


## STATE-OF-THE-ART REVIEW

# New insights into the function and pathophysiology of the ectodomain sheddase A Disintegrin And Metalloproteinase 10 (ADAM10)

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The ‘A Disintegrin And Metalloproteinase 10’ (ADAM10) has gained considerable attention due to its discovery as an ‘ $\alpha$ -secretase’ involved in the nonamyloidogenic processing of the amyloid precursor protein, thereby possibly preventing the excessive generation of the amyloid beta peptide, which is associated with the pathogenesis of Alzheimer’s disease. ADAM10 was found to exert many additional functions, cleaving about 100 different membrane proteins. ADAM10 is involved in many pathophysiological conditions, ranging from cancer and autoimmune disorders to neurodegeneration and inflammation. ADAM10 cleaves its substrates close to the plasma membrane, a process referred to as ectodomain shedding. This is a central step in the modulation of the functions of cell adhesion proteins and cell surface receptors. ADAM10 activity is controlled by transcriptional and post-translational events. The interaction of ADAM10 with tetraspanins and the way they functionally and structurally depend on each other is another topic of interest. In this review, we will summarize findings on how ADAM10 is regulated and what is known about the biology of the protease. We will focus on novel aspects of the molecular biology and pathophysiology of ADAM10 that were previously poorly covered, such as the role of ADAM10 on extracellular vesicles, its contribution to virus entry, and its involvement in cardiac disease, cancer, inflammation, and immune regulation. ADAM10 has emerged as a regulator controlling cell surface proteins during development and in adult life. Its involvement in disease states suggests that ADAM10 may be exploited as a therapeutic target to treat conditions associated with a dysfunctional proteolytic activity.

**Abbreviations**

ACE2, angiotensin-converting enzyme 2; ACS, acute coronary syndrome; AD, Alzheimer’s disease; ADAM, A Disintegrin And Metalloproteinase; AGEs, advanced glycation end products; APP, amyloid precursor protein; BP, bullous pemphigoid; BTC, betacellulin; DLBCL, diffuse large B-cell lymphoma; Dsg, desmoglein; ECD, Ectodomain; EMT, epithelial-to-mesenchymal transition; Eph, erythropoietin-producing human; EPHB2, EphrinB2; ER, endoplasmic reticulum; EVs, extracellular vesicles; GC, gastric cancer; H1 $\alpha$ ,  $\alpha$ -hemolysin; HF, hair follicles; HL, Hodgkin lymphoma; LAG3, lymphocyte activation gene-3; LPC, liver progenitor cells; MBZ, marginal zone B-cell compartment; MM, Multiple myeloma; MMP, matrix metalloproteinase; NICD, Notch intracellular domain; NL, non-Hodgkin lymphoma; OSCC, oral squamous cell carcinoma; PACAP, pituitary adenylate-cyclase-activating polypeptides; PC, prohormone convertase; PCa, prostate cancer; PD-1, programmed cell death protein-1; PDAC, pancreatic adenocarcinoma; PD-L1, programmed-death-ligand 1; PI3K, phosphoinositide-3-kinase; PV, pemphigus vulgaris; RA, rheumatoid arthritis; RAR, retinoid acid receptor; RIP, regulated intramembrane proteolysis; s, soluble; SH3, Src homology 3-binding domain; siRNAs, small interfering RNAs; SLE, systemic lupus erythematosus; T2DM, diabetes mellitus type 2; TAC1, transmembrane activator and CAML interactor; T-ALL, T-cell acute lymphoblastic leukemia; TIMP3, tissue inhibitor of metalloproteinase-3; TNBC, triple-negative breast cancer; tspan, tetraspanin; vWF, von Willebrand factor.

