ADAM and ADAMTS Family of Metalloproteinases: Role in Cancer Progression and Acquisition of Hallmarks

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Abstract

The adamalysins, which include the ADAMs and ADAMTSs, are multidomain, multifunctional proteins of the metzincin superfamily of zinc-dependent metalloproteinases that play a key role in extracellular matrix remodeling and regulation of the tissue microenvironment. While ADAMs are mostly membrane-anchored proteinases, the ADAMTSs are secreted proteinases and/or adhesion molecules. A major function of the ADAMs is ectodomain shedding of membrane-bound growth factors, receptors, cytokines, chemokines, and proteoglycans. The adamalysins are also involved in a multitude of biological processes including fertilization, organogenesis, hemostasis, cell adhesion, intracellular signaling, angiogenesis, and ECM assembly and turnover. These metalloproteinases exert both promoting and inhibitory effects on tumorigenesis and serve as biomarkers of cancer progression and prognosis. Dysregulated expression of adamalysins leads to acquisition of cancer hallmarks such as increased cell proliferation, apoptosis evasion, migration, neovascularization, invasion, and metastasis. In addition, aberrant expression of these proteases also results in drug resistance. Of late, the adamalysins have emerged as potential molecular targets for cancer therapeutics. This chapter summarizes current knowledge on the different types of ADAMs and ADAMTSs, their general structure, functions, role in cancer progression, and acquisition of major cancer hallmarks as well as their potential as diagnostic and prognostic aids and therapeutic targets based on available literature.

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1 Introduction

Cancer, a multifactorial, heterogeneous disease, arises due to sequential accumulation of mutations that promote clonal selection of cells characterized by uncontrolled proliferation, apoptosis evasion, invasion of surrounding tissues, and metastasis to other organs [1, 2]. Tumor invasion, an essential prerequisite for cancer metastasis, involves remodeling of the extracellular matrix (ECM), a process initially considered to be the prerogative of the matrix metalloproteinases (MMPs) [3]. It has now become apparent that adamalysins, which include the ADAMs (*A Di*sintegrin *A*nd *M*etalloproteinase) and ADAMTSs (*A Di*sintegrin *A*nd *M*etalloproteinase with *T*hrombospondin motifs), are also key players in ECM homeostasis and regulation of the tissue microenvironment [4–7]. The metalloproteinase system is in turn regulated by *t*issue *i*nhibitors of *m*etalloproteinases (TIMPs) [8] and *r*eversion-inducing *c*ysteine-rich protein with *K*azal motifs (RECK) [9, 10].

The adamalysins are multidomain, multifunctional proteins of the metzincin superfamily of zinc-dependent metalloproteinases [11]. While ADAMs are mostly membrane-anchored proteinases, the ADAMTSs are secreted proteinases and/or adhesion molecules [12]. Although 40 different proteins have been recognized as members of the ADAMs family, only 25 of these are believed to function in humans (Table 1). Of these, only 13 ADAMs display proteolytic activity. Information on ADAMs is constantly updated in http://people.virginia.edu/~jw7g/Table_of_the_ADAMs.html and http://degradome.uniovi.es/). Members of the ADAMs family are localized to specific organs such as, the heart (ADAM9, -17, -19) [13], kidney (ADAM19) [14], lungs (ADAM33) [15], teeth (ADAM28), and pancreas (ADAM-9, -10, -17) [16].

The human family of ADAMTs comprising 19 known members [17] is classified based on their preferred substrates as the aggrecanases or proteoglycanases (ADAMTS1, 4, 5, 8, 9, 15 and 20), the procollagen N-propeptidases (ADAMTS2, 3 and 14), the cartilage oligomeric matrix protein-cleaving enzymes (ADAMTS7 and 12), the von Willebrand Factor proteinase (ADAMTS13), and orphan enzymes (ADAMTS6, 10, 16, 17, 18 and 19). Table 2 lists the various ADAMTs. Data on ADAMTs is available at http://www.lerner.ccf.org/bme/apte/adamts.

The adamalysins play a central role in biological processes including fertilization, organogenesis, hemostasis, cell adhesion, intracellular signaling, angiogenesis, and ECM assembly and turnover. Mutations and aberrant expression of ADAMs and ADAMTs have been implicated in diverse pathologies including thrombotic thrombocytopenic purpura, inflammatory bowel diseases, airway diseases,

Table 1 ADAMs: chromosomal loci, tissue expression and functions

ADAM	Chromosomal locus	Tissue distribution	Function	Reference (s)
ADAM 1a,b	12q24.13	Sperm	Sperm–egg binding and fusion, interaction with the integrins: α6β1 and α9β1	[121, 122]
ADAM2	8p11.22	Sperm	Sperm–egg binding and fusion, interaction with the integrins: α4β1, α6β1 and α9β1	[123, 124]
ADAM6	14q32.33	Testis	Not fully defined	[125]
ADAM7	8p21.2	Testis	Not fully defined but it interacts with the integrins like α4β1, α4β7 and α9β1	[126, 127]
ADAM8	10q26.3	Lung, kidney, brain, macrophage, neutrophils	Cancer cell migration, neutrophil infiltration and shedding of CD23	[128]
ADAM9	8p11.23	Breast, pancreas, lung, stomach, and skin	Promotion of cell adhesion, invasion, binding to integrins, shedding of HB-EGF, tumor necrosis factor-p75 receptor, cleavage of amyloid precursor protein (APP) and digestion of fibronectin and gelatin	[129]
ADAM10	15q22	Brain, breast, liver, oral cavity, ovary, prostate, colon, kidney	Promotion of cell growth and migration, release of TNFα, digestion of collagen IV, gelatin and myelin basic protein; cleavage of delta, APP, L1, and CD44 and shedding of HB-EGF	[130–132]
ADAM11	17q21.3	Brain	Not fully defined but may act as a tumor suppressor	[133]
ADAM12	10q26.3	Liver, stomach, colon, brain, breast, osteoblast, muscle, placenta and chondrocytes	Promotion of cell growth, muscle formation, binding to integrins, insulin-like growth factor binding protein-3 (IGFBP-3) and IGFBP-5, shedding of HB-EGF, digestion of collagen IV, gelatin, and fibronectin	[134]
ADAM15	1q21.3	Brain, prostate, lungs, stomach, endothelium smooth muscle, chondrocyte, and osteoclast	Promotion of cell growth, Expressed in arteriosclerosis, binds to integrins: αVβ3, α5β1 and α9β1 and helps in digestion of collagen IV and gelatin	[135, 136]

