasion and metastasis of gastric cancer both *in vitro* and *in vivo* by regulating the expression of MMP-9 and cathepsin K[85]. Coculture of *cathepsin k*+ fibroblasts enhanced the invasion of cathepsin K breast-tumor epithelial cells and this was blocked by cathepsin K inhibitors[86]. Immunostaining revealed strong cathepsin K expression in most primary melanomas and all cutaneous melanoma metastases. Therefore, cathepsin K may play an important role in melanoma invasion and metastasis by mediating intracellular degradation of matrix proteins after phagocytosis[87]. Cathepsin K contributes to prostate tumor progression in bone[88]. *Cathepsin L* knockout retarded cell proliferation and tumor growth and significantly reduced the tumor invasion[2]. Cathepsin S may serve as a useful prognostic indicator and potential target for noninvasive therapy[89]. Cathepsin S was shown to play novel roles in cancer cell migration and invasion,such as colorectal carcinomas[90], gastric cancer[91] and hepatocellular carcinoma[92]. A gene knockout approach to determine the role of cathepsin S in pancreatic islet cell cancer showed that mutants of cathepsin S impaired tumor invasion[2]. Cathepsin X upregulation was also directly associated with higher invasiveness *in vitro*[93]. Recent reports demonstrate that adhesion, migration, and invasiveness of tumor cells are dependent on the inactivation of the tumor suppressive function of profilin 1 by cathepsin X[94].

Cathepsins mediate dissemination of cancer cell

Lysates of primary malignant melanoma lesions exhibited significantly higher cathepsin A activity than dysplastic and normal pigmented nevi, and cathepsin A activity in lysates of metastatic lesions of malignant melanoma was significantly higher than in primary focus lysates. Therefore, cathepsin A may play a role in malignant transformation and metastatic dissemination of malignant melanoma[60]. In addition, cathepsin B may play a role in the dissemination of squamous carcinoma cells[95]. The reduced migration and invasion of tumor cells with reduced cathepsin B levels *in vitro* provides circumstantial evidence for a contribution of cathepsin B in tumor cell dissemination from primary tumors[96]. Cathepsin B and D are involved in AGR2-mediated dissemination of pancreatic cancer cells[97]. Cathepsin D is proposed to facilitate early phases of tumor progression such as cell proliferation and local dissemination[98]. Cathepsin L and other lysosomal proteins may play a role in the dissemination of tumor cells via the lymphatic system[99].

Cathepsins mediate degradation of ECM and collagen

Cathepsin B can directly facilitate tumor progression *via* degradation of components of the basement membrane and ECM[100] Inhibition of cathepsin B activity attenuates ECM degradation and inflammatory breast cancer invasion[101]. In addition, RNA interference-mediated knockdown of cathespin B in tumor cells reduced collagen I degradation *in vitro* and bone metastasis *in vivo*. Similarly, intraperitoneal administration of the highly selective cathepsin B inhibitor CA-074 reduced metastasis in tumor-bearing animals[102]. Thyroid carcinoma with extra-capsular invasions and metastasis had high cathepsin B activities and tended to show high type I and Ⅳ collagen degrading abilities[103]. Cathepsin B localizes to discrete cytoplasmic granules in non-invasive tumors, although it exists in a more diffuse cytoplasmic pattern in invasive tumors[104,105]. Subcellular fractionation by immunoblot and enzymatic analysis confirmed that the invasive EJ cells had active cathepsin B localized to the plasma membrane, while non-invasive RT4 cells had cathepsin B confined to lysosomes. Furthermore, immunoblot analysis revealed that invasive EJ cells contained the mature form of cathespin B, which had a molecular weight of 25 kD, while the non-invasive RT4 cells had predominantly precursor forms, which had molecular weights between 30 and 35 kDa. *In vitro* degradation assays using plasma membrane fractions isolated from invasive EJ cells and non-invasive RT4 cells demonstrated that the plasma membrane of EJ cells had the ability to degrade purified laminin, and the degradative products were similar to those obtained using purified cathepsin B[106]. Stromal cathepsin K expression levels were significantly higher in invasive SCC than in other epidermal tumors. Therefore, cathepsin K may play a crucial role in SCC progression by promoting extracellular matrix degradation, thereby facilitating SCC growth and invasion into surrounding tissue and vasculature[77]. Acidification of the local envi-

ronment caused by increased anaerobic glycolysis in cancer cells facilitates the activity of extracellular cathepsin L. In an acidic environment, cathepsin L is able to degrade components of the ECM such as collagen types I and Ⅳ, fibronectin, and laminin. Cathepsin Z can upregulate the proteins associated with ECM remodeling such as MMP2, MMP3 and MMP9, thereby implying that cathepsin Z might play an important role in hepatocellular carcinoma invasion and metastasis[107].