## Introduction

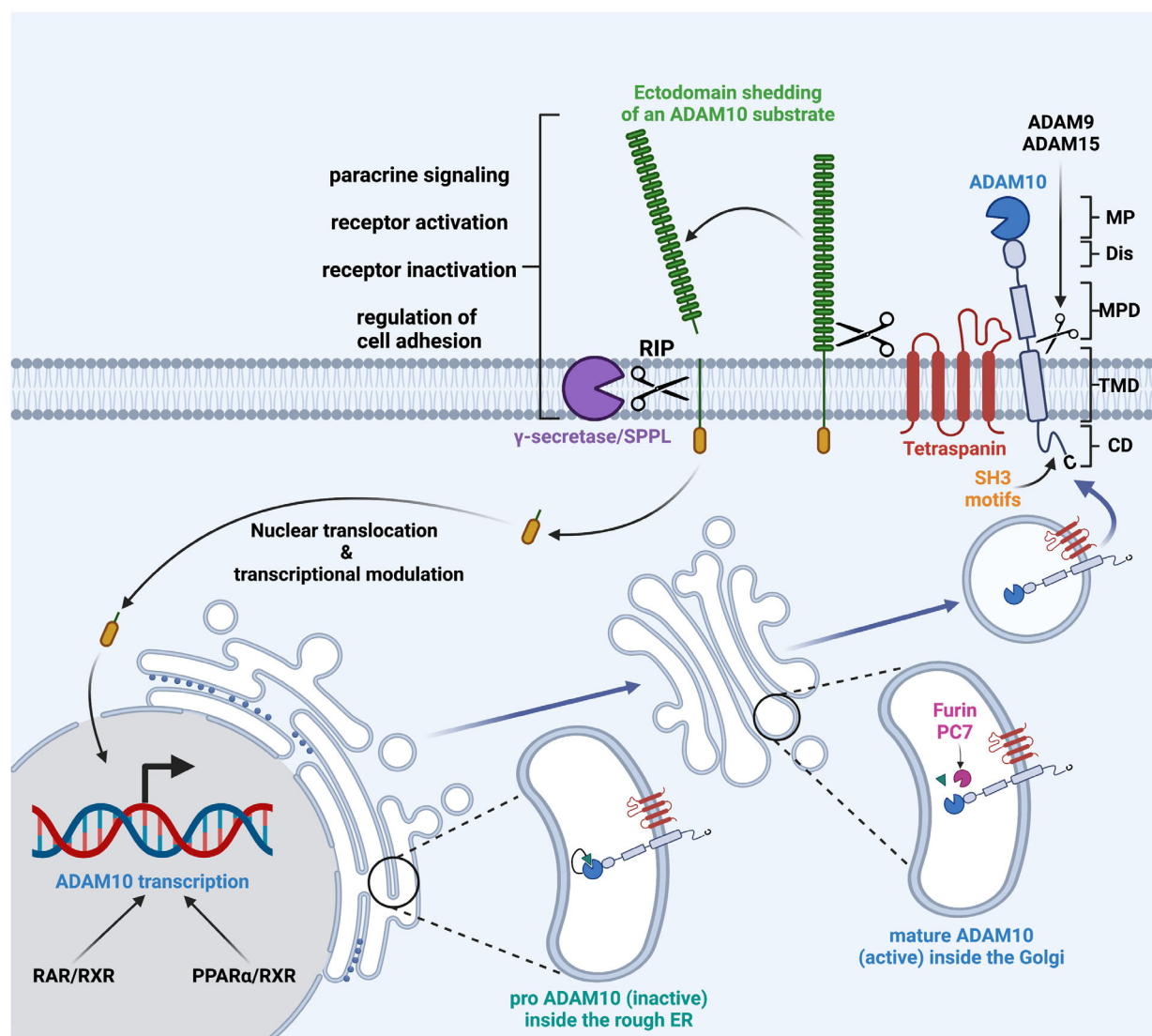
Proteolysis is a pivotal cellular function, which is mainly defined as a breakdown process as exemplified by proteolytic degradation of protein substrates in the proteasome and in the lysosome. Proteases are instrumental to recognize specific protein substrates to hydrolyze site-specifically peptide bonds. This site-directed proteolysis has been developed in evolution to regulate various protein features such as the activity of enzymes, protein–protein interactions, or the localization of the proteins. This has implications for cell proliferation, cell death, differentiation, neurogenesis, fertilization, immunity, and tissue remodeling to name only a few of the many functions of proteases [1]. Among the about 600 proteases in the human body, there are very peculiar ones exemplified by the family of A Disintegrin And Metalloproteinases (ADAM) proteases. The 22 human ADAM members are multi-domain and multifunctional proteins with or without a catalytic domain. The involvement of the active ADAM proteases in a diversity of biological processes such as the regulation of cell–cell and cell-matrix interactions, the modulation of development, differentiation, migration, and receptor-ligand signaling is well documented [2,3]. Those ADAM proteases with a catalytic domain usually cleave their transmembrane protein substrates in close proximity to the membrane, a process which is now widely known as ‘ectodomain shedding’ [4]. This process is also of importance for regulated intramembrane proteolysis (RIP) since ectodomain shedding generates membrane stubs which can be further subject to proteolytic processing by intramembrane proteases, for example, by the  $\gamma$ -secretase complex in case of type 1 transmembrane proteins [5]. It is estimated that about 2–4% of the proteins on the cell surface are substrates for ectodomain shedding [6,7]. The number of shed ADAM substrates may even be larger depending on the cell type or physiological context. The main functions of shedding of ADAM substrates are paracrine signaling, inactivation of receptors or activation of receptors (Fig. 1) as impressively documented by the activation of the Notch receptor, where ectodomain shedding triggers RIP and a release of a cytoplasmic domain, which is involved in the nuclear transcriptional regulation of specific target genes [8].

This review aims to focus on one of the most interesting ADAM proteases, ADAM10. A wealth of information has been collected on why the ubiquitously expressed ADAM10 is of specific interest. It should be noted that ADAM17 represents the structurally most closely related ADAM proteinase involved in

epidermal growth factor receptor, interleukin-6, and TNF $\alpha$  signaling with a function in immune system regulation and cancer development [9]. ADAM17 activity is inducible by external stimuli, whereas ADAM10 appears more in a constitutively active state with an important role in the development of tissues [9]. ADAM10's involvement in the nonamyloidogenic processing of the amyloid precursor protein (APP) [10–12] and its direct involvement in Notch signaling [13,14] are only the two most prominent examples of why it is of interest for many researchers. A number of recent reviews already covered aspects of the general biology, regulation, and the pathophysiological role of ADAM10 (e.g., [15–17]). Here, we try to specifically focus on those aspects of the ADAM10 molecular biology and pathophysiology, which were only poorly discussed to date. After a brief introduction to ADAM10's biology and its general regulation, we will introduce novel knowledge on ADAM10's role on extracellular vesicles (EVs), in what sense ADAM10 contributes to viral infections, cancer progression, inflammation, immune biology, and cardiac disease. We will conclude with the best studied roles of ADAM10 in neurological diseases, its possible modulation by pharmacological means and exploitation as a drug target.