(continued)

Table 1 (continued)

ADAM	Chromosomal locus	Tissue distribution	Function	Reference (s)
ADAM17	2p25	Macrophage, ovary, prostate, kidney, colon, and breast tissue	Promotion of cell growth, binding with integrins: shedding of signaling molecules/surface receptors (TNFα, TGF-β, TNF-p75 receptor, ErbB4, TNF-related activation induced cytokine HB-EGF, APP, Notch, L-selectin and CD44)	[137]
ADAM18	8p11.22	Brain, testis, kidney	Not fully defined	[138]
ADAM19	5q32–q33	Testis	Formation of neuron, digestion of neuregulin and interacts with the integrins like α4β1, α5β1	[128]
ADAM20	14q24.1	Testis	Formation of sperm	[139]
ADAM21	14q24.1	Testis	–	[139]
ADAM22	7q21	Brain	–	[140]
ADAM23	2q33	Brain, Heart	Not fully defined but it interacts with the integrins like αVβ3	[140]
ADAM28	8p21.2	Testis, lung, lymphocyte, pancreas, uterus	IGFBP-3 cleavage, promotion of cell growth, binding with integrins: α4β1, α4β7, α9β1; digestion of myelin basic protein and IGFBP-3	[141, 142]
ADAM29	4q34	Testis	–	[143]
ADAM30	1p13–p11	Testis	–	[144]
ADAM32	8p11.23	Testis	–	[145]
ADAM33	20p13	Lung (fibroblast, smooth muscle)	Interactions with integrins; cleavage of APP, Kit-ligand-1 (KL-1) and insulin B chain	[146]

osteoarthritis, atherosclerosis, neurodegeneration, and cancer. Adam-19 KO mouse suffers from developmental defects and embryos died due to abnormalities of the heart and other cardiovascular system disorders [18]. The proteolytic activities, regulation of growth factors and cytokines and the ability to degrade ECM components, suggest that these enzymes may be involved in cell migration, invasion, angiogenesis, and metastatic spread of tumor cells [19, 20]. This chapter summarizes current knowledge on different types of ADAMs and ADAMTSs, their general structure, functions, role in cancer progression, and acquisition of major cancer

Table 2 ADAMTs: chromosomal loci, tissue expression and functions

ADAMT	Chromosomal locus	Tissue distribution	Function	Reference (s)
ADAMTS1	21q21	Ovary, breast, bronchial epithelial cells, fetal lung, placenta, smooth muscle, uterus, adrenal cortex, adipocytes, ciliary ganglion, prostate, olfactory bulb, breast stromal fibroblasts and myoepithelial cells	Promotion of cell growth, cell survival and invasion, Binding to heparin, HB-EGF and AR shedding, digestion of aggrecan and versican, syndecan 4, TFPI-2, semaphorin 3C, nidogen-1, -2, desmocollin-3, dystroglycan, mac-2, gelatin, amphiregulin, TGF-α	[89, 100, 147, 148]
ADAMTS2	5q35	Adipocyte, skeletal muscle, superior cervical ganglion, uterus, placenta, heart, liver, lung, tongue, smooth muscle, breast stromal fibroblasts	Processing of collagen I and II N-propeptides, Glucocorticoids (in monocytes) and IL-6	[149]
ADAMTS3	4q21 (NM014243.1)	Skeletal muscle, tendon, cartilage, bone, breast myoepithelial cells, CD105+ endothelial cells, CD34+ cells and pineal gland	Processing of collagen N-propeptides, fibrillar procollagen type II and biglycan	[150]
ADAMTS4	1q23	Brain, heart, ovary, spinal cord, adrenal cortex, ciliary ganglion, trigeminal ganglion, retina, pancreas (islets), fetal lung and breast myoepithelial cells	Digestion of aggrecan, brevican and versican, reelin, biglycan, matrilin-3, α2-macroglobulin, COMP, IL-1 + oncostatin M, TNFα, S100A8, S100A9, leptin, IL-6	[31, 151, 152]
ADAMTS5	21q21	Brain, adipocyte, uterus, breast myoepithelial cells, uterus, placenta	Promotion of invasion, Digestion of aggrecan, versican, reelin, biglycan, matrilin-4, brevican, α2-macroglobulin cleavage, IL-1, TNFα, S100A8, S100A9, leptin, IL-6	[153–155]

(continued)

Table 2 (continued)

ADAMT	Chromosomal locus	Tissue distribution	Function	Reference (s)
ADAMTS6	5q12	Heart, breast myoepithelial cells, superior cervical ganglion, trigeminal ganglion, appendix	Regulation of TNFα	[151]
ADAMTS7	5q24	Liver, heart, skeletal muscle, trigeminal ganglion, adrenal cortex, intervertebral disc and breast stromal fibroblasts	Regulation of PTHrP, acts on COMP	[156, 157]
ADAMTS8	11q24	Skeletal muscle, heart, lungs, liver, superior cervical ganglion, adrenal cortex, breast stromal fibroblasts and luminal epithelial cells	Inhibitor of angiogenesis, helps in digestion of aggrecan	[102]
ADAMTS9	3p14	Dorsal root ganglion, breast and myoepithelial cells	Digestion of aggrecan, versican, TNFα, IL1 + oncostatin M and leptin	[56, 158]
ADAMTS10	19p13	Brain, uterus, breast stromal fibroblasts and CD8+ T cells	Acts on fibrillin-1	[159]
ADAMTS12		Liver, bone marrow, atrioventricular node, intervertebral disc, breast stromal fibroblasts and myoepithelial cells	Acts on COMP	[160, 161]
ADAMTS13	9q34	Liver, CD71+ early erythroid cells, lung, thyroid, breast myoepithelial cells; prostate, brain	Cleavage of von Willebrand factor (vWF) and IL-1	[162]
ADAMTS14	10q22	Thalamus, brain, uterus, bone marrow, fetal thyroid, adipocyte, cerebellum, bone, skin, fibroblasts, breast myoepithelial and luminal epithelial cells	Processing of collagen N-propeptides such as fibrillar procollagen type I (pNα1 and pNα2 chains)	[163]
ADAMTS15	11q24	Colon, brain, heart, uterus, musculoskeletal system, breast myoepithelial cells, Liver (fetus), Kudney (fetus)	Digestion of aggrecan and versican	[57, 58, 93]

