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Role of meprin metalloproteases in metastasis and tumor microenvironment

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Abstract

A crucial step for tumor cell extravasation and metastasis is the migration through the extracellular matrix, which requires proteolytic activity. Hence, proteases, particularly matrix metalloproteases (MMPs), have been discussed as therapeutic targets and their inhibition should diminish tumor growth and metastasis. The metalloproteases meprin α and meprin β are highly abundant on intestinal enterocytes and their expression was associated with different stages of colorectal cancer. Due to their ability to cleave extracellular matrix (ECM) components, they were suggested as pro-tumorigenic enzymes. Additionally, both meprins were shown to have pro-inflammatory activity by cleaving cytokines and their receptors, which correlates with chronic intestinal inflammation and associated conditions. On the other hand, meprin β was identified as an essential enzyme for the detachment and renewal of the intestinal mucus, important to prevent bacterial overgrowth and infection. Considering this, it is hard to estimate whether high activity of meprins is generally detrimental or if these enzymes have also protective functions in certain cancer types. For instance, for colorectal cancer, patients with high meprin β expression in tumor tissue exhibit a better survival prognosis, which is completely different to prostate cancer. This demonstrates that the very same enzyme may have contrary effects on tumor initiation and growth, depending on its tissue and subcellular localization. Hence, precise knowledge about proteolytic enzymes is required to design the most efficient therapeutic options for cancer treatment. In this review, we summarize the current findings on meprins' functions, expression, and cancer-associated variants with possible implications for tumor progression and metastasis.

Keywords Metalloprotease · Meprin · ADAM · Astacin · Ectodomain shedding · Inhibition

Tissue remodeling and metastasis are crucial mechanisms for tumor spreading/or progression. Proteases that can remodel extracellular matrix (ECM) and build up a tumor-beneficial microenvironment are therefore potent tools for cancer cells to adjust the ECM. Furthermore, disruption of ECM and cleavage of adhesion molecules can promote invasion and metastasis of cancer cells.

Meprin α and meprin β are zinc-dependent metalloproteases that exhibit unique molecular and functional properties among all extracellular proteases. The major expression sites of meprins are enterocytes in the small intestine and colon, the brush border membrane of proximal tubuli in the kidney, and to minor extend the epidermis, blood vessels, lung, brain, and certain immune cells [1–7]. Meprin α and meprin β are two individual enzymes encoded by genes on different chromosomes and thus distinct promoter usage [4, 8, 9]. However, they share 41% sequence identity and have a similar domain structure with the exception of a so-called inserted domain in meprin α, which is located between the EGF- and TRAF-domain. Meprin α is maturated by furin cleavage on the secretory pathway, thereby losing its C-terminus and transmembrane anchor, which makes meprin α a secreted protease [10, 11]. In the endoplasmic reticulum, two meprin monomers build a dimer *via* a disulfide bridge between the MAM-domains, which further associate to non-covalently linked oligomers in the extracellular space [10]. Interestingly, when co-expressed in the same cell, meprin α and meprin β can form heterodimeric enzyme complexes that tether soluble meprin α to the cell membrane, which probably modifies its function and substrate spectrum [11–13]. Of note, meprin knock-out mice are viable and show no severe phenotype, indicating that meprins are either not essential proteases for murine development or that meprin activity can be compensated by other enzymes [14, 15].

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However, meprin α– and meprin β–deficient mice exhibit diminished ECM deposition in the skin, which points toward their function in collagen maturation [16, 17]. Interestingly, expression of meprins is also found in a variety of tumors and cancer cells that might benefit from their activity as extracellular proteases with a broad substrate spectrum, which includes degradation and modulation of ECM proteins, maturation of cytokines and growth factors, and cleavage of adhesion molecules.

In this review, we focus on expression and regulation of meprins in tumors and cancer cells, as well as on their role on substrate cleavage with regard to ECM remodeling, angiogenesis, cancer cell invasion, and metastasis.

