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ADAM proteases: Emerging role and targeting of the non-catalytic domains

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Abstract

ADAM proteases are multi domain transmembrane metalloproteases that cleave a range of cell surface proteins and activate signaling pathways implicated in tumor progression, including those mediated by Notch, EFGR, and the Eph receptors. Consequently, they have emerged as key therapeutic targets in the efforts to inhibit tumor initiation and progression. To that end, two main approaches have been taken to develop ADAM antagonists: (i) small molecule inhibitors, and (ii) monoclonal antibodies. In this mini-review we describe the distinct features of ADAM proteases, particularly of ADAM10 and ADAM17, their domain organization, conformational rearrangements, regulation, as well as their emerging importance as therapeutic targets in cancer. Further, we highlight an anti-ADAM10 monoclonal antibody that we have recently developed, which has shown significant promise in inhibiting Notch signaling and deterring growth of solid tumors in pre-clinical settings.

Keywords

ADAM10; ADAM17; Integrins; Therapeutic antibody; Notch signaling

1. Background

Proteolytic processing and subsequent release of membrane-bound proteins is a post-translational mechanism that governs the biological activity of the cleaved molecules [1–3]. This process, referred to as ‘protein ectodomain shedding’, is mediated by membrane-anchored ADAM metalloproteases [4–9], which shed a wide range of membrane-attached proteins implicated in growth factor signaling, cell migration and cell-adhesion [10]. In this mini-review, we will discuss the salient features of this unique class of proteases, the regulation of their activity via conformational rearrangements in their ectodomains and their potential as therapeutic targets during cancer progression. We will also discuss a novel anti-ADAM10 monoclonal antibody that has made significant headway towards treatment of solid tumors in pre-clinical setting.

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CRediT authorship contribution statement

Nayanendu Saha: Conceptualization, Writing - review & editing, Writing - original draft. **Dorothea Robev:** Software, Writing - review & editing. **Juha P. Himanen:** Writing - review & editing, Formal analysis, Funding acquisition. **Dimitar B. Nikolov:** Formal analysis, Writing -review & editing, Funding acquisition.

Conflicts of interest

The authors declare that they have no competing interest.

ADAMs contain several conserved domains: an N-terminal signal sequence followed by a pro-domain, a metalloprotease domain (MP), a disintegrin domain (D), a cysteine-rich domain (C), an EGF-like domain (except ADAM10 and ADAM17), a transmembrane domain and a cytoplasmic domain [11]. The signal sequence guides the inactive ADAM proenzymes into the secretory pathway [12,13]. The prodomain acts as a chaperone during *trans*-Golgi transport and also inhibits premature MP domain activation [14,15]. The MP domain confers zinc-dependent proteolytic activity and contains a consensus HEXGHXXGXXHD motif that coordinates the zinc atom [16]. Despite being well studied, the substrate-specificities of the ADAMs are poorly understood [17]. They seem to be dictated, at least in part, by the ADAM D and C domains, which mediate protein-protein, and specifically substrate-enzyme, interactions. The D domains of ADAMs are also implicated in integrin-mediated cell-adhesion. In the case of ADAM15, a consensus RGD sequence in the D domain [17] is needed for interaction with the α5β1 and α5β3 integrins, while the importance of the C domain for proper substrate cleavage has been documented for ADAM13 and ADAM17 [8,18]. Swapping of the C domain of ADAM13 with that of ADAM10 leads to loss of function and failure to induce hyperplasia in *Xenopus laevis* embryos [19], deterring major developmental events. Likewise, a chimeric construct of ADAM17, with its D + C domains replaced by those of ADAM10, fails to shed interleukin (IL)-1R–II from the cell surface of the fibroblast cell line EC-2 [18].

2. Conformational regulation of ADAMs and intracellular signaling

Cleavage by ADAM proteases is regulated at many levels [8,11]. It is known that ADAM-mediated cleavage is essential for G-protein-coupled [20,21] or stress-induced [22] EGF receptor transactivation, and it is modulated by intracellular signaling in response to growth factors, phorbol esters, and changes in tyrosine kinase activity [8]. Interestingly, while ADAM family members harbor cytoplasmic protein-docking motifs [8], cytoplasmically-truncated ADAM10 and ADAM17 are fully functional [23], suggesting only a minor role for the cytoplasmic domains in controlling downstream signaling.

ADAM17 is suggested to be regulated by cysteine oxidation that modulates the conformation of its extracellular domain [24,25]. Furthermore, the notion that the ADAM activity is regulated by the presence of two distinct conformations “active” or “open” and “latent” or “closed” (Fig. 1) is supported by the crystal structures of related snake venom metalloproteinases. Indeed, these structures reveal two radically different conformations resulting from alternative disulfide-bonding arrangements of the D + C region [26,27].