(continued)

Table 2 (continued)

ADAMT	Chromosomal locus	Tissue distribution	Function	Reference (s)
ADAMTS16	5p15	Breast myoepithelial cells	Regulated by follicle stimulating hormone; forskolin cAMP; Transcription factors: Wilm's tumor-1; Egr-1 and Sp1	[164]
ADAMTS17	15q26	Breast myoepithelial cells	–	[165]
ADAMTS18	16q23	Ciliary ganglion, heart, skin, brain and breast myoepithelial cells	–	[166, 167]
ADAMTS19	5q23	Dorsal root ganglion, breast myoepithelial cells	–	[168]
ADAMTS20	2q12	Brain, appendix, heart, liver, skeletal muscle, pituitary, trigeminal ganglion, breast myoepithelial cells	–	[169]

hallmarks as well as their potential as diagnostic aids and therapeutic targets based on available literature.

2 Structure of Adamalysin Family of Proteins

The adamalysins family of proteins shows sequence similarities with the MMP family members as well as the reprolysin family of snake venomases [21, 22]. Based on their structure, the adamalysin family proteins are classified into the membrane-anchored ADAMs and the secreted ADAMTSs (Fig. 1).

The ADAM family members have a complex structure with multiple domains. The structural elements from the amino terminus comprise a *signal peptide* that marks the protein for the secretory pathway, a *prodomain* that ensures accurate folding of the protein and prevents catalytic activity of the metalloproteinase domain via a cysteine-switch mechanism until it is cleaved in the Golgi apparatus, a *metalloproteinase domain*, with the consensus sequence HEXGHXXGXXHD [23], a highly conserved *disintegrin domain* that interacts with integrins and mediates cell adhesion [24, 25], a *cysteine-rich domain* involved in substrate recognition and cell adhesion [26], an *EGF-like domain*, a *transmembrane domain*, and a *cytoplasmic tail* that contains phosphorylation sites and interacts with proteins containing the Src homology domain [27].

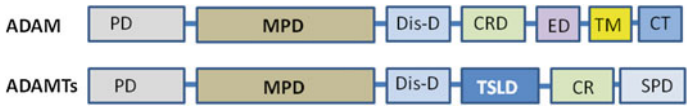

Fig. 1 General structure of adamalysin family of proteins. ADAM family members contain a propeptide domain (PD), a metalloproteinase domain (MPD), disintegrin domain (Dis-D), cysteine-rich domain (CRD), EGF-like domain (ED), transmembrane (TM) and cytoplasmic tail (CT). On the other hand, the secretory ADAMTs do not possess a functional TM, CT and ED but contain a thrombospondin-like domain (TSLD) and spacer domain (SPD)

The activation of ADAMs involves removal of the prodomain from the precursor protein by a proprotein convertase of furin type or by an autocatalytic process [28, 29]. Analysis of the crystal structure revealed that the disintegrin and cysteine-rich domains form a C-shaped structure, restricting accessibility for protein binding. Isoforms of ADAM9, ADAM11, ADAM12, and ADAM28 are secreted proteins that lack the transmembrane and cytoplasmic domains. The ADAM19 isoform lacks the propeptide, metalloproteinase, and disintegrin domains. Splice variants of ADAM15 and ADAM22 have also been identified.

Unlike the ADAMs, the ADAMTS do not possess the EGF-like, transmembrane and cytoplasmic domains [30, 31]. These proteins are characterized by the presence of a thrombospondin type I sequence repeat (TSR) motif. Some of the members contain one or two additional specific C-terminal modules such as a mucin domain (ADAMTS-7, and -12). Members of the ADAMTs family differ in the carboxy-terminal region downstream of the TSR, known as the ancillary domain. The ancillary domains provide substrate-binding specificity and ensure correct tissue compartmentalization, whereas cleavage site specificity is endowed by the protease domain. The ADAMTS differ from the ADAMs in their cysteine signatures. A unique family of seven ADAMTS-like (ADAMTSL) proteins that include ADAMTSL 1–6 and papilin, contain the ancillary domains of ADAMTS but lack the catalytic domains may modulate the activities of the ADAMTSs. The ADAMTS with the exception of ADAMTS4 as well as the ADAMTSL undergo posttranslational modifications that involve the addition of *N*-linked carbohydrate essential for activity.

3 Functions

Like the MMPs, both ADAMs and ADAMTs exhibit catalytic activity. Several ADAMs degrade ECM substrates and insulin-like growth factor binding proteins (IGFBPs). For example, ADAM10 cleaves type IV collagen, ADAM12 cleaves gelatin, type IV collagen and fibronectin, ADAM15 digests type IV collagen and gelatin, and ADAM28 cleaves IGFBP-3. Unlike ADAMs which due to their

membrane localization are predominantly involved in ectodomain shedding of proteins from the cell surface, the ADAMTS being secreted proteases are primarily involved in proteolytic events in the ECM. The ADAMTS1, 2, 3, 4, 5, 7, 8, 9, 14, 15, 16, 18, and 20 have been documented to degrade the ECM. ADAMTS1 remodels the ECM via proteolytic degradation of chondroitin sulfated proteoglycans and collagen [32]. ADAMTS-4 and ADAMTS-5 cleave aggrecan and are referred to as aggrecanases. These proteases also cleave brevican and versican [33, 34], while ADAMTS-2 is known to process procollagen chains [35]. However, in contrast to MMPs, most ADAMTS proteases do not cleave short peptides. Furthermore, proteolysis by ADAMTS may require posttranslational modifications of the substrate. ADAMTS2 processes procollagen efficiently when it is in the triple-helical conformation, but is unable to cleave the heat-denatured form. Mutation of ADAMTS13, a von Willebrand factor-cleaving protease, causes thrombotic thrombocytopenic purpura, a potentially fatal disease.