## A brief recapitulation of ADAM10's biology

Transcription factors can bind to specific transcription factor binding motifs within the promoter region of ADAM10 [18]. These include sites for binding of the nuclear retinoic acid receptor (RAR/RXR) and the peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), which both can stimulate ADAM10 mRNA synthesis [18,19]. Also for the 3' untranslated region of ADAM10, binding of miRNAs that can inhibit ADAM10's transcription was described [20,21]. The human ADAM10 coding region consists of 16 exons encoding for a transmembrane-spanning protein composed of 729 amino acids with a glycosylated extracellular domain, one single transmembrane domain, and a cytosolic domain of 55 amino acids. The protease contains a pro-peptide of 193 amino acids, which is usually subject to proteolytic removal when passing the Golgi compartment (Fig. 1). It should be noted here that surface biotinylation experiments in THP1 cells revealed a considerable fraction of pro-ADAM10 still at the cell surface in contrast to ADAM17 where only mature ADAM17 was found [22]. Both a prohormone convertase (PC7) and furin may exert the cleavage event involved in the maturation of ADAM10 [23,24].



**Fig. 1.** ADAM10 from synthesis to membrane function. ADAM10 is a major ectodomain sheddase involved in the proteolytic release of extracellular domains of a large spectrum of transmembrane proteins. Depicted is ADAM10 with its protein domains as a catalytically inactive precursor protein synthesized in the ER and transported through the Golgi apparatus where furin/PC7 activates the protease through a removal of its prodomain. Subsequent exocytosis delivers surface-expressed ADAM10, and ectodomain shedding of ADAM10 substrates can happen. Certain tetraspanins (e.g., Tspan15) are bound to ADAM10 during the transit from the ER to the cell surface. Tspans possibly modulate ADAM10's activity, half-life, substrate specificity, and endocytosis. Shedding can trigger extra- and intracellular signaling. The latter process is dependent on  $\gamma$ -secretase/SPPL (Signal Peptidase Like Protease) mediated RIP leading to intracellular protein fragments interfering with nuclear transcription factors. ADAM10 expression and activity can be modulated by pharmacological means. Transcriptional activation of ADAM10 is followed as an attractive strategy to increase ADAM10-mediated ectodomain shedding. CD, cytoplasmic domain; Dis, disintegrin domain; MP, Metalloproteinase domain; MPD, membrane proximal domain; PPAR $\alpha$ , peroxisome-activated receptor alpha; RAR, retinoic acid receptor; RXR, retinoic X receptor; TMD, transmembrane domain. Figure generated using Biorender.

Interestingly, mutations within the prodomain of ADAM10 were described in two Alzheimer's disease (AD) patients [25], suggesting an inhibitory role of this domain for the proteolytic  $\alpha$ -secretase activity. The pro-domain removal is usually analyzed by immunoblot analysis, revealing two ADAM10-specific bands

representing pro (inactive) and mature (active) ADAM10. The latter still consists of a large, glycosylated extracellular part containing the metalloproteinase and a disintegrin domain [16]. A putative regulatory role is assumed for the cytosolic part of ADAM10, containing a Src homology 3-binding domain (SH3) and

SH3 binding proteins [26,27] (Fig. 1). Regulation of ADAM10 is of central importance. The shedding of ADAM10 itself by ADAM9 and ADAM15 represents an interesting regulatory feature, which triggers  $\gamma$ -secretase-mediated intramembrane proteolysis of the remaining ADAM10 membrane stub [28–30]. As discussed below, the interaction of ADAM10 with certain membrane-embedded tetraspanins also regulates the trafficking and stability of the protease and may also be important in determining substrate specificity [31] (Fig. 1). It has not yet been fully understood where in a given cell the cleavage event of an ADAM10 substrate takes place. For the Notch1 receptor cleavage, the cell surface seems to be the place of shedding, [32] but for many other substrates, it is conceivable that cleavage also occurs *en route* to the cell surface or even in endocytic organelles.

From a functional point of view, studies in classical and conditional ADAM10-knockout mice provided information on the multiple roles of this protease in diverse tissues, cell types, and developmental stages. The full deficiency of ADAM10 in mice leads to an early embryonic lethality around 9.5 days of embryogenesis, which is explained by ADAM10's contribution in the Notch signaling pathway. A lack of ADAM10 causes defects in somite development, cardiovascular and nervous system abnormalities [14]. To circumvent the embryonic lethality, various conditional ADAM10 knockout mice were generated, revealing essential functions of ADAM10-mediated ectodomain shedding in development and homeostasis of the cardiovascular system, central nervous system, synapses, immune system, epidermis and hair, intestine, kidney, and endothelium to name only a few (summarized in [2,16,33]). These studies also contributed to the discovery of about 100 different substrates of ADAM10 [12]. The most prominent transmembrane proteins, next to the Notch receptor, undergoing ADAM10-mediated cleavage are represented by different classes of cadherin proteins, the APP, Fas-ligand, ephrin, prion protein, growth factors, and many more. Due to the cleavage of the APP protein within the neurotoxic amyloid beta peptide sequence, ADAM10 represents the relevant  $\alpha$ -secretase *in vivo*, accelerating the nonamyloidogenic pathway and counteracting amyloid beta production [11,34].