Cathepsins mediate angiogenesis

Angiogenesis is controlled by the balance between positive and negative angiogenic factors. It has been shown that cathepsins may influence the production and degradation of both angiogenic activators and inhibitors. There is a close relationship between the intensity of angiogenesis and overexpression of the cathepsin B protein in cancer cells in resected colon adenocarcinoma[108]. A correlation between high levels of lymphangiogenesis and cathepsin D in laryngeal carcinoma was determined, which also correlated with laryngeal carcinoma lymph node metastasis[109]. Stromal cathepsin D expression correlates with microvessel density in ovarian tumors[110]. Additionally, a significant association between cathepsin D expression in host stromal cells and vascular density has been described in breast cancer tumors[111]. Cathepsin H was identified to play an important role in the establishment and development of functional tumor vasculature and increase the metastatic potential of human hepatoma cell lines. Deletion of *cathepsin H* significantly impairs angiogenic switching of the pre-malignant hyperplastic islets and results in a reduction in the subsequent number of tumors. Furthermore, the tumor burden in *cathepsin H* null RT2 mice was significantly reduced, which correlated with defects in the blood vasculature and increased apoptosis[112]. Selective cathepsin S deficiency impaired angiogenesis and tumor cell proliferation, thereby impairing angiogenic islet formation and the growth of solid tumors, whereas the absence of its endogenous inhibitor cystatin C resulted in the opposite phenotypes[113]. The *cathepsin S* gene targeted siRNA-mediated knockdown of cathepsin S expression, lead to potent suppression of MHCC97-H cell proliferation, invasion and angiogenesis. Using the gene knockout approach to determine the role of cathepsin S in pancreatic islet cell cancer showed that mutants of cathepsin S had impaired tumor formation and angiogenesis and significantly reduced levels of tumor invasion[2]. In a syngeneic colorectal carcinoma murine model that both tumor and tumor-associated cells contribute cathepsin S to promote neovascularization and tumor growth[114].

Cathepsins induce epithelia-mesenchymal transition

Epithelial to mesenchymal phenotype transition is a common phenomenon during embryonic development, wound healing, and tumor metastasis. This transition involves cellular changes in cytoskeleton architecture and protein expression[115]. Some studies have established the importance of some members of the cathepsin family in mediating this process. A functional study found that cathepsin Z could increase colony formation in soft agar and promote cell motility. Further studies found that the metastatic effect of cathepsin Z is associated with its role in inducing epithelia-mesenchymal transition (EMT) by upregulating mesenchymal markers (fibronectin and vimentin) and downregulating epithelial markers (E-cadherin and α-catenin)[107]. Snake venom cystatin (sv-cystatin) is a member of the cystatin family of cysteine protease inhibitors. Expression of the sv-cystatin gene in MHCC97-H cells inhibits tumor cell invasion and metastasis by reducing the proteinase activity and EMT[116].

Cathepsins and cancer autophagy

Autophagy participates in tumor growth and maintenance by supplying metabolic substrate, limiting oxidative stress and maintaining cancer stem cell population[117]. Cathepsin A involves in chaperone-mediated autophagy by triggering degradation of lysosome-associated membrane protein type 2a (lamp2a)[51]. Mature cathepsin D also involved in autophagy and playing a crucial role in the control of cell and tissue homeostasis[56]. In human malignant glioblastoma M059J cells, cathepsin D functions as an anti-apoptotic mediator by inducing autophagy under cellular stress[118]. Autophagy inhibition suppresses the upregulation of XO, which is induced by cathepsin S inhibition, resulting in reduced ROS generation, DNA damage, and cell death[119]. Enhanced autophagy and reduced expression of lysosomal enzymes induced regional autophagic cell death under EBV infection in nasal natural killer/T-cell lymphomas[120]. The relationship of autophagy and cathepsin in tumor is still unclear, need to further investigate.

Cancer therapy targeting cathepsins

Cathepsin S may serve as a useful prognostic indicator and potential target for noninvasive therapy[89]. A selected cathepsin S antibody, Fsn0503, significantly blocked the invasion of a range of tumor cell lines, most significantly HCT116 colorectal carcinoma cells, through the inhibition of extracellular cathepsin S-mediated proteolysis[90]. Silencing cathepsin S expression suppressed the migration and invasion of gastric cancer cells *in vitro*. Subsequent secretomics revealed that cathepsin S silencing resulted in changes in the expression levels of 197 proteins, one-third of which are implicated in cellular movement[92]. Notably, this will enable the development of individualized treatments for cancer patients according to their cancer type and its progression. In fact, cathepsin inhibitors are already being tested in clinical trials and hold promise for combined cancer therapies[10,55].