Considering the fact that only half of the proteins of the ADAMs and ADAMTS family display catalytic activity, it is apparent that the functions of these proteins extend beyond proteolytic activity and ECM remodeling. The first identified ADAMs (ADAM-1 and -2) were shown to induce the fusion of the sperm with the egg through interactions with the disintegrin domain. ADAM-15, a component of adherens junctions, is believed to regulate cell adhesion through interaction with various integrins via the disintegrin domain [36]. ADAM-10 regulates central nervous system development by cleaving the NOTCH protein [37]. ADAMs play a key role in signal transduction by interacting with tyrosin kinases and cytoskeletal components through their cytoplasmic domain [38].

One of the most important functions of the proteolytic ADAMs is their ability to cleave membrane-bound growth factors, receptors, cytokines, chemokines, and proteoglycans, thereby releasing the mature soluble forms, by their *sheddase* activity. ADAM-17, a prototype sheddase that cleaves pro-tumor necrosis factor-α (pro-TNF-α), is also known as TNF-α converting enzyme (TACE) [39–41]. In addition to TNF-α, ADAM-17 is also involved in shedding other membrane proteins such as proTGF-α, pro-amphiregulin and pro-epiregulin. ADAM-17 as well as ADAM9 and ADAM12 are responsible for shedding pro-heparin-binding epidermal growth factor (pro-HB-EGF) thereby regulating cell proliferation. ADAM-10 is responsible for shedding the low-affinity immunoglobulin E receptor CD23 [40, 42]. Some ADAMTS also participate in ectodomain shedding, such as ADAMTS1 which sheds syndecan-4 besides enhancing the shedding of HB-EGF. The sheddase activity of ADAMs is thought to be regulated through the PKC and MAPK pathways [43].

Regulated intramembrane proteolysis (RIP) is a highly conserved signaling process by which membrane-bound signaling proteins are cleaved before being released into the cytoplasm. In most cases, RIP is preceded by ectodomain shedding. The membrane proteins Notch, CD44 and amyloid precursor protein, first undergo ADAM-dependent ectodomain cleavage followed by RIPping by γ-secretase [44].

4 Adamalysins in Cancer

There is substantial evidence to implicate the role of adamalysins in the aetiopathogenesis of various cancer types. The adamalysins exert both promoting and inhibitory effects on tumorigenesis. These dual roles probably reflect the complex interplay between the tumor, the surrounding stroma and the immune system (Figs. 2 and 3).

ADAMs and ADAMTs are primarily involved in processing the ligands of growth factor receptors thereby facilitating extracellular matrix remodeling to promote tumor progression and metastasis. Overexpression of several members of the ADAM family proteins has been reported in diverse malignancies. These include ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17, ADAM19, and ADAM28 [22]. ADAM-9 is upregulated in a number of cancers including renal, breast, and prostate cancer [45–47]. Upregulation of ADAM10 expression has been documented in diverse malignancies including cancer of the

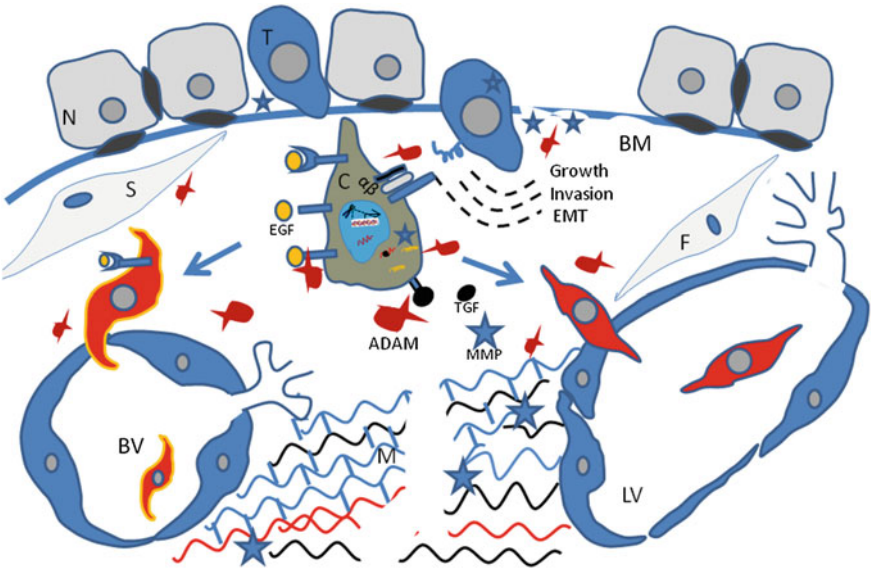

Fig. 2 The role of ADAM family of metalloproteinases in cancer. ADAM-mediated cancer cell proliferation and progression. ProADAMs are activated by furin or matrix metalloproteinases (MMPs). The sheddase activity of ADAMs cleaves and releases the cell surface ligands such as heparin-binding epidermal growth factor (HP-EGF), transforming growth factor TGFα and epidermal growth factor receptor (EGFR) to promote cancer. The interaction of ADAMs with integrins or syndecans on the cells enables cleavage of substrates, enhances invasion/metastasis or promotes proliferation signals. Many membrane-anchored molecules like chemokines, cytokines and their receptors, may interact with various ADAMs and promote cancer cell proliferation, angiogenesis, lymphangiogenesis and thus contribute to cancer cell progression. *N* nontransformed cell, *T* transformed cell, *S* stromal cell, *F* fibroblast cell, *BM* basement membrane, *BV* blood vessel, *LV* lymphatic vessel