### New perceptions from studying the structures of ADAM10 and Tspan15

X-ray crystallography was applied to unravel the protein structure of the extracellular domain of ADAM10 [35]. The protease presents as a compact conformation resembling an arrowhead. The metalloproteinase

domain is enveloped by the disintegrin and cysteine-rich domain, possibly restricting access of substrates. A new type of autoregulation of the mature enzyme was revealed [35]. Since the active site of the enzyme is masked by the cysteine-rich domain, substrate access seems only possible after structural rearrangement, as demonstrated by the binding of a modulatory antibody directed against this region. A very short opening of the ADAM10 structure was suggested, allowing capture and processing of exposed substrates at the cell surface such as the Notch receptor and APP, respectively. An alternative model of assembly of the closed form with its substrate and subsequent arrangement to expose the cleavage site of the substrate and the catalytic site of the protease was put forward [35]. Interestingly, for both ADAM10 and ADAM17 a scramblase-mediated flip of negatively charged phosphatidylserine from the inner to the outer membrane leaflet has been revealed, causing a rapid activation of the protease [36]. In addition, accessory proteins could play a role in regulating the specificity and access to substrate proteins. ADAM10 binds tightly to certain tetraspanins (e.g., Tspan12 and Tspan15) and is embedded in the 'tetraspanin web', possibly allowing membrane compartmentalization of protease and substrates [37]. Tetraspanins, as typical four membrane-spanning proteins, appear as essential in the regulation of ADAM10 protease function [31]. The best studied case here is the interaction of ADAM10 with Tspan15. Similar to Tspan12 [38], Tspan15 binds to ADAM10 already in the endoplasmic reticulum (ER). The complex of both proteins is rapidly exported and delivered to the plasma membrane [39] where ADAM10 is active and most likely stabilized. Interestingly, the dependency is also the other way around. The expression level of endogenous Tspan15 also depends on the ADAM10 binding, suggesting an intimate functional link between both proteins [40]. To better understand this protease–tetraspanin interaction, a cryo-EM structure of an vFab-ADAM10-Tspan15 complex was generated [41]. The ADAM10-Tspan15 binding site is located in a conserved site within the variable region of the large extracellular loop of Tspan15. Additional contact sites may be present between the transmembrane domains of both proteins [41]. It is discussed (<https://www.biorxiv.org/content/10.1101/2022.10.22.513345v1>) that when Tspan15 is bound to ADAM10 the protease is found in an open state exposing the catalytic site about 20 Å from the cell surface. This positioning of the catalytic site seems dependent on two interfaces within Tspan15. One of the interface regions is not conserved in the different C8-Tspan proteins possibly explaining their suspected role in determining cleavage specificity.



## Involvement of ADAM10 in human diseases

ADAM10 expression or dysfunction has been linked to different human diseases (Fig. 2). Its involvement in different types of brain disorders (AD, prion disease, fragile X-syndrome, and Huntington's disease) has been appreciated. In how far selected human diseases are linked with the role of ADAM10 has been reviewed [16,17]. Here, we will mainly summarize new information about ADAM10's role in cancer, inflammation, immune disorders, viral infections, myocardial infarction, and neurological disorders.

## ADAM10 and cancer

Even though the implication of novel targeted and individualized therapeutic options has led to a substantial improvement in the curative therapy and overall survival of malignant diseases, cancer remains among the leading causes of death worldwide. Although the recognition of proteases as essential components in the biology and progression of cancer are not new, the precise molecular mechanisms that put proteases in the spotlight of tumor development often remain elusive and some studies are limited to drawing correlative connections between protease expression profiles and different tumor entities.

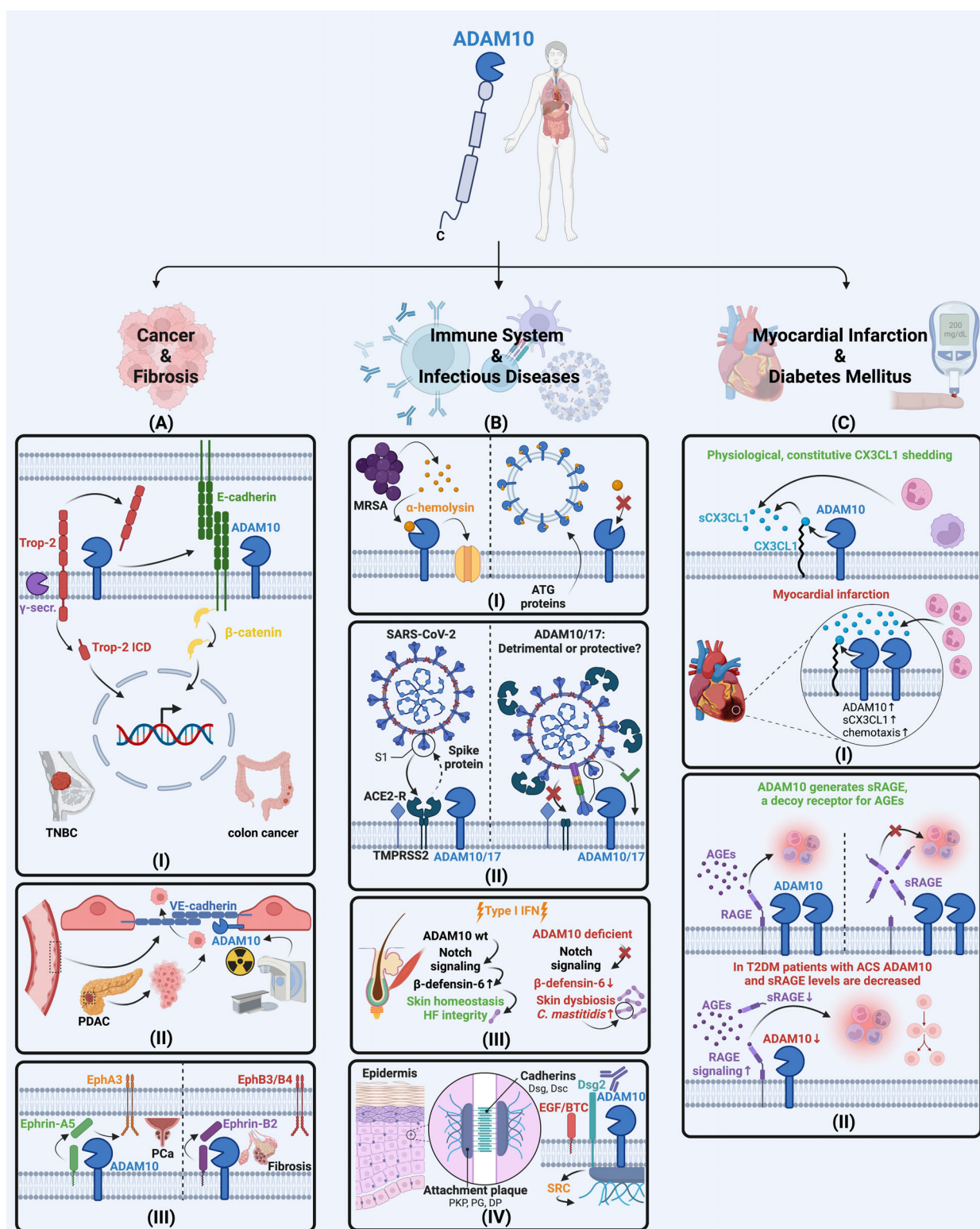
In this context, ADAM10 as a highly expressed protease in many different tumor entities has raised considerable attention. The ways by which ADAM10 can affect carcinogenesis and cancer progression are multidimensional and include the proteolytic release of proteins from the cell surface, including growth factors, cytokines, receptors, and various types of adhesion molecules. The subsequent stimulation of other cells expressing corresponding receptors can trigger pro-tumorigenic intracellular signaling pathways. A prominent example is the role of ADAM10 as a sheddase for the release of EGF and betacellulin (BTC), which leads to the stimulation of downstream pro-proliferative pathways after binding to receptors belonging to the EGFR/HER family [42]. Also, the shedding of surface proteins can drastically alter the tumor cell response to targeted therapies. Among the family of ADAM proteases, the role of ADAM10 and ADAM17 in malignant diseases is best documented and the two proteases were identified as drivers for cancer progression and emerged as potential biomarkers in many tumor entities. This observation is supported by the beneficial effects of selective ADAM