CONCLUSION

The contribution of cathepsins in the invasion process in human cancers is well documented, although the precise mechanisms by which cathepsins exert their effect are still under active investigation. Each cathepsin member exerts different functions in tumor metastasis process:

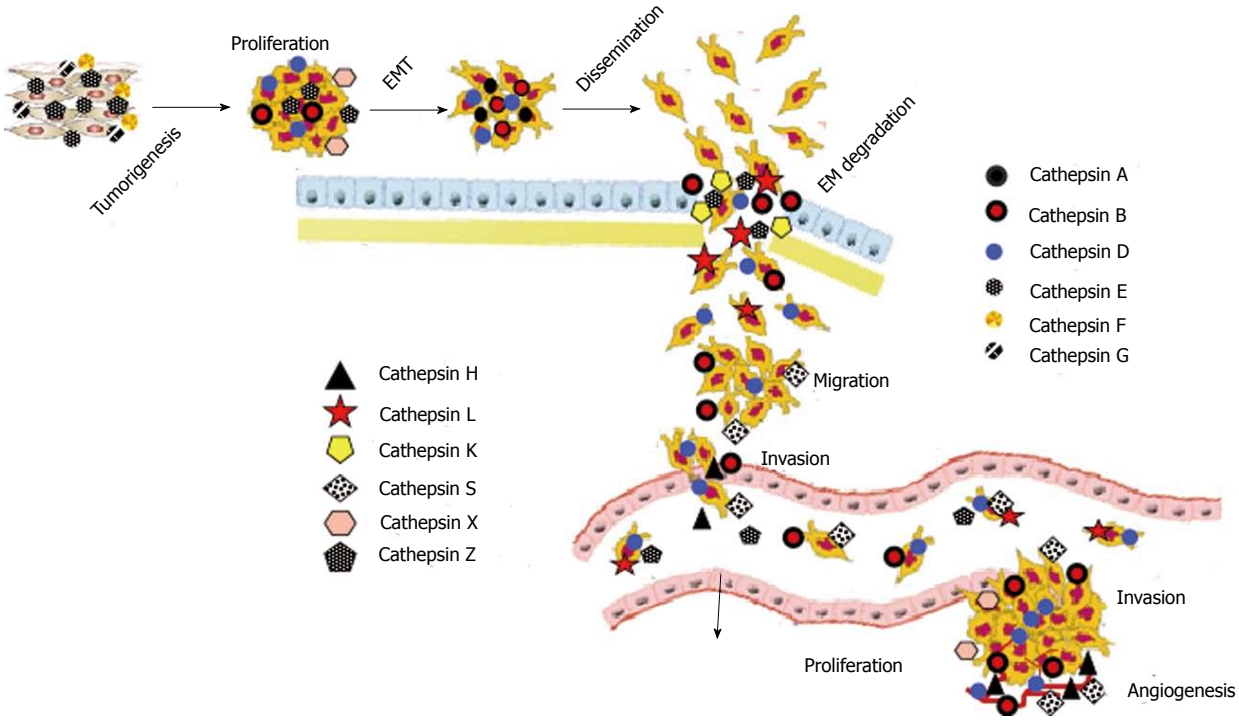

Figure 1 Role of cathepsins in tumor metastasis process. Cathepsin E, F, G, Z promote cell tumorigenesis; tumor cells are induced proliferation by cathepsin B, D, E, X; cathepsin X mediates tumor cell epithelia-mesenchymal transition (EMT); cathepsin A, B, D induces tumor cells dissemination; cathepsin B, K, L, Z degradate ECM, cathepsin B, D, H, L, S, Z increase the motility and invasive of tumor cell, and tumor cells invade to surrounding tissues, blood, and lymph vessels, and metastasize to distant sites; In metastatic sites, cathepsin B, D, H mediate tumor cell proliferation, cathepsin B, D, H, S mediate angiogenesis, and metastatic tumor forms.

(1) cathepsins can activate other proteases, thereby indirectly affecting invasion by participating in proteolytic cascades; Cathepsin B has been shown to directly activate MMP-1 and MMP-3, which in turn can cleave components of the ECM such as collagen, gelatin and tenascin; thus, facilitating the migration of tumor cells through the extracellular space[121]; (2) cathepsins directly cleave components of the BM/ECM, such as laminin, fibronectin, tenascin-C, and type Ⅳ collagen, which leads to limited proteolysis of the ECM[122-126]; (3) cathepsins can inactivate cell adhesion proteins by cleaving the cell surface protein E-cadherin, which is the principal component of adherens junctions. E-cadherin cleavage abrogates its cell-cell adhesion function and promotes tumor cell invasion; (4) cathepsins mediate angiogenesis; and (5) cathepsins induce EMT (Figure 1).

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