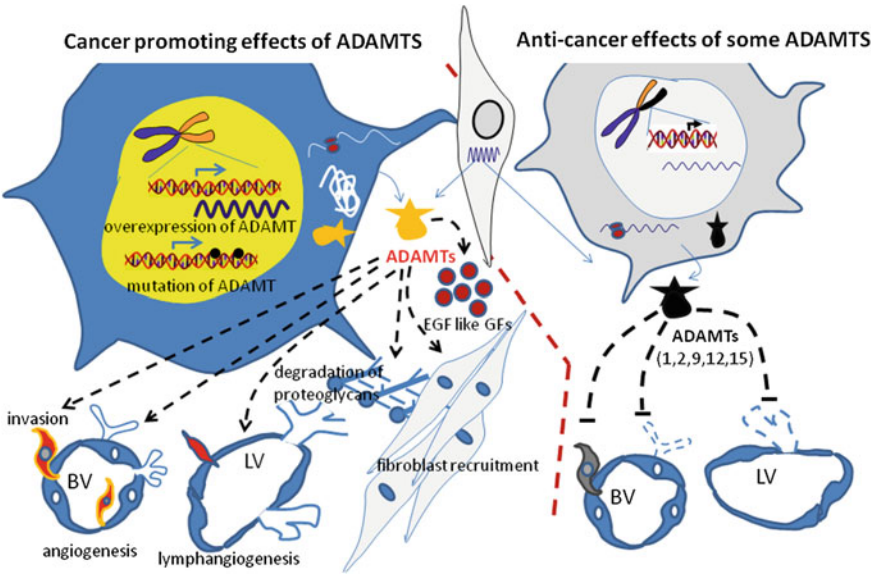

Fig. 3 The pro/anticancer effects mediated by different members of ADAMTS family of proteases. Many of the ADAMTSs family members are produced by stromal or cancer cells. Epigenetic modification of ADAMTS genes is mainly responsible for their expression. Their contribution to cancer progression is not fully understood. While most members exert cancer-promoting effects, other members (including ADAMT-1, 2, 9, 12 and 15) are involved directly or indirectly in inhibiting carcinogenesis. ADAMTs thus have either positive or negative influence on angiogenesis or lymphangiogenesis, or affect cancer-promoting signaling pathways through the degradation of extracellular components such as thrombospondin 1/2, nidogen 1/2, VEGF sequestration, activation of pro-angiogenic factors (HB-EGF, amphiregulin, IGFBP2), digest extracellular matrix components (proteoglycans), and recruitment of fibroblasts involved in cancer growth

stomach, oral cavity, ovary, uterus, colon, prostate as well as leukemia [22, 48]. ADAM15 has been reported to be overexpressed in breast, prostate, stomach, and lung cancer [22]. ADAM-17 expression is increased in breast cancer tissues with higher expression in advanced-grade compared to low-grade tumors. Patients displaying a higher expression of ADAM17 have a shorter overall survival than those with low expression [49]. The increased level of ADAM29 has been suggested to have a significant prognostic value for patients with CLL [50]. Likewise ADAMTS1, ADAMTS4, ADAMTS5, ADAMTS6, and ADAMTS14 are also upregulated in malignant tumors [22, 51].

Several adamalysins are also downregulated in malignant tumors due to loss by mutation or epigenetic silencing. Interestingly most of these belong to the ADAMTS family including ADAMTS1, ADAMTS3, ADAMTS5, ADAMTS8, ADAMTS9, ADAMTS10, ADAMTS15, and ADAMTS18. These proteins apparently function as tumor suppressors [51]. ADAMTS1 is poorly expressed in hepatocellular carcinoma (HCC) [52]. Expression profiling has shown downregulation

of ADAMTS8 gene expression in breast carcinoma, non-small cell lung cancer (NSCLC), and brain cancers [53–55]. Knockdown of ADAMTS-9 and ADAMTS-15 increases the tumorigenic potential of breast, gastric, and colon cancer cells [56, 57]. Clinical studies on patients with breast cancer revealed reduced ADAMTS15 expression that correlates with a higher probability of cancer development and increased mortality [58]. Notably, ADAMTS15 gene is not only epigenetically silenced, but also frequently mutated in colon and pancreatic carcinomas [57, 59, 60]. Studies on cancer cell lines indicated that ADAMTS18 gene is frequently epigenetically silenced that was subsequently confirmed in tissue samples from cancer patients [61].

5 Adamalysins and Cancer Hallmarks

Dysregulated functions and activities of adamalysins lead to acquisition of cancer hallmarks such as increased cell proliferation, apoptosis evasion, migration, invasion, and neovascularization. In addition, aberrant expression of these proteases also results in drug resistance.

5.1 Cell Proliferation and Apoptosis

Apoptosis evasion, a key hallmark capability of cancer, plays a critical role in promoting cell proliferation and cell survival. ADAM family of proteolytic enzymes regulates cell proliferation by cleaving growth factors or cell surface proteins. The EGF receptor ligands (heparin-binding EGF, amphiregulin, betacellulin, epiregulin) are synthesized as transmembrane proteins and all these require ectodomain shedding for their activation [62, 63].

ADAM9 has been reported to facilitate cell proliferation and cell survival by promoting the degradation of E-cadherin. Silencing of ADAM9 reduced ESCC cell proliferation and migration by inhibiting EGF receptor-AKT signaling [64]. ADAM9 has been reported to be involved in the proteolytic cleavage of the HB-EGF precursor and contribute to melanoma progression [65].

ADAM-10 has a broad substrate range and contains the six EGFR ligands, TNF, epireguline, HB-EGF and EGF. It also contributes to E-cadherin shedding [66, 67]. ADAM-10 promotes cell proliferation by modulating β-catenin signaling and regulating cyclin D1 levels [68]. ADAM-10 knockout (KO) embryos suffer from cell growth arrest and apoptosis associated with overexpression of full-length E-cadherin [67]. ADAM10 plays a role in regulated intramembrane proteolysis (RIP), which is part of the Notch/Delta signaling pathway involved in the cleavage of Notch membrane receptor and tumor promotion [69–71]. ADAM12 that promotes HB-EGF shedding was found to be overexpressed in colorectal, breast, liver, and stomach cancer [22]. ADAM-12 has been shown to increase stromal cell apoptosis and decrease tumor cell apoptosis.

ADAM17, a potent inducer of tumor growth and cell division promotes the cleavage of different substrates including TGF-β [72]. ADAM-17 cleavage of amphiregulin enhances proliferation of cancer cells. ADAM-17 cleaves and releases bioactive epigen that serves as a ligand of EGFR and promotes growth and tumorigenesis. ADAM17-catalyzed HB-EGF shedding was demonstrated to induce mitogenic ERK1/2 signaling [73].