1 Expression of meprin metalloproteases in tumor and cancer cells

Meprin α and meprin β are two related proteases of the astacin protease family. Although sharing 41% amino acid sequence identity, the proteases are encoded on different chromosomes and expressed individually by different promoter and transcription factors. Concomitant, expression and function of meprins varies in tumors and cancer cells. In recent years, increased expression and activity of meprin α was reported in various tumors (Table 1).

The earliest identification of meprin α in a neoplasm was in colorectal cancer and the colon carcinoma cell line Caco-2 [18]. In cell culture experiments as well as in tumor tissue sections, basolateral sorting and accumulation of meprin α in the stroma was observed, which was in contrast to the physiological apical sorting of meprins, e.g., in enterocytes (Fig. 1). Later on, expression of meprin α on the mRNA- and protein level was further characterized in different tumor stages: colonic adenomas, primary tumor stages I–IV, and in liver metastasis [25]. Increased protein levels were detected in transition from benign adenomas to malignant primary tumors. Interestingly, meprin α mRNA expression in the intestine was found to be tightly restricted to a certain pool of enterocytes that were defined as rather early differentiated cells [26]. Here, meprin α was even suggested as a marker gene for this particular cell population. Thus, dysregulation of meprin α expression or activity likely influences intestinal epithelial proliferation and differentiation, which may be linked to colon cancer [18]. A pro-migratory effect for colon cancer cells was seen in cells expressing both meprin α and meprin β, leading to membrane-bound meprin α forming heterodimers with meprin β (Fig. 1) [11–13]. Although *MEP1B* mRNA was not detectable in colorectal cancer at that time, the authors speculated that meprin β could be expressed in a subpopulation of cancer cells that migrate away from the tumor mass by cleaving adhesion molecules.

Recently, another possibility to tether meprin α to the membrane was described. Biasin et al. demonstrated that meprin α can bind to heparan sulfate of lung vascular epithelial cells, which leads to disrupted barrier integrity *in vitro* [27]. Thus, equal membrane-tethering could take place in cancer cells expressing heparan sulfate [28]. Nevertheless, membrane-bound substrates being exclusively cleaved by membrane-tethered meprin α are unknown so far.

Interestingly, high meprin α protein levels but no meprin α activity were observed in liver metastasis of colorectal cancer patients, indicating a lack of meprin α activators that are not expressed by the cancer cells itself but by tumor stromal cells [25, 29]. In contrast, OuYang et al. identified meprin α expression in human hepatocellular carcinoma (HCC) and suggested the protease as a prognostic predictor and risk factor with poor survival of patients [20]. Further *in vitro* characterization highlighted a role of meprin α in proliferation, migration, and invasion of cancer cells *via* activation of the extracellular signal-regulated kinases/zinc finger E-box-binding homeobox 1 (ERK/ZEB1) pathway that has also been described for colorectal cancer progression [20, 30]. Meprin α–mediated invasiveness has also been observed earlier in the meprin α–expressing human breast cancer cell line MDA-MB-435, where invasiveness decreased when cells were treated with the meprin α inhibitor actinonin [31]. Moreover, meprin α as well as MMP7 expression could be decreased in the breast cancer cell line by treating the cells with a-difluoromethylornithine (DFMO), which increases ERK phosphorylation. Further experiments showed restored meprin α expression with a mitogen-activated protein kinase kinase (MEK) inhibitor [31, 32]. This finding seems to be contrary to the observation of OuYang et al., but could indicate a feedback-loop between the mitogen-activated protein kinase (MAPK) pathway and meprin α. Increased meprin α mRNA expression was identified to be regulated by the

Table 1 Reported meprin expression in cancer

Meprin	Cancer type	Function	Reference
Meprin α	Colorectal cancer	ECM degradation, metastasis	[18]
Meprin α	Renal cell carcinoma	Angiogenesis?	[19]
Meprin α	Hepatocellular carcinoma	Proliferation, migration, invasion, EMT	[20, 21]
Meprin α	Pancreatic cancer	Neoangiogenesis	[22]
Meprin β	Pancreatic neuroendocrine tumor	–	[23]
Meprin β	Endometrial cancer	Metastasis?	[24]