Like other proteins undergoing protein disulfide isomerase (PDI)-mediated thiol disulfide exchange, ADAM17 contains a conserved CxxCC motif, and mild reducing or oxidizing conditions alter its enzymatic activity [24]. Interestingly, facilitating disulfide exchange via a thiol isomerase was reported to favor the inactive ADAM17 conformation, while inhibiting the isomerase enhances the ADAM17 activity [25]. Other studies suggest that reactive oxygen species (ROS) also regulate the activity of ADAM proteases through similar conformational changes in their ectodomains [28–33]. An important source of ROS at cell membranes is a family of NADPH oxidases (NOXs) that get stimulated by activated receptor tyrosine kinases (RTKs), including EGF, PDGF and insulin receptors [34]. It has been

elegantly demonstrated that an elevated level of ROS due to oxidative stress, common in tumors [35], stimulates ADAM-mediated shedding [30], cross-activation of RTKs [29], and contributes to tumor resistance to therapy [36,37]. Furthermore, an elevated level of ROS inhibits protein tyrosine phosphatases (PTPs) by reversible oxidation of their conserved active-site cysteine residue [38], which in turn increases RTK activity. The oxidation-dependent changes in the conformations of ADAM10 and ADAM17 suggest that RTK-stimulated ROS production could directly activate ADAMs. This implies a mechanism where conformational changes in the ADAM ectodomains mediate ADAM-RTK cross activation.

3. Oncogenic substrates of ADAM10 and ADAM17

ADAM10 and ADAM17 shed various cell-surface proteins and activate signaling pathways important in oncogenic development. Prominent oncogenic substrates include receptors/ligands of the erbB, Eph and Notch families, cytokines, cadherins, FAS ligand, Slit and L-selectin [39]. ErbB ligands are initially cell-surface tethered and their proteolytic release by ADAM10 and ADAM17 [40] is a key regulatory switch to trigger downstream autocrine signaling that drives tumor progression [39,41,42]. The erbBs display de-regulated signaling in many human cancers due to overexpression and/or mutations, including in some of the most intractable and common tumors, with EGFR and HER2 prominent in breast, ovarian and colon cancer [43]. In addition, elevated ADAM17-mediated cleavage of erbB2/erbB4 in tumors is associated with constitutive receptor activity and poor prognosis and undermines receptor-targeted therapies [44,45].

Eph receptors and their membrane-bound ephrin ligands control cell migration and positioning during normal and oncogenic development [46,47]. We documented that ADAM10 binds to Eph/ephrin receptor/ligand complexes and cleaves the ephrin ligands *in trans*. This disrupts the Eph/ephrin molecular tethers between cells, causing de-adhesion and retraction [48], as well as termination of Eph signaling. This function of ADAM10 was found to be dependent on the Eph kinase activity [48]. ADAM10, thereby, acts as a switch between cell-cell adhesion and segregation in response to the Eph phosphorylation status. This is important in the context of Eph-dependent oncogenesis, where aberrant Eph expression can contribute to tumorigenesis [46,47].

Notch receptors (Notch1–4) are single pass transmembrane proteins that undergo regulated intramembrane proteolysis by ADAM10 and γ-secretase. The proteolytic steps are triggered by Notch binding to DLL/Jagged cell-surface-attached ligands. This initiates ADAM10-mediated shedding of the ligand [49] and receptor ectodomains [50]. Subsequently, release of the Notch intracellular domain (NICD) by γ-secretase activates transcription of target genes, a pathway that is conserved in all phyla [51]. Notch signaling controls cell fate and differentiation, proliferation, epithelial-mesenchymal transition (EMT) and cell survival, while de-regulated Notch signaling promotes progression of both hematological and solid cancers [52]. Notch activity is particularly associated with a ‘stem-like’ phenotype in a subpopulation of tumor cells termed as cancer stem cells (CSCs) or tumor initiating cells (TICs). The CSCs not only initiate and sustain tumor growth, but also promote metastasis, chemoresistance, and angiogenesis [53,54]. This is especially evident in colorectal cancer

(CRC) [55], where endothelial-expressed Notch ligands promote paracrine signaling and stem cell phenotype in tumor cells [56]. Accordingly, inhibition of Notch depletes CSCs and inhibits metastasis [57–60]. Notch signaling and CSCs are also associated with drug resistance, and inhibition of Notch signaling is widely reported to increase sensitivity to both chemo- and targeted therapies [61–65]. Importantly, it has been demonstrated that ADAM10 gene deletion is embryonic lethal in mice and the embryonic defects match the defects observed in Notch deficient animals. This suggests that the abnormalities associated with the absence of ADAM10 arise due to a failure to activate Notch signaling [57].