The expression of membrane-anchored ADAM28m and secreted-type ADAM28s was found to be significantly higher in breast carcinomas compared to nonneoplastic breast tissues. Treatment of ADAM28-expressing MDA-MB231 breast carcinoma cells with insulin-like growth factor-I (IGF-I) increased cell proliferation, cleavage of IGF binding protein (IGFBP)-3, and IGF-I cell signaling. However, treatment with ADAM inhibitor, anti-ADAM28 antibody or siRNA silencing of ADAM-28, attenuated these processes as well as growth of xenografts in mice. These results suggest that ADAM28 enhances proliferation of breast cancer cells by releasing IGF-I released from the IGF-I/IGFBP-3 complex [74].

ADAMTS1 is reported to play a role in breast cancer development and progression. Induced overexpression of ADAMTS1 results in poor survival and accelerated tumor growth in mouse models of breast cancer. Overexpression of full-length ADAMTS-1 in CHO cells enhances tumor growth [75]. A recent study showed a link between overexpression of ADAMTS1 and tumor growth rate in a fibrosarcoma model.

5.2 Cell Migration, Invasion, and Metastasis

Excessive cell proliferation coupled with apoptosis evasion enables accumulation of mutations that facilitate cell migration, invasion, and metastasis which are the most important events in tumor progression responsible for cancer morbidity and mortality. Adamalysins that play an important role in sculpting the tumor microenvironment are invaluable biomarkers of disease progression and therapeutic outcome.

ADAM9 abrogates cell–cell contact and facilitates cellular migration by promoting the degradation of E-cadherin. ADAM9 was found to reduce cellular migration, invasion, and induction of the epithelial marker E-cadherin in pancreatic cancer [76]. The possible binding of DIS domain of ADAM9 to α6β4 and α2β1 integrins and subsequent proteolytic activity of ADAM9 enables cleavage of laminins and promotes invasion in cancer of the breast, pancreas, stomach, skin, liver, and lung [22]. Phosphorylation of the cytoplasmic domain of ADAM9 by PKCδ has been reported to lead to HB-EGF shedding. Abety et al. (2012) demonstrated increased proliferation and reduced apoptosis in coculture of melanoma cells and ADAM-9(−/−) fibroblasts, as well as in ADAM-9(−/−) mice injected melanoma cells. The data indicate that stromal expression of ADAM-9 influences melanoma development both in vitro and in vivo by targeting TIMP-1 and sTNFR1. Chang et al. (2015; 2016) provided evidence to indicate that ADAM9 is a potential candidate for targeted therapy of non-small cell lung carcinoma

(NSCLC). Downregulation of ADAM9 expression by RNA interference-mediated gene silencing in human A549 NSCLC cells inhibited cell proliferation, migration and invasion, and induced apoptosis. ADAM9 gene silencing also suppressed tumor growth in a mouse model of lung metastasis [77].

ADAM-10 contributes to E-cadherin shedding and subsequent release of soluble E-cadherin in the extracellular environment thereby promoting cell migration. Overexpression of ADAM10 was demonstrated to drive metastasis in various cancers. Knockout of ADAM10 by siRNA enhanced the antitumor activity of the VEGFR inhibitor sorafenib as evidenced by reduced proliferation, migration and invasion, and induction of apoptosis in hepatoma cells in vitro, and suppressed tumor growth in vivo. This was associated with inhibition of PI3K and AKT phosphorylation implying the involvement of ADAM10 in the activation of PI3/Akt signaling pathway [78].

ADAM17 is involved in the proteolysis of collagen IV of the ECM as well as the release of several integrins from the cell surface, suggesting that ADAM17 has a profound influence on the invasive activity of different cancer cells. Furthermore, ADAM17 as a primary upstream component for multiple EGFR pro-ligands may also activate MEK/ERK and PI3K/Akt pathways, which contribute to invasiveness. Primary blood blasts CD13+ CD33+ from patients with acute myeloid leukemia (AML) expressed ADAM17 transcript with higher surface expression in subtype M4 (myelomonocytic) and M5 (monocytic) specimens than in M0 and M1/M2 (early and granulocytic) specimens. Knockdown of CD13 revealed that it is required for downregulation of ADAM17. Interaction of ADAM17 with CD13 is believed to be essential for ADAM17 mediated cell growth, migration, and invasion [79].

ADAMTS-1 is involved in tumor progression and facilitates local invasion and lymph node metastasis. It is overexpressed in pancreatic cancer. Further, the overexpression of a catalytically inactive ADAMTS-1 impedes these events, which strongly suggests a prometastatic role for this metalloprotease mediated by its proteolytic activity. Elevated ADAMTS-1 expression has also been associated with high risk of bone and lung metastasis in breast cancer patients. It has been proposed that ADAMTS-1 could facilitate the spread of tumor cells through the degradation of versican, a predictor of metastatic relapse in human breast cancer. Similarly, ADAMTS5 promotes brain tumor invasion [22].

Overexpression of ADAMTS-1 promotes pulmonary metastasis of TA3 mammary carcinoma and Lewis lung carcinoma cells associated with angiogenesis, invasion, shedding of the transmembrane precursors of heparin-binding epidermal growth factor (EGF) and amphiregulin (AR), and activation of the EGF receptor and ErbB-2. However, the proteinase-dead mutant of ADAMTS-1 (ADAMTS-1E/Q) inhibits metastasis. Overexpression of the NH(2)- and COOH-terminal fragments generated by auto-proteolytic cleavage of ADAMTS-1 also inhibits pulmonary tumor metastasis as well as Erk1/2 kinase activation induced by soluble heparin-binding EGF and AR. These results suggest that the metalloproteinase activity of ADAMTS-1 is essential for its prometastatic activity [80].

5.3 Angiogenesis

Angiogenesis, the formation of new blood vessels from preexisting microvasculature plays a central role in tumor growth, invasion, and metastasis. The transformation from a microscopic prevascular lesion to a rapidly expanding highly vascularized referred to as an "*angiogenic switch*" occurs when the pro-angiogenic factors outweigh the effect of angiostatic molecules. Angiogenesis is a complex and tightly regulated process involving the activation of diverse intracellular signaling pathways, chiefly vascular endothelial growth factor (VEGF) signaling. Specific ADAMTSs play a pivotal role in regulating tumor angiogenesis. Multiple mechanisms have been proposed to explain the inhibition of angiogenesis by members of the ADAM and ADAMTS family.