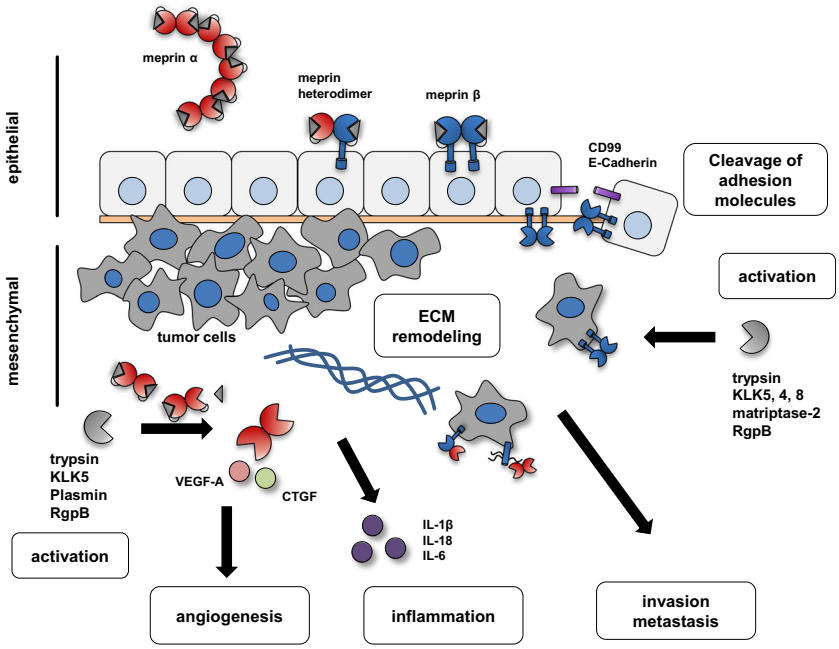

Fig. 1 Under physiological conditions, meprins are mainly located at apical sites of epithelial cells and expressed as homo- or heterodimers. Upon mislocalization due to the loss of cell polarity and their activation by tryptic proteases, meprins can degrade and remodel ECM components on the basolateral site and promote tumor growth *via* induction of angiogenesis and inflammation. Furthermore, cleavage of adhesion molecules can induce loss of intercellular adhesion and promote invasion and metastasis of cancer cells

oncogene Reptin in HCC [21, 33]. Here, the authors did not observe a pro-proliferative effect of meprin α, but both silencing meprin α itself or *via* silencing of Reptin reduced migration and invasion of HuH7 and Hep3B in accordance with OuYang et al.. Meprin α was also suggested as a prognostic marker for differentiation of pancreatic cancer (PCA) from chronic pancreatitis [22]. Here, meprin α expression was also found at the basolateral cell membrane of PCA cells and linked to neovascularization.