inhibitors (especially directed against ADAM10/ADAM17) throughout different cancer types. The following part will provide a brief summary of known ADAM10-mediated mechanisms in cancer (in part reviewed by [17,43] and summarized in Table 1) and will provide a more in-depth insight into more recent advances in the field (summarized in Fig. 2A).

## New ADAM10-related tumor entities and their postulated pathophysiological mechanisms

### Trop-2: A universal ADAM10-dependent driver for cancer progression and metastasis

The monomeric transmembrane protein Trop-2 is a signal transducer in epithelial cells [44], with implications for the development and progression of various malignant diseases [45,46]. For a homologue family member, Trop-1, it has been demonstrated that proteolytic cleavage within a thyroglobulin-domain activates proliferation-stimulating molecular properties. Similarly, for Trop-2 proteolytic events have been characterized, involving RIP and the release of an intracellular domain that translocates to the nucleus together with  $\beta$ -catenin (Fig. 2AI). Recent findings suggest ADAM10 as a key regulator and sheddase of Trop-2 [47]. Proteolysis at R87-T88 leads to a profound structural rearrangement of Trop-2, triggering cancer cell growth and driving metastatic spread both in cell-based experiments and *in vivo*. The cleavage of Trop-2 in cultured cells could be abolished using pharmacological approaches (GI254023X), ADAM10-specific siRNAs and shRNAs. Although a more detailed molecular understanding of downstream effects of the ADAM10-mediated, post-translational Trop-2 processing remains elusive, these findings bear translational potential. In this context, the development of an anti-Trop-2 antibody-SN-38 drug conjugate Sacituzumab govitecan-hziy (Trodelvy®) that is successfully being used in patients with metastatic triple-negative breast cancer (TNBC) is of clinical interest [48]. Besides, also in colon cancer Trop-2 unveils its clinical significance as it is upregulated upon tumor progression [49] and its physical interaction with ADAM10 at the cell membrane was implicated to be the major effector mechanism leading to higher rates of metastatic dissemination, worse relapse-free and overall survival. The tight interaction of Trop-2 and ADAM10 therefore triggers ADAM10-mediated cleavage of E-cadherin, a disruption of intercellular junctions and the activation of pro-metastatic  $\beta$ -catenin signaling (Fig. 2AI). Mechanistically,  $\beta$ -catenin acts as a scaffold



protein for the Ras/Raf/ERK/ezrin complex, which plays a key role in regulating PI3K/Akt signaling. The translocation of  $\beta$ -catenin to the nucleus induces

transcriptional changes and hereby alters the gene expression of cell proliferation, differentiation, and angiogenesis-promoting factors.