Transfection of both the full-length ADAMTS1 and catalytic domain-deleted ADAMTS1 (delta ADAMTS1) inhibited endothelial cell proliferation, migration, and tube formation by inducing apoptosis. These effects were abolished following immunoprecipitation of the secreted protein from the medium. Both full ADAMTS1 and delta ADAMTS1 gene transfer into tumor-bearing mice significantly inhibited tumor growth as well as angiogenesis and induced apoptosis. These results demonstrate that the antiproliferative and antiangiogenic effects of ADAMTS1 are independent of its protease activity [81].

ADAM-15 expressed in smooth muscle cells, umbilical vein endothelial cells, and activated endothelial cells is documented to regulate angiogenesis [82]. In ADAM-15-deficient mice, angiogenesis was found to be inhibited [83]. The presence of Arg-Gly-Asp (RGD) sequence in the disintegrin domain that binds integrins has been suggested to play a role in regulating angiogenesis. The recombinant human disintegrin domain (rhdd) of ADAM15 was found to be a potent inhibitor of tumor formation and angiogenesis. ADAM-15 RDD decreases tumor growth associated with reduced vascularization of MDA-MB-231and B16F10 cells [84]. rhddADAM15 inhibited the proliferation of Bel-7402 hepatoma cells via the mitogen-activated protein kinase pathway and reduced the activation of Src. In addition, rhddADAM15 inhibited the proliferation, migration, and tube formation of vascular endothelial EA.hy926 cells in vitro and angiogenesis in zebrafish in vivo [85]. However, contrary to these reports, mice with sufficient or deficient ADAM-15 showed no difference in tumor vascularity between wild-type and mutant mice [83].

ADAMTS-1 and ADAMTS-8 have been established as antiangiogenic factors [86]. The thrombospondin motifs of ADAMTS-1/-8 interact directly with a membrane glycoprotein receptor CD36 of endothelial cells or directly through VEGF binding [87, 88]. The TSP-1 repeats in ADAMTS-1 are believed to contribute to its antiangiogenic activity by trapping VEGF [87, 89].

ADAMTS-2 plays a crucial role in processing fibrillar procollagen to mature collagen. Recombinant ADAMTS-2 reduces proliferation of endothelial cells, inhibits vasculature, and induces apoptosis associated with dephosphorylation of Erk1/2 and MLC. ADAMTS-2 also suppressed growth and vascularization of tumors induced in nude mice by HEK 293-EBNA cells. The antiangiogenic

properties of ADAMTS-2 were shown to be mediated by nucleolin, a receptor found in the nucleus and the cell membrane [90].

ADAMTS5 and 8 ADAMTS-8 have been demonstrated to exert antiangiogenic function in tumors. Overexpression of full-length ADAMTS5 inhibited B16 melanoma growth in mice by suppressing angiogenesis through the central TSR (TSR1) presumably by downregulating the pro-angiogenic factors VEGF, placental growth factor (PlGF), and platelet-derived endothelial growth factor (PD-EGF). This was associated with diminished cell proliferation and enhanced apoptosis. Catalytically active ADAMTS5 proteolytic fragment also suppressed angiogenesis in vitro [91]. ADAMTS8 was shown to block angiogenesis via the inhibition of FGF-induced vascularization and VEGF-induced angiogenesis. Mice with a single silenced Adamts9 allele showed spontaneous neovascularization, thus confirming the antiangiogenic activity of ADAMTS9 [92].

Decreased ADAMTS15 expression correlated with a worse prognosis in mammary carcinoma [58]. Kelwick et al. [93] investigated the effects of ADAMTS15 on MDA-MB-231 and MCF-7 breast cancer cells by stable expression of either a wild-type (wt) or metalloproteinase-inactive (E362A) protein. While neither form influenced cell proliferation or apoptosis, both forms suppressed cell migration on fibronectin or laminin matrices. The wt ADAMTS-15 but not the E362A mutant inhibited endothelial tubulogenesis and angiogenesis indicating that catalytic functionality is essential for antiangiogenic effects. Experimental metastasis assays in nude mice revealed decreased spread to the liver for both the wt and mutant forms, with enhanced lung colonization for cells expressing wt ADAMTS-15 implying tissue niche-dependent effects [93].

Unlike other ADAMTSs, which exert antiangiogenic effects, ADAMTS-4 has been shown to promote angiogenesis in Ewing's sarcoma. It is noteworthy that ADAMTS-4 undergoes an autocatalytic processing similar to that described for ADAMTS-1, which affects the balance between protumorigenic and antitumorigenic functions of this metalloprotease.

6 Adamalysins and Chemoresistance

Resistance to chemotherapeutic drugs, especially multidrug resistance is a major obstacle in cancer treatment. Several adamalysin family members are reported to induce drug resistance given their intricate involvement in proliferation, migration and invasion. Large-scale expression analysis of drug-resistant cells using high-density oligonucleotide microarrays revealed altered expression of 13 genes encoding MMPs, ADAMs, ADAMTSs, and TIMPs in drug-resistant sublines when compared with sensitive MCF-7 breast cancer cells [94]. Recent research is focused on developing strategies to overcome chemoresistance by silencing these molecules.

Increased expression of ADAM-17 that leads to growth factor shedding and growth factor receptor activation is postulated to induce drug resistance. In multidrug-resistant colorectal carcinoma (CRC), an inverse correlation was observed between the expression levels of ADAM-17 and miR-222. Transfection of HCT116/L-OHP and HCT-8/VCR cells with miR-22 mimics reduced ADAM-17 expression and sensitized these cells to apoptosis induced by anticancer drugs. Pharmacological inhibition of ADAM-17 in conjunction with chemotherapy may have greater therapeutic efficacy [95].

Wang et al. [96] reported that hypoxia-induced resistance to cisplatin treatment in Hep3B and HepG2 hepatocarcinoma cells is mediated by upregulation of ADAM-17 via HIF1-α. Furthermore, overexpression of ADAM17 inhibited cisplatin-induced apoptosis and enhanced the phosphorylation of epidermal growth factor receptor (EGFR) and Akt, suggesting that ADAM17 causes cisplatin resistance via the HIF1α/EGFR/PI3K/Akt pathway [96].