Expression of meprin β has also been described in pancreatic neuroendocrine tumors and respective liver metastasis; however, a functional consequence has not been addressed so far [23]. Nevertheless, some studies suggested a potential role for meprin β particularly in migration and invasion of cancer cells. In accordance with mislocalized basolateral expression of meprin α in colon carcinoma, basolateral expression of meprin β was recently observed in endometrial cancer [24]. The authors tested a genetic variant of meprin β G32R, which was annotated in the BioMuta database [34] (https://hive.biochemistry.gwu.edu/biomuta/proteinview) of large-scale screenings from endometrial cancer samples. *In vitro* characterization of this variant showed accelerated meprin β activation and increased invasion of transfected HeLa cells through a collagen IV matrix [24]. In accordance with this, meprin β is capable of cleaving various adhesion molecules that would normally anchor adjacent cells to surrounding tissues (Fig. 1). One of those adhesion molecules and a substrate of meprin β is CD99, a type I transmembrane protein expressed in cells of the hematopoietic system and at intercellular borders of endothelial cells [35–39]. Homophilic CD99 interaction plays an essential role for transendothelial migration (TEM) of immune cells, and CD99 expression is also a hallmark of Ewing's sarcoma [39–42]. Cleavage of CD99 by meprin β was investigated with regard to TEM both (i) *in vitro* by transmigrating Lewis lung carcinoma cells through an endothelial bEnd.3 cell monolayer in the presence of recombinant meprin β and (ii) *in vivo* in an acute inflammation mouse model [36, 37]. Besides the physiological function on migrating immune cells, cleavage of CD99 by meprin β could also presume a tumor invasion- and metastasis-beneficial event. In polarized Madin-Darby Canine Kidney (MDCK) cells and Caco-2 cells, the epithelial adhesion protein E-cadherin has been described as a substrate of meprin β [43]. As an important intercellular junction protein, E-cadherin was considered a tumor suppressor, since downregulation promoted progression of adenoma to invasive carcinoma [44, 45]. Dysregulated basolateral sorting of meprin β in tumor tissue could therefore lead to cleavage of E-cadherin and subsequent detachment of cancer cells and β-catenin-induced proliferation. In contrast with *MEP1A* expression, a cancer-specific transcription variant of meprin β, namely meprin β′, was identified in both human and murine cancer cells. Of note, meprin β′ expression was stimulated using retinoic acid or phorbol myristal acetate (PMA) [46–48]. In both species, the 5′ UTR of meprin β′ mRNA differs from normal meprin β mRNA with the exception that murine meprin β′ is also alternatively spliced, resulting in a different signal peptide (bold) and propeptide sequence (italic) (murine meprin β: **MDARHQPW FLVFATFLLVSG***LPAPEKFVKDID*…; murine meprin β′: **MNSTAGPASRSRHSFKCRMKLLKAPRDG***MYMMTFGVKDID*…). However, a physiological consequence of human and murine meprin β′ with regard to altered mRNA or protein stability, intracellular transport, or activation has not been investigated yet. Of note, signal peptide prediction of the

murine meprin β′ sequence revealed only a weak signal peptide consensus sequence, indicating also potential differences in intracellular sorting compared with normal murine meprin β.

Besides this major cancer-related alteration within the sequence of meprin β, different single nucleotide variants (SNVs) for *MEP1A* and *MEP1B* that were observed in different tumors are listed in the BioMuta database [34]. For *MEP1B*, most SNVs were found in melanoma, uterine cancer, lung cancer, and liver cancer, resulting in several amino acid residue changes within the protein sequence (Fig. 2a). Interestingly, some SNVs can be found in the conserved zinc-binding motif (HExxHxxGxxHxxxRxDR) in the catalytic domain that might disrupt the proteases' catalytic activity (Fig. 2b, underlined). A mutation of R238 to glutamine was found in melanoma, malignant glioma, and uterine cancer and would alter the substrate specificity of meprin β and the preference for negatively charged amino acids at the P1′ position [49]. So far, no SNVs were listed that affect the trypsin-activation site (R61), the meprin β dimerization (C305) or the ADAM10/17 cleavage motif (Q(595)IQL) upstream of the EGF-like domain (Fig. 2b). Most tumor-associated SNVs for *MEP1A* are also found in melanoma, followed by lung cancer, uterine cancer, and stomach cancer (Fig. 2c). Again, the conserved zinc-binding motif can be disrupted by several amino acid residue exchanges (Fig. 2d, underlined). Furthermore, two SNVs were found in liver and pancreatic cancer that prevented homo-dimerization of meprin α or formation of a meprin α/β enzyme complex, which tethers meprin α to the cell surface. The mutation A727S in the transmembrane region of meprin α could be detected with high frequency in lung cancer and might cause folding problems or aberrant helix interactions resulting in a loss of function. If and how these mutations affect cellular localization, proteolytic activity, or posttranslational modification and thus may promote tumor growth or metastasis need to be elucidated. Recently, Schäffler et al. investigated a meprin β G32R variant, which was found in endometrial cancer and showed accelerated activation of the protease and pro-invasive properties for HeLa cells [24]. However, to investigate if the SNVs observed for meprin α and meprin β are driver or bystander mutations, suitable animal/xenograft models are needed.