4. ADAM proteases as therapeutic targets

Since the ADAM proteases are involved in ectodomain shedding in a wide range of disease-related pathways, they are considered to be attractive targets for drug development. Studies with hepatocellular carcinoma cell lines highlight the importance of ADAM10 as anti-tumor therapeutic target, showing that downregulation of ADAM10 using siRNA markedly suppresses cell proliferation, cell migration and cell invasion in vitro, as well as tumor growth in vivo [66]. In addition, ADAM10 is over-expressed in oral squamous cell carcinoma (OSCC), where it contributes to OSCC invasion by interacting with integrin αvβ6 [67]. Likewise, ADAM17 is over-expressed in esophageal squamous cell carcinoma [68] and plays a significant role in the progression of glioma by upregulating the EGFR-P13K-AKT pathway [69]. Furthermore, microarray analysis revealed that ADAM17 is over-expressed on the surface of several types of cancer cells, including ovarian, breast and prostate [70]. In ovarian cancer, ADAM10 and ADAM17 cleave the calcium independent cell adhesion molecule Nectin-4 [71]. The cleaved ectodomain of Nectin-4 facilitates formation of spheroids that eventually invade the mesothelial layer to establish tumors at secondary sites [72].

ADAM9, another member of the family, is overexpressed in several cancers, including ovarian, clear cell carcinoma [73], lung adenocarcinoma [74], glioma, gastric, breast, and liver cancers [75]. In liver cancer, ADAM9 was shown to evade tumor immunity by cleaving the MHC class 1 polypeptide–related sequence A. Interestingly, it was established that ADAM9 interacts with β1 integrins (but does not cleave them) promoting melanoma, thus highlighting the importance of nonproteolytic ADAM functions in cancer progression [76]. Likewise, the cysteine-rich domain of ADAM12 is necessary for tumor cell adhesion [77]. The expression levels of ADAM12 were found to be significantly elevated in small cell lung cancer patients [78]. Amongst other cancer types, ADAM12 is responsible for cavernous sinus invasion in pituitary adenomas [79]. Owing to the low expression levels of ADAM12 in normal tissues, as compared to its high expression levels in several cancers (including both mRNA and protein), ADAM12 can be a useful biomarker [80]. ADAM15 mRNA and protein levels are increased in prostate cancer, where it triggers angiogenesis and angioinvasion of tumor cells causing unrestrained tumor growth [81]. In ovarian cancer, ADAM15 disrupts the binding of αvβ3 integrin to its extracellular matrix ligand vitronectin, thereby regulating tumor migration and invasion. Mechanistically, the RGD-binding motif of ADAM15 interacts with αvβ3 integrin and loosens the adhesion of tumor cells to the underlying matrix [82]. ADAM8 promotes growth and progression of triple negative breast cancer (TNBC) that lacks estrogen, progesterone and HER-2 receptor gene expression. In

pancreatic cancer cells, ADAM8 enhances the binding of β1 integrin to endothelial cells. Thus, it promotes tumor cell migration and invasion by augmenting the ERK1/2 signaling pathway [83,84]. Recently, ADAM23, was found to be involved in breast cancer progression and dissemination of circulating tumor cells [85]. ADAM28 promotes lung metastasis by cleaving and inactivating the von Willebrand factor, VWF. VWF is a proapoptotic protein and its inactivation prolongs cancer cell survival and metastasis [86,87]. In TNBC, ADAM33 has been reported to be downregulated by DNA hypermethylation, suggesting that this protease could be potentially used as a biomarker for TNBC and other basal-like breast cancers [88].

Interestingly, some of the catalytically 'dead' human ADAM proteases, such as ADAM11 and ADAM29, were shown to promote integrin α4-dependent adhesion of immune cells. The studies revealed that the disintegrin domains of these ADAM proteases mediate cell-cell adhesions via interactions with the integrins α4β1 and α4β7 [89].

The ADAMTS (A Disintegrin and Metalloprotease domains with thrombospondin motifs) are secreted, multi-domain endopeptidases, and close relatives of the ADAMs [90]. They have been implicated in both oncogenic and tumor-suppressive signaling events. Specifically, they regulate the inflammatory microenvironment of tumors. For instance, ADAMTS4 causes macrophage infiltration in the environs of colorectal cancer [91]. Elevated expression of ADAMTS 1, 8, 9 and 18 were also observed in pancreatic cancer patient samples [92]. Table 1 documents the various ADAM proteases implicated in major cancer types.