**Fig. 2.** Involvement of ADAM10 in human diseases. ADAM10 is involved in a multitude of human diseases, and its pathophysiological implications are not limited to ectodomain shedding, but also include receptor functions and intracellular signaling events. Recently described roles of ADAM10 in cancer and fibrosis (A), the immune system and infectious diseases (B), and myocardial infarction and diabetes mellitus (C) are indicated. *Trop-2 is a universal ADAM10-dependent driver for cancer progression and metastasis (AI)*. The trans-membrane protein undergoes ADAM10-mediated ectodomain shedding, and the residual membrane stub is subsequently processed by the  $\gamma$ -secretase. RIP leads to the generation of an intracellular fragment (Trop-2-ICD) that translocates to the nucleus together with  $\beta$ -catenin. The triggered pro-tumorigenic/pro-metastatic signaling plays a role in the progression of TNBC as well as colon cancer. *ADAM10 activation by ionizing radiation has implications for patients undergoing radiation therapy (AII)*. Ionizing radiation in therapeutic doses increases the endothelial permeability and enhances tumor cell migration. The dysregulated maintenance of the endothelial barrier is caused by increased VE-cadherin cleavage by ADAM10. In pancreatic ductal adenocarcinoma patients (PDAC), a high ADAM10 and ephrinB2 expression after radiation therapy is associated with a worse prognosis due to increased fibrosis and metastasis. *Ephrins and Eph receptors are regulated by ADAM10 and modulate cancer progression and fibrosis (AIII)*. Through an interaction with the EphA3/ephrin-A5 complex and the subsequent proteolytic release of ephrin-A5, ADAM10 promotes metastasis, migration, and invasion in PCa. Soluble ephrin-B2 which activates the EphB3/B4 complex is a key pro-fibrotic marker in lung and skin diseases and is generated by ectodomain shedding in an ADAM10-dependent manner. *ADAM10-containing exosomes contribute to a protection against bacterial toxins (BI)*. The MRSA-derived pore-forming  $\alpha$ -hemolysin uses ADAM10 as a cellular receptor in many tissue compartments. ATG proteins induce the formation of ADAM10-containing EVs, which act as decoy receptors to neutralize soluble  $\alpha$ -hemolysin, thus preventing its binding to the host cell. *ADAM10 in viral infections (BII)*. SARS-CoV-2 enters host cells through an interaction with ACE2 and TMPRSS2. ADAM10/17 have both been implicated in the cleavage of ACE2 and soluble ACE2 might act as a decoy receptor, thus preventing virus entry into target cells. However, ADAM10/17 were also facilitating virus entry by proteolytically priming the SARS-CoV-2 spike protein. *Skin homeostasis and hair follicle integrity rely on faultless ADAM10-dependent Notch signaling (BIII)*. Altered ADAM10 expression disrupts Notch signaling and subsequently influences the  $\beta$ -defensin-6 expression upon type I IFN stimulation. This results in skin dysbiosis and a predominance of *Corynebacterium mastitidis*. *ADAM10's implications in a rare and severe autoimmune disease: PV (BIV)*. The ADAM10-mediated proteolytic release of epidermal growth factor (EGF) and BTC contributes to suprabasal acantholysis in PV. ADAM10 is also involved in the turnover of Dsg2 since it is a sheddase of the desmosomal protein. ADAM10 modulates downstream Src-dependent signaling events. In certain autoantibody profiles, an inhibition of ADAM10 decelerates the progression of PV. *ADAM10 and myocardial infarction (CI)*. An increased ADAM10-expression in infarction tissue enhances the generation of soluble CX3CL1, which in turn increases the chemotactic recruitment of immune cells and sustains inflammation with subsequent tissue damage of the myocardium. *ADAM10 in metabolic diseases: diabetes mellitus type 2 (CII)*. AGEs exert their detrimental effects inter alia by binding to the multiligand receptor RAGE which undergoes ADAM10-mediated ectodomain shedding. Soluble RAGE (sRAGE) can act as a decoy receptor, thus preventing the binding of AGEs to cell-bound RAGE. T2DM patients (diabetes mellitus type 2) with ACS exhibit decreased ADAM10 levels, so that AGEs can bind to more cell surface RAGE which increases pro-inflammatory and proliferative intracellular signaling.

### ADAM10 activation by ionizing radiation has implications for patients undergoing radiation therapy

Besides the activation of our immune system, the physical integrity of vascular endothelial barriers, formed by tightly adhering cells that express VE-cadherin, represents a major obstacle for a tumor cell to overcome. VE-cadherin is an ADAM10 substrate and undergoes ectodomain shedding, leading to a reduced surface expression, and thus increased endothelial permeability [50]. Ionizing radiation in therapeutic doses leads to an increase in endothelial permeability and enhances the transmigration of tumor cells [51]. As an experimental system, irradiated monolayers of primary human umbilical vein endothelial cells (HUVEC) were assessed for their permeability. The described effect is accompanied by an increased maturation of ADAM10, augmented shedding of VE-cadherin and a dysregulated maintenance of the endothelial barrier (Fig. 2AII). ADAM10-specific pharmacological inhibition (GI254023X) counteracts these irradiation-related effects and reduces tumor cell transmigration. Kabacik and Raj [52] suggested that irradiation induces reactive

oxygen species (ROS) production which raises intracellular calcium levels, leading to an activation of ADAM10. Interestingly, the induction of ADAM10 by radiation therapy gives rise to increased fibrosis, resistance, and epithelial-to-mesenchymal transition (EMT) in pancreatic cancer [53].

In pancreatic ductal adenocarcinoma (PDAC) patients who received neoadjuvant stereotactic body radiation therapy, an upregulation in genes associated with fibrosis, extracellular matrix formation, and EMT was found. ADAM10 and ephrinB2 (EPHB2) are pro-fibrotic drivers of postradiation tumor progression [53]. In PDAC patients, high expression of ADAM10 and ephrinB2 after radiation therapy was correlated with a bad prognosis. The increased shedding of ephrinB2 (see the detailed explanation below) can be successfully abrogated using pharmacological ADAM10-selective inhibitors or genetic models, which led to suppressed fibrosis and a delay in tumor progression in a murine PDAC model. These effects are reversed by adding recombinant ephrinB2-FC, suggesting that reduced ADAM10-mediated ephrinB2