2 Posttranslational regulation of meprin metalloproteases

Meprins are expressed as zymogens with an N-terminal propeptide blocking the active site cleft of the catalytic domain. Thus, meprins require activation by other proteases in order to gain catalytic activity by loss of the inhibitory propeptide. Therefore, expression of meprin-activating enzymes in tumor tissue and cancer cells is a substantial aspect

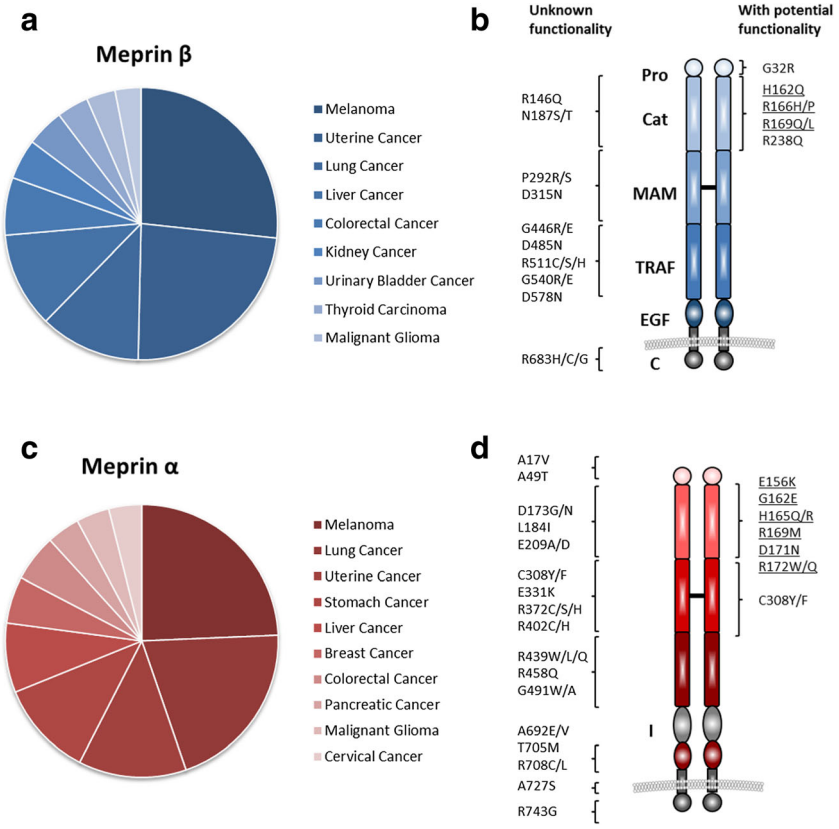

Fig. 2 SNVs of *MEP1B* and *MEP1A* annotated in the BioMuta database were mainly identified in melanoma, lung cancer, and uterine cancer (**a**, **c**). Selected and most frequently identified SNVs with potential functional consequence or unknown functionality are assigned to each domain of meprin metalloproteases. The domain structure of meprins consists of a propeptide (Pro), astacin-like catalytic domain (Cat), MAM (meprin, A5-protein, and receptor protein-tyrosine phosphatase μ) domain, TRAF (tumor necrosis factor receptor–associated factor) domain, EGF (epidermal growth factor)-like domain, transmembrane anchor, and C-terminal cytosolic tail (**b**). An additional inserted domain (I) is found in meprin α (**d**). SNVs within the conserved zinc-binding motif in the Cat domain are underlined