Owing to the importance and therapeutic potential of ADAM proteases in cancer progression, attempts have been made to develop ADAM inhibitors to impede cancer growth. The two major approaches taken so far are discussed in the following paragraphs.

5. Small molecule ADAM inhibitors

Most of the small molecule ADAM inhibitors described to date are hydroxamate-based and are either specific for ADAM17 or selective for both ADAM10 and ADAM17. These inhibitors chelate the zinc from the active site of the proteases, thereby rendering them inactive. Amongst the dual inhibitors for ADAM10 and ADAM17, INCB3619 was one of the first to be investigated for anti-cancer activity [42,93,94]. In in vitro assays, the compound reduces the shedding of an array of EGFR ligands, which increases the susceptibility of non-small cell lung cancer cells to the EGFR tyrosine kinase inhibitor gefitinib [42]. Unlike the first-generation inhibitors, INCB3619 is remarkably free of musculoskeletal toxicity in animal models. INCB3619 also inhibits non-small cell lung, breast, head and neck carcinomas in animal models [42,93,94]. Of late, another structurally related inhibitor, INCB7839, underwent early clinical trials in HER-2 positive breast cancer patients with no evidence of musculoskeletal side effects or bone marrow toxicity. This particular inhibitor decreases the shedding of EGFR and HER-2 ligands [95]. Besides the INC class of dual inhibitors, the PF-series, including PF-5480090, was found to be specific for ADAM17 and does not inhibit ADAM10 [96]. PF-5480090 inhibits proliferation of a wide panel of breast cancer cell lines independent of their molecular subtype [97].

Specifically, in the case of TNBC where ADAM17 is expressed at higher level than in non-TNBC, PF-5480900 significantly decreases (i) the release of the EGFR ligand TGF alpha and (ii) the levels of phosphorylated EGFR, leading to proliferation inhibition of TNBC [97]. In addition to small molecule compounds, it has been shown that small hairpin RNAs, specific to ADAM17, significantly inhibit cell proliferation, invasion and tumor growth of non-small cell lung cancer in vitro [98].

Little progress has been made with regard to ADAM10-specific small molecule inhibitors. One such molecule, GI254023X, blocks migration and invasion of breast cancer cell lines with hardly any effect on proliferation. In cell-based assays, GI254023X impedes shedding of interleukin receptors and chemokine ligands [99–101]. Amongst the other ADAM proteases, a six-amino acid cyclic peptide, designated as BK-1361, inhibits the activation of ADAM8 and decreases tumor burden and metastasis of implanted pancreatic tumor cells. Specifically, it downregulates the ERK1/2 signaling pathway [83,84]. No small molecule inhibitors have been reported for ADAM28, though in animal models of lung cancer, ADAM28-targeting siRNA inhibits metastasis [86]. ADAM15 is known to be functionally associated with the progression of bladder cancer. Indeed, knock-down of ADAM15 in a human xenograft model of bladder cancer causes 45% tumor regression compared to controls [102]. A novel ADAM15-specific sulfonamide inhibitor, designed by structural modeling of the catalytic domain, also decreases tumor growth in animal model of bladder cancer [102].

6. Monoclonal antibodies targeting the ADAMs

The second approach for therapeutic intervention entails the generation of monoclonal antibodies (mAbs) targeting the ADAMs. Compared to small molecule inhibitors, mAbs can be highly target-specific, thereby reducing the risk of toxic side effects. Of late, a mAb that binds to both the catalytic (MP) and disintegrin-cysteine rich domains of ADAM17 has been shown to have significant therapeutic potential [103,104]. The mAb D1 (A12) inhibits tumor growth in an animal model of ovarian cancer and blocks the shedding of ADAM17 substrates, including TNF-alpha, TGF-alpha, HG-EGF and amphiregulin [103–105]. In a mouse model, the mAb is highly stable in circulation and retains its ability to bind ADAM17 over a prolonged period of time [103]. Another anti-ADAM17 mAb, MEDI3622, inhibits cancer progression in several different pre-clinical models [106]. Mutagenesis and molecular docking studies revealed that this mAb recognizes a unique surface loop present in the MP domain of ADAM17 [107]. In cell–based studies, MEDI3622 blocks the release of known ADAM17 substrates, including amphiregulin, epiregulin and heregulin [106].