**Table 1.** Summary of ADAM10's role in different types of cancer.

Tumor entity	Cancer biology	Role of ADAM10	Therapeutic potential	References
Glioblastoma	<ul style="list-style-type: none"> <li>• Malignant transformation of astrocytes</li> <li>• Most aggressive brain tumor in adults (WHO grade IV)</li> <li>• Aggressive infiltration in the brain parenchyma results in poor prognosis</li> </ul>	<ul style="list-style-type: none"> <li>• Low ADAM10 expression levels in surgical specimens were correlated with improved survival</li> <li>• Neuroligin-3 (NLGN3) undergoes ADAM10-mediated ectodomain shedding at the cell surface and high levels of NLGN3 have been associated with high-grade GBM</li> <li>• NLGN3 promotes cell proliferation through P13K–mTOR and acts through oncogenic focal adhesion kinase signaling</li> <li>• ADAM10-mediated N-cadherin cleavage promotes a more invasive tumor phenotype and metastasis</li> <li>• Natural killer cells recognize glioblastoma with ligands binding to the NKG2D receptor: NKG2D binds to two ligands that are shed by ADAM10/ADAM17 (MICA and ULBP2)</li> <li>• Sustained surface expression of these receptors (by preventing them from undergoing proteolysis) enhances antitumor immunogenicity in glioblastoma</li> <li>• ADAM10 was correlated with higher levels of M1 macrophage-associated genes and thus with better survival</li> <li>• The initiation of Notch1 signaling by ADAM10 might exert pro-oncogenic effects</li> </ul>	<ul style="list-style-type: none"> <li>• Using GI254023X, the growth of glioblastoma could be attenuated in patient-derived xenografts and in cell models</li> <li>• An inhibitory antibody against ADAM10 reduces tumor growth and migration through abrogated N-cadherin cleavage</li> <li>• ADAM10 affects the invasiveness and progression of glioblastoma</li> <li>• Pharmacological or genetic strategies to inhibit/downregulate ADAM10 might reduce glioblastoma invasiveness</li> </ul>	[100,170–175]
Breast cancer	<ul style="list-style-type: none"> <li>• The human epidermal growth factor receptor HER2 is associated with increased cell proliferation and serves, when overexpressed, as an oncogene in 10–20% of all invasive ductal breast cancers of no special type (NST), predicting a rather poor prognosis</li> <li>• HER2-positive breast cancer can be treated with the monoclonal antibody trastuzumab, which initially leads to a good response</li> <li>• The cancer often relapses in a more aggressive form with increased trastuzumab insensitivity.</li> </ul>	<ul style="list-style-type: none"> <li>• HER2 undergoes ADAM10-mediated ectodomain shedding, that releases the HER2 ectodomain (ECD) and generates a truncated form of the receptor, which displays a constitutive activity</li> <li>• ADAM10 promotes HER2 receptor activation through the cleavage of its ligand BTC</li> <li>• ADAM10 expression is upregulated, following trastuzumab treatment and is predictive for a reduced progression-free survival by mediating therapy resistance</li> <li>• A compensatory HER3 upregulation in response to trastuzumab-mediated HER2 loss has been observed</li> <li>• ADAM10 liberates the HER3 ligand from the cell surface</li> <li>• ADAM10/17 are expressed in many cases of TNBC, a tumor entity with a very poor prognosis due to limited treatment targets</li> <li>• ADAM10 was implicated in the regulation of the PD-1/PD-L1 tumor checkpoint system.</li> </ul>	<ul style="list-style-type: none"> <li>• Pharmacological or genetic strategies to inhibit/downregulate ADAM10 in HER2 overexpressing breast cancer cells lead to increased trastuzumab sensitivity</li> <li>• GI254023X treatment and RNAi knockdown of ADAM10 decreased the <i>in vitro</i> migration of TNBC cell lines</li> <li>• Pharmacological or genetic strategies to inhibit/downregulate ADAM10 are considered as a new adjuvant therapeutic strategy to increase and prolong the sensitivity of breast cancer to targeted therapies and thus ameliorate survival rates</li> </ul>	[79,176–180]