when investigating meprin functions. Due to the activation site of meprins, containing arginine or lysine residues in the P1 position, tryptic serine proteases have been described to activate meprin metalloproteases both *in vitro* and *in vivo* (Fig. 1). In 1993, pancreatic trypsin was identified as the first meprin-activating enzyme, cleaving at Arg65 (meprin α) or Arg61 (meprin β), and was therefore discussed as the most relevant activation mechanism of meprins in the intestinal lumen [50]. Interestingly, expression of trypsin is also found in a variety of cancer cells from ovary, prostate, lung, and colon [51–54]. Especially in colorectal carcinogenesis, high trypsin expression is linked to poor prognosis of patients [54]. As a secreted enzyme, trypsin can either directly cleave components of the ECM or activate other ECM degrading enzymes like MMPs. However, targeting trypsin as a therapeutic approach is not suitable due to its contribution as a digestive enzyme and also as an activator of other enzymes within the intestinal tract. Although described as the most potent activator of meprins in the intestine, trypsin is most likely not directly getting access to membrane-bound meprins on enterocytes due to the mucus barrier that shields the epithelial layer [55]. This has probably a good reason since active membrane-tethered meprin β was shown to decrease cell adhesion [43], which would be detrimental for the intestinal epithelium. Recently, the secreted bacterial protease RgpB from *Porphyromonas gingivalis* was shown to potently activate meprin β at the cell surface [56]. *P. gingivalis* is the major pathogen for periodontitis, but was also shown to be associated with colorectal cancer tissue [57, 58]. The physiological role of meprin β in the intestine is mucus detachment by cleaving its major component mucin 2 [59]. The constant renewal of the mucus layer prevents bacterial overgrowth and infection [55]. Importantly, only soluble shed meprin β can get access to the cleavage site in mucin 2 [59]. Hence, activation of meprin β at the plasma membrane of enterocytes, e.g., by RgpB, would prevent its shedding by ADAM proteases, consequently resulting in mucus accumulation, which may serve as source of infection for invasive bacteria. In turn, chronic intestinal inflammation could be the basis for tumor development. Other serine proteases and meprin-activating enzymes are human tissue-kallikreins (KLKs) [60]. Physiological meprin-activation by KLKs likely occurs in differentiating keratinocytes in the epidermis. Since KLKs are also expressed in certain cancers, e.g., colorectal cancer, co-expression with meprins would lead to their activation [61, 62]. Of note, some serine proteases can only activate meprin α or meprin β while others can activate both (Fig. 1). It has been shown that KLK5 can cleave the propeptide of both meprin α and meprin β, while KLK4 and KLK8 can only activate meprin β [60]. Similarly, membrane-bound serine protease matriptase-2 was shown to activate meprin β on the cell surface but does not reach the secreted meprin α [63]. In contrast, the secreted protease plasmin activates only meprin α [29, 64]. This can take place in tumor stroma of colorectal cancer, where meprin α was secreted to the basolateral site [18]. In coculture experiments with Caco-2 cells and intestinal fibroblasts, plasminogen activators produced by fibroblasts were able to activate meprin α [29]. Hence, meprin α could degrade ECM and basement membrane proteins like fibronectin, nidogen, or laminins in tumor stroma and promote tumor-beneficial tissue remodeling [35, 65, 66].

Lottaz et al. identified meprin α expression in liver metastases from colorectal cancer [25]. Interestingly, meprin α purified from isolated metastasis showed no proteolytic activity compared with the primary tumor, indicating that (i) meprin α activity might not be required for metastasis and formation of the metastatic niches and that (ii) meprin α activators are probably secreted by surrounding cells and tissues as observed in the coculture experiment with Caco-2 cells and intestinal fibroblasts [25, 29]. This is in accordance with the observation that the urokinase-type plasmin activator-system was not active in liver metastasis due to overexpression of respective inhibitors [67].

Unlike meprin α, which is secreted due to proteolytic processing by furin in the secretory pathway, meprin β is transported and tethered to the cell surface. However, meprin β can be shed by ADAMs 10 and 17 from the plasma membrane into the extracellular space, thereby reaching a different subset of substrates [56, 68]. Of note, it has been shown that only inactive pro-meprin β is shed by ADAMs for an unknown reason [56]. Therefore, soluble meprin β like meprin α requires further activation by other enzymes in the extracellular space. Interestingly, some membrane-bound meprin β substrates like the interleukin 6 receptor (IL-6R) or the amyloid precursor protein (APP) cannot be cleaved by soluble meprin β, indicating a tight regulatory mechanism by other proteases that can impair substrate accessibility on the cell surface or intracellular interactions [69]. On the other hand, the membrane-bound adhesion molecule CD99 was shown to be cleaved by both soluble and membrane-bound meprin β [36, 37].

Collectively, functionality of meprin metalloproteases is regulated not only by transcription but also by a variety of post-translational events that alter localization, activation, and substrate availability, which have to be considered for investigation of these proteases' roles, e.g., on cancer cells and tumorigenesis.