In another study, a mAb (A300E) recognizing the membrane-proximal cysteine-rich region of human ADAM17 was reported. It was further modified to generate a recombinant scFv (single-chain variable fragment) containing the variable regions of the heavy and light chains. Using this scFv, a bispecific antibody was constructed that recognizes ADAM17 on tumor cells and CD3 on T-cells. In the presence of primary peripheral blood mononuclear cells, this bispecific antibody specifically kills prostate tumor cells expressing ADAM17 on the cell surface [108]. A300E, when coupled to doxorubicin or Pseudomonas exotoxin A, is able to kill the MDA-MB-231 TNBC cell line in an ADAM17-dependent manner [109].

Amongst the other ADAM proteases, a monoclonal antibody raised against the catalytic site of ADAM9 suppresses cancer cell proliferation and exhibits anti-tumor activity in a gastric cancer xenograft model [110]. ADAM8 was found to promote breast cancer development and brain metastasis in mouse models, and a commercial antibody to ADAM8 blocks transendothelial migration of breast cancer cells in in vitro assays [111].

7. Mechanism of action and therapeutic potential of the 8C7 anti-ADAM10 mAb

Though ADAM10 is implicated in several different cancers, including breast, pancreatic, melanoma and bladder carcinoma, no ADAM10 specific mAb has been developed so far for therapeutic intervention. Furthermore, Notch is the most prominent tumor-related ADAM10 target, and previous attempts to inhibit tumorigenic Notch signaling by blocking the γ-secretase activity or disrupting the formation of Notch-ligand complexes caused intestinal toxicity [112]. Nevertheless, Notch-inhibitory mAbs that do not exhibit toxicity have proved to be promising cancer therapeutic leads [113]. We, therefore, generated a highly specific anti-ADAM10 mAb (8C7) for the potential treatment of solid tumors. This antibody binds to the cysteine-rich domain of ADAM10 and targets not only the rapidly dividing cells at the invasive font of the tumors, but also the undifferentiated tumor stem cells. We documented that 8C7 mAb primarily acts via inhibiting Notch signaling in tumors. It also effectively prevents tumor relapse after chemotherapy in pre-clinical models without exhibiting any dose-limiting toxicity in animals [114].

Our in vitro and in vivo data indicate that 8C7 recognizes an active conformation of ADAM10 prevalent in tumors, as opposed to the inactive/latent ADAM10 ectodomain conformation present in normal tissues. It should be noted that currently there is no structural information regarding the open, activated ADAM10 conformation, and only the structure of the closed, autoinhibited conformation has been reported, where access to the proteinase active site is blocked [115]. The transition to the active ADAM conformation, as discussed in the previous sections of this review, is dependent on disulfide isomerization and oxidative conditions of the tumor microenvironment [29]. Consequently, in tumor cells, oxidizing conditions promote binding of the 8C7 mAb to ADAM10, while reducing conditions inhibit binding.

The crystal structure of 8C7 bound to the ADAM10 D + C domain [114] revealed the ADAM10 epitope recognized by 8C7. This ADAM10 region is stabilized by two intra-molecular disulfide bonds, C594–C639 and C632–C645, which are part of a CxxCC motif, a consensus PDI target sequence (Fig. 2). Mutating the CxxCC motif to AxxAC abrogates binding of 8C7 to ADAM10.

To understand how the 8C7 mAb inhibits ADAM10 function, the ADAM10–8C7 complex structure was compared to the structures of full-length snake venom metalloproteases VAP1 and Atragin, with similar MP + D + C domain architectures [26,27]. This comparison (Fig. 3A) shows that the MP domain, residing within the concave side of the D + C region, occupies the same space where the 8C7 mAb binds. It is, therefore, likely that 8C7 displaces the ADAM10 MP domain upon binding, thus inhibiting substrate cleavage on the cell

surface. The recent crystal structure of the complete ADAM10 ectodomain corroborates this hypothesis (Fig. 3B). In that structure, ADAM10 adopts a closed conformation, with the MP and the D + C domains positioned similarly to what was observed in the Atragin structure [115].