Cancer stem cells (CSCs) are known to mediate chemoresistance in patients with metastatic colorectal cancer. Analysis of the effect of ADAM-17 inhibition by siRNA knockdown or by TAPI-2 revealed a role for ADAM17 on cancer stem cell (CSC) phenotype and chemosensitivity to 5-fluorouracil (5-FU) in colorectal cancer via cleavage and release of soluble Jagged-1 and -2 and activation of Notch signaling [97].

ADAM10 is upregulated in several cancers and is associated with advanced tumor stage and grade. Small interfering RNA (siRNA) knockdown of ADAM10 decreased cell proliferation, migration, and invasion and increased cisplatin-induced apoptosis in bladder cancer cell lines indicating that ADAM10 is a candidate therapeutic target [98].

7 Epigenetic Modifications of Adamalysins

Epigenetic mechanisms including aberrant DNA methylation at CpG islands and histone modifications play a fundamental role in the development and progression of cancer. In addition, microRNAs also control target gene expression posttranscriptionally.

Significantly higher methylation of ADAM23 was observed in estrogen receptor (ER) positive breast cancers compared to ER negative cases [99]. The frequency of ADAMTS1 methylation was significantly higher in gastric cancer and positively correlated with depth of tumor invasion and tumor node, metastasis and stage [100]. Downregulation of ADAMTS9 in multiple myeloma was associated with promoter methylation [101]. ADAMTS8, a novel tumor suppressor that inhibits EGFR signaling and phosphorylation of MEK and ERK was frequently silenced by promoter methylation in nasopharyngeal, esophageal squamous cell, gastric, and colorectal carcinomas [102]. Using high-resolution melting (HRM) as a tool for analysis of promoter methylation, higher degree of methylation of ADAMTS9 and ADAMTS18 was observed in several cancers indicating gene silencing [61, 103].

ADAMTS12 promoter is epigenetically silenced in tumor cells by hypermethylation, whereas in the surrounding stromal cells, expression of this protease is higher presumably as a protective response [104]. Methylation of *ADAMTS19* gene promoter was linked to altered in vivo migration and invasion capabilities of CRC cells [105].

ADAM17 was identified as a direct target of miR-145, a tumor suppressor miR that is significantly downregulated in glioma cells. Ectopic expression of miR-145 decreased in vitro proliferation, migration, and invasion of glioma cells as well as the expression of ADAM17 and EGFR [106]. High expression of ADAM9 in bladder cancer was found to correlate inversely with miR-126 and indicated poor prognosis. While knockdown of ADAM9 ameliorated invasiveness of bladder cancer cells, restoration of miR-126 levels suppressed invasion [107].

8 Therapeutic Potential

Adamalysins have emerged as potential molecular targets for cancer therapeutics. Synthetic molecules targeting ADAMs such as KB-R7785, a GM6001-derived hydroxamate have been developed [108]. KB-R7785 is believed to inhibit ADAM17 and block the synthesis of TNF-α, inhibit ADAM10 processing of CD44 and consequent cell migration. Drugs targeting the cysteine-rich region of ADAM-12 have been suggested to inhibit invasion and metastasis [109].

ADAM-17 has been implicated in the development and progression of breast cancer and is an independent predictor of prognosis [49]. Several strategies have been developed to target ADAM-17 including selective low-molecular-weight inhibitors [49, 110, 111]. An inhibitory humanized monoclonal antibody D1(A12), that binds to both the catalytic domain and the disintegrin/cysteine-rich domain of ADAM-17, was found to inhibit the proteolysis of several substrates as well as tumor growth in an animal model of ovarian cancer and in triple-negative breast cancer cell lines [112–114].

The ADAM10 inhibitor GI254023X was shown to suppress proliferation and induce apoptosis of H929 multiple myeloma cells and acute T-lymphoblastic leukemia Jurkat cells by preventing Notch1 activation [115, 116].

Overexpression of the ErbB family of receptors in human tumors is associated with poor prognosis and resistance to therapy. An attractive approach to prevent ErbB-mediated tumor growth and survival is to block sheddase activity. The selective potent, orally bioavailable small-molecule ADAM inhibitor, INCB3619, blocks the shedding of ErbB ligands including heregulin and reduces tumor cell survival. INCB3619 also inhibits gefitinib-resistant HER3 signaling and augments gefitinib blockade of EGFR signaling. Combining INCB3619 with a lapatinib-like dual inhibitor of EGFR and HER-2/neu kinases inhibited growth of MCF-7 and HER-2/neu-transfected MCF-7 human breast cancer cells. The second-generation sheddase inhibitor INCB7839 when combined with lapatinib suppressed the growth of HER-2/neu-positive BT474-SC1 human breast cancer xenografts in vivo.

These findings underscore the scope for ADAM inhibition in pharmacological intervention, either alone or in combination with other drugs [110, 117, 118].

Wiernik et al. [119] tested whether combination treatment through CD16 signaling and targeting CD33 (CD16 × 33 bispecific killer cell engager (BiKE) plus ADAM17 inhibitor could activate NK cells against acute myelogenous leukemia (AML). They found that the combination inhibited CD16 shedding in NK cells, and enhanced NK cell activation highlighting its potential for patients with relapsed AML or for adjuvant antileukemic therapy posttransplantation [119].

9 Conclusion

Adamalysins are relatively new players in cancer biology. Recent evidences suggest their role in cancer cell growth and proliferation [62, 63]; invasion and metastasis [22]; angiogenesis and cancer cell stemness [120]. These enzymes release membrane-bound growth factors, receptors, cytokines, and other molecules by shedding and RIPping, resulting in the activation of key signaling pathways. They also act on integrins or syndecans and influence cell–cell adhesion. These enzymes cleave ECM molecules and facilitate metastasis of cancer cells to metastasize to distant organs. The adamalysis have dual roles, while some members promote tumor development and progression, several others function as tumor suppressors. Although understanding the complex roles of adamalysins in cancer is technically challenging, the emerging knowledge and exciting new discoveries will provide deeper mechanistic insights into the tumor microenvironment besides enabling drug development.

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