3 Meprins promote inflammation, cell proliferation, and angiogenesis

Tumor development and progression is often accompanied by inflammation within the tumor microenvironment and release of pro-inflammatory cytokines by immune cells. Meprin expression was observed in various inflammatory diseases such as inflammatory bowel disease (IBD), vasculitis, and renal and urogenital injury [14, 70–72]. Since meprins can cleave adhesion molecules like CD99 and E-cadherin and affect

remodeling of the ECM, they have a pro-migratory function not only for metastatic cancer cells but also for inflammatory cells, which was recently shown in meprin β knock-out mice employing a model of acute inflammation (air pouch/carrageenan) [37]. Additionally, expression of meprin β is associated with the production of several pro-inflammatory cytokines like interleukin (IL-)1β, IL-18, and IL-6 in macrophages (Fig. 1) [73]. For activation of IL-1β and IL-18, propeptides of these cytokines need to be cleaved off proteolytically, which can be carried out by caspases inside the cell [74–76]. However, both meprin α and meprin β were also shown to activate pro-IL1β and pro-IL18 *in vitro* and *in vivo* [77–80]. Although controversially discussed, this might be possible due to the release of the preforms through gasdermin pores, recently shown to be important for active IL-1β secretion *via* inflammasomes in programmed necrosis [81, 82]. Furthermore, meprin α and membrane-bound meprin β were recently shown to shed the IL-6R from the cell surface, thereby triggering the pro-inflammatory trans-signaling process of IL-6, which was also described for ADAM proteases [69, 83, 84].

In Caco-2 cells, meprin α is capable of activating the EGF receptor/mitogen-activated protein kinase (EGFR/MAPK) signaling pathway by shedding of transforming growth factor α (TGFα) and epidermal growth factor (EGF), thereby enhancing cancer cell proliferation and migration [30]. Moreover, EGFR activation by meprin α was also shown to induce oxidative stress in macrophages, which drives development of atherosclerosis [85]. Elevated EGFR activation is also involved in tumor-associated angiogenesis, a crucial mechanism to provide nutrients to the highly proliferative cancer cells [86]. A well-described angiogenesis-inducing cytokine is vascular endothelial growth factor (VEGF), which promotes proliferation of endothelial cells and requires activation by several proteases that are also associated with ECM remodeling [86–88]. *In vitro* experiments revealed a pro-angiogenic role of meprin α, which potentially arises due to VEGF-A cleavage (Fig. 1) [35, 89]. This was further confirmed in knock-down experiments of meprin α in zebrafish [89]. Injection of specific morpholinos in early embryos, targeting *Mep1a* mRNA, resulted in impaired vessel formation in the developing fish. Hence, meprin α might have multiple pro-tumorigenic functions, either directly influencing tumor cell differentiation and proliferation or the tumor microenvironment by recruiting and inducing vessel growth for oxygen and nutrient supply for the tumor. Furthermore, cleavage of pro-inflammatory cytokines by both meprin α and meprin β can induce a tumor-beneficial inflammation.

4 Conclusion

In this review, we highlight expression, posttranslational regulation, and potential pro-tumorigenic substrate cleavage mechanisms of meprin metalloproteases (Fig. 1). Meprin α and meprin β were detected in several tumors and metastases like colorectal and pancreatic cancer, hepatocellular and renal cell carcinoma, and endometrial cancer. Additionally, meprins are also expressed in a variety of cancer cell lines, further strengthening their impact on tumor growth and cell proliferation. Under physiological conditions, meprin expression is restricted to certain organs, cell types, and apical epithelial sites. However, whenever mislocalized, meprins can switch to harmful enzymes that degrade ECM proteins of the basal lamina, activate pro-inflammatory cytokines, and lead to detachment of cells, which are all cancer-beneficial pathways promoting tumor progression.

Meprin metalloproteases and other proteolytic enzymes are important molecular scissors that modulate tumor development and progression. However, among the almost 200 different human metalloproteases, it is of importance to distinguish between cancer-promoting and cancer-inhibiting functions of these enzymes. This is the basis for the molecular understanding of distinct cancer entities and will help to endeavor therapeutic windows for cancer treatment also using specific protease inhibitors.

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