7.1. Future prospects

Targeting the MP domains of ADAM proteases, particularly of ADAM10 and ADAM17, for the treatment of various diseases, has been unsuccessful so far mostly because the proteinase active site is highly conserved, resulting in toxicity due to the interactions of drugs with other matrix metalloproteinases. Recently, it has been shown that the non-catalytic ADAM10 and ADAM17 domains, specifically the D and C domains, confer substrate-specificities, and it is expected that future efforts will concentrate on targeting these domains for successful therapeutic intervention. This endeavor could also be extrapolated to other ADAM family members, which differ from ADAM10 and ADAM17 in that they contain an additional EGF domain. For instance, ADAM9, ADAM12, ADAM13 and ADAM15 [19,75,77,82] bind to a variety of integrins via their non-catalytic domains promoting adhesion of tumor cells. Likewise, the ancillary disintegrin, cysteine-rich and thrombospondin domains of ADAMTS dictate substrate-specificity, and thus regulate the diverse functions of these secreted proteases [90]. Structural studies have already shown specific molecular regions and surfaces outside of the ADAM MP domain that mediate ADAM-substrate interactions, providing attractive targets for novel small-molecule and antibody therapeutics. Furthermore, a large and ever-growing amount of DNA sequencing data from healthy individuals and patients provides a great opportunity to not only understand better the molecular mechanisms of ADAM-mediated signaling, but to also identify and/or validate therapeutic target regions on the molecular surface of the ADAM family members. One such source is the sequencing data from the Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center [disseminated through cBioportal, http://www.cbioportal.org/ [116,117]]. The use of genomic and proteomic data should also provide in the future the basis for “personalized/precision medicine” as well as novel “targeted therapeutics” developments [118,119].

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Abbreviations:

MP	Metalloprotease domain
D	Disintegrin domain
C	Cysteine rich domain
VEGF	Vascular endothelial growth factor

OSCC	Oral squamous cell carcinoma
ScFv	Single chain variable fragment
PDI	Protein disulfide isomerase
TNBC	Triple negative breast cancer
MMP	Matrix metalloproteinase

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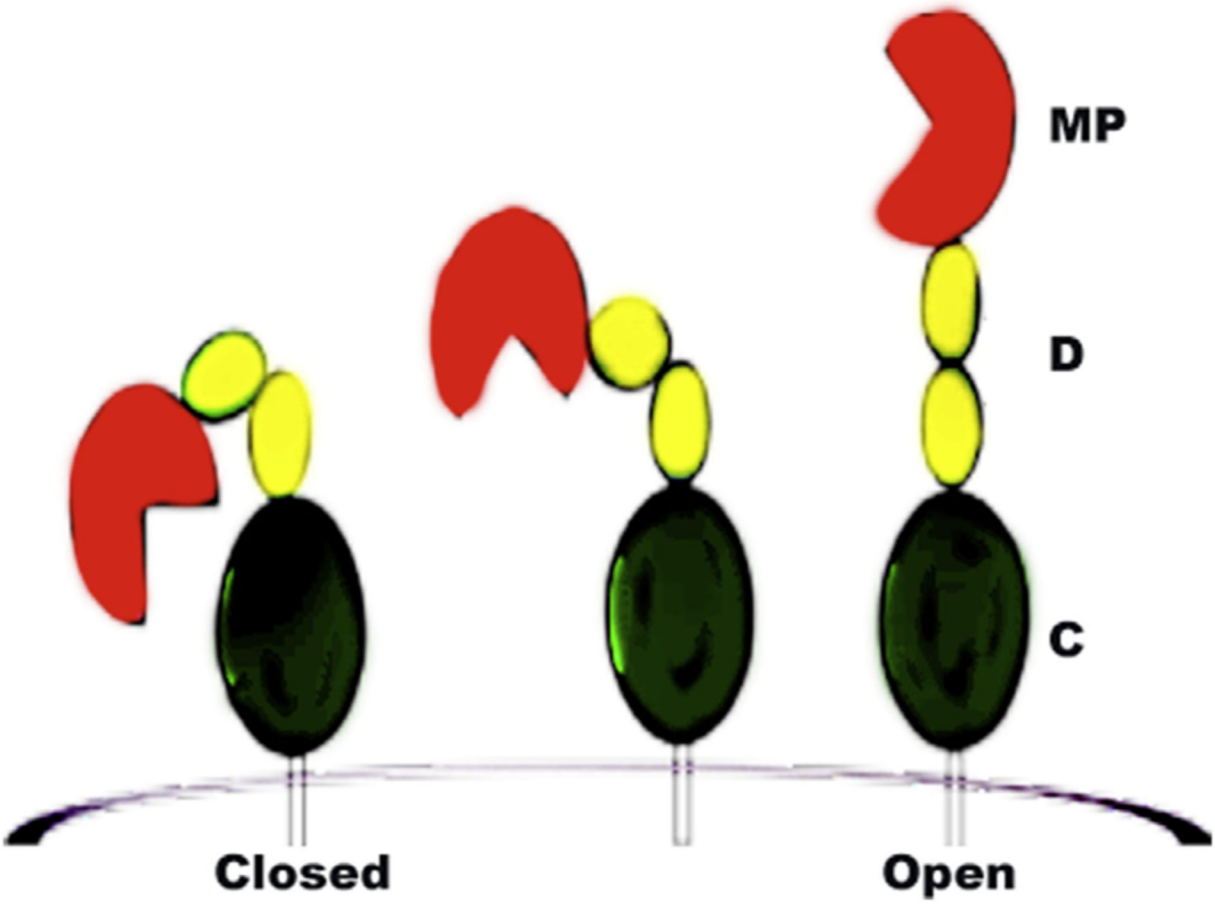

Fig. 1.