**Table 1.** (Continued).

Tumor entity	Cancer biology	Role of ADAM10	Therapeutic potential	References
Oral squamous cell carcinoma	<ul style="list-style-type: none"> <li>The malignant transformation of epithelial cells in the oral cavity is responsible for the formation of this invasive carcinoma (OSCC)</li> </ul>	<ul style="list-style-type: none"> <li>OSCC cell lines and tissue samples display a high expression of ADAM10, especially in specimens derived from metastatic lesions</li> <li>ADAM10 seems to exert important nonproteolytic, rather adhesive functions: ADAM10 overexpression in OSCC cells alters MMP9 and MMP7 expression levels in an integrin-dependent fashion, which could contribute to a more invasive tumor phenotype</li> <li>Tissue inhibitor of metalloproteinase-3 (TIMP3) as an ADAM10 inhibitor has repressive effects on OSCC proliferation, angiogenesis, invasiveness, and migration</li> <li>TIMP-3 promotor hypermethylation in OSCC reduces TIMP-3 mRNA levels and DNA methyltransferase inhibition (DNMTi) or repression of TIMP-3 mitigates tumor cell growth and migration</li> <li>The explicit connection between altered TIMP-3 expression in OSCC due to dysmethylation and ADAM10-dependent cancer progression remains elusive</li> <li>A link between TIMP-3 loss and a pathological increase in ADAM10 activity/expression seems possible</li> <li>OSCC tumors are associated with low expression of the MICA stress receptor, which is regulated by ADAM10</li> <li>Increased ADAM10 levels in OSCC are thus likely to result in an increased MICA cleavage, accompanied by reduced antitumor immunogenicity</li> </ul>	<ul style="list-style-type: none"> <li>RNAi-mediated ADAM10 knockdown reduces the migratory and invasive capacity of OSCC cells</li> <li>Pharmacological or genetic strategies to inhibit/downregulate ADAM10 might be a new adjuvant therapeutic strategy to treat OSCC patients</li> </ul>	[181–184]
Hodgkin lymphoma	<ul style="list-style-type: none"> <li>Hodgkin lymphoma (HL) is a malignant disease of the lymphatic system, caused by a clonal proliferation of lymphocytes</li> <li>Characterized by the presence of lacunar histiocytes and Reed-Sternberg cells</li> </ul>	<ul style="list-style-type: none"> <li>Through the shedding of stress receptors, such as MICB and ULBP2, ADAM10 contributes to the formation of an immunosuppressive environment in HL</li> <li>ADAM10 inhibition with designed specific inhibitors (LT4 and MN8) abrogates the proteolysis of NKG2D-L <i>in cellula</i> and results in increased susceptibility of HL cells to immune system-mediated killing</li> <li>ADAM10 and CD30 are present in EVs released from HL cells</li> </ul>	<ul style="list-style-type: none"> <li>ADAM10 inhibition normalizes CD30 levels at the cell membrane and thus ameliorates HL sensitivity to targeted anti-CD30 therapies like Iratumumab</li> </ul>	[144,185–187]
Non-Hodgkin lymphoma	<ul style="list-style-type: none"> <li>Non-Hodgkin lymphoma (NL) is used as a collective term for many different malignant</li> </ul>	<ul style="list-style-type: none"> <li>In Epstein-Barr virus-positive DLBCL, NOS (not otherwise specified) an increased expression of PD-L1 has been detected</li> </ul>	<ul style="list-style-type: none"> <li>Comparable to HER2-positive breast cancer, pharmacological or genetic strategies to</li> </ul>	[66,179]

**Table 1.** (Continued).

Tumor entity	Cancer biology	Role of ADAM10	Therapeutic potential	References
	entities, including Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL) and marginal zone lymphoma	<ul style="list-style-type: none"> <li>Strikingly, anti-PD-L1 monoclonal antibodies sometimes fail to exert antitumor effect, even if PD-L1 expression has been determined</li> <li>Proteolytic shedding of PD-L1 by ADAM10/17 was assumed</li> </ul>	<ul style="list-style-type: none"> <li>inhibit/downregulate ADAM10 as a new adjuvant therapeutic approach to increase NL sensitivity to anti-PD-L1 immune therapy are discussed</li> <li>ADAM10 inhibition prevents the proteolysis-mediated loss of the corresponding therapeutic target(s)</li> </ul>	
Multiple myeloma (MM)	<ul style="list-style-type: none"> <li>A malignant clonal expansion of plasma cells, that makes up more than 30% of the bone marrow volume</li> <li>The disease is characterized by an extensive secretion of immunoglobulins, accompanied by structural bone defects and kidney damage due to Ig deposits</li> </ul>	<ul style="list-style-type: none"> <li>Genotoxic stress (induced by doxorubicin) in MM cells leads to an upregulation of ADAM10, resulting in increased proteolytic cleavage of MICA and MICB</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacological or genetic strategies to inhibit/downregulate ADAM10 may enhance NK cell-mediated killing of MM cells</li> </ul>	[188]
T-cell acute lymphoblastic leukemia	<ul style="list-style-type: none"> <li>T-cell acute lymphoblastic leukemia (T-ALL) arises from malignant thymocytes and is associated with altered NICD (NICD) levels (&lt;1% of the cases)</li> <li>Various Notch mutations are present in more than 50% of T-ALL cases</li> <li>Downstream target genes of Notch are in control of cell cycle and cell growth signaling pathways and are connected to the malignant transformation of T-cells</li> </ul>	<ul style="list-style-type: none"> <li>Since ADAM10-mediated ectodomain shedding of Notch1 constitutes the most important limiting factor for the release of NICD and subsequent Notch1 signaling, the protease also contributes to pro-oncogenic Notch signaling in T-ALL due to proteolysis of cancer-associated Notch1 mutants</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacological or genetic strategies to inhibit/downregulate ADAM10 may counteract aberrant Notch1 signaling in T-ALL and thus decrease cancer progression</li> </ul>	[189–191]

cleavage is responsible for the observed antitumor effects [53]. Furthermore, ADAM10 inhibition enhanced radiation-mediated tumor killing and significantly decreased metastatic spread. Even though an exclusive inhibition of ADAM10 presents itself as unsuitable for monotherapy, due to a lack of cytotoxicity, it might serve as an additive to traditional chemo-/radiation therapy, aiming at an antifibrotic tumor microenvironment and reduced metastasis.

### Ephrins and Eph receptors are regulated by ADAM10 and modulate cancer progression and fibrosis

Another aspect referring to the molecular landscape of tumor cells, which has received considerable research and translational interest, is receptor tyrosine kinases and their ligands. Ephrins form a large family of cell surface ligands that are either glycosyl-phosphatidylinositol-linked (ephrin-A1-6) or

transmembrane proteins (ephrin-B1-3) [54]. Their binding to Eph receptors (erythropoietin-producing human hepatocellular receptors), a large family of receptor tyrosine kinases on the surface of adjacent cells, induces bidirectional signaling events [55]. The Ephrin-Eph axis impacts tissue-patterning and cell adhesion during the formation of blood vessel walls and controls cell motility in a promigratory fashion during embryonic development [56].

EphA8-levels are significantly increased in