ADAM domains and proposed conformations. The ‘closed’ and ‘open’ ectodomain conformations of ADAM10 and ADAM17 are proposed to reflect alternate disulfide bonding arrangements of the D + C region. Both ADAM10 and ADAM17 contain a CxxCC motif, a consensus site for PDI-mediated disulphide exchange. Thus, their ectodomain conformations are influenced by redox effects.

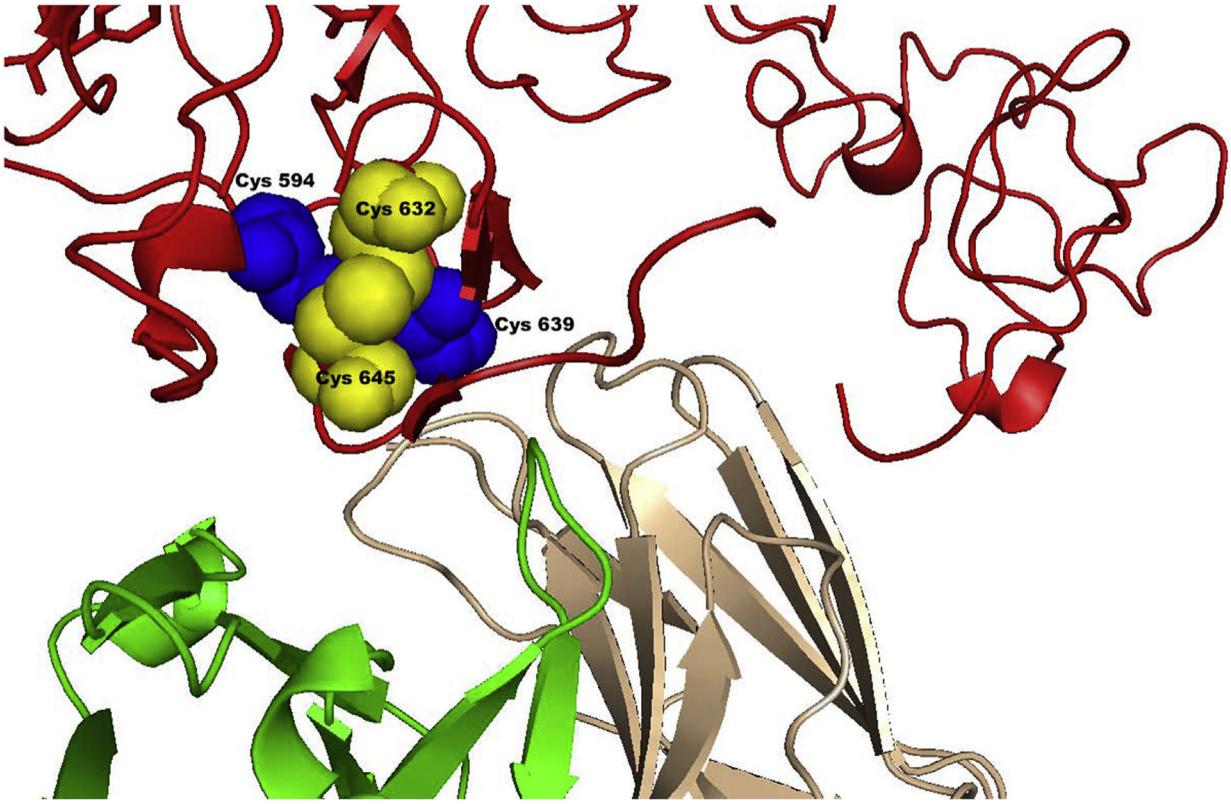

Fig. 2.

A close up-view of the disulfide-bonding pattern in the mAb (8C7)-bound ADAM10. The disulfide forming cysteines are shown as blue and yellow spheres. The ADAM10 D and C domains are represented in red. The heavy chain of the 8C7 mAb is in green and the light chain in wheat [114].

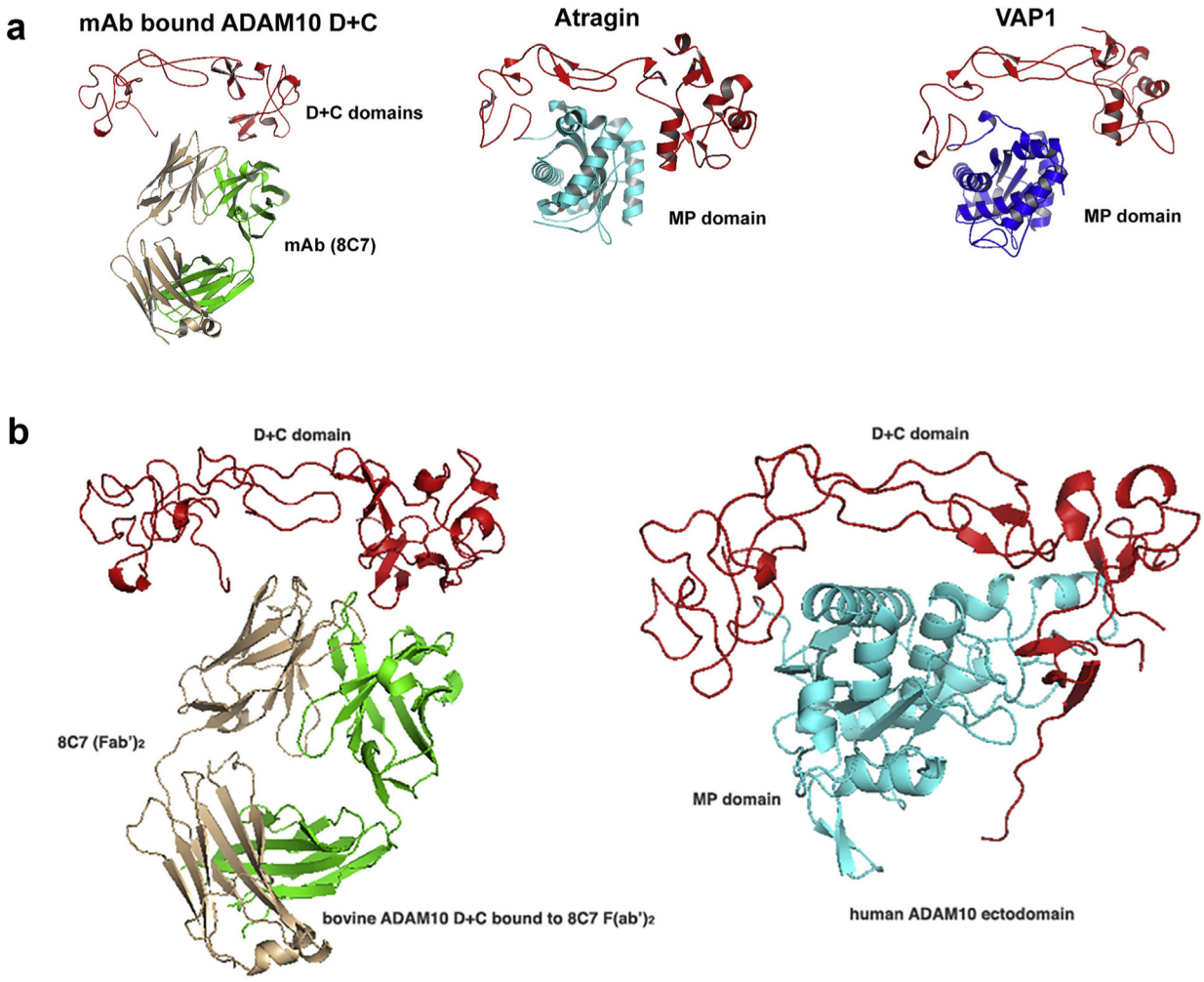

Fig. 3.

Comparison of the mAb 8C7-bound ADAM10 D + C structure with the structures of the related snake venom metalloproteinases Atragin and VAP1 (**3A**), as well as the structure of the complete ADAM10 ectodomain (**3B**) [115].

Table 1.

ADAM proteases and associated major cancer types.

ADAM/ADAMTS	Cancer types	References
ADAM8	Triple negative breast cancer, Pancreatic	[83,84]
ADAM9	Ovarian, lung, glioma, breast, gastric, liver	[73–76]
ADAM12	Small cell lung, pituitary adenomas	[77–80]
ADAM15	Ovarian	[81,82]
ADAM10	Colon, hepatocellular, oral squamous cell carcinoma	[66,67,114]
ADAM17	Esophageal, glioma, ovarian, breast, prostate	[68–71]
ADAM23	Breast	[85]
ADAM28	Lung	[86,87]
ADAM33	Breast	[88]
ADAMTS4	Colorectal	[91]
ADAMTS 1, 8, 9, 18	Pancreatic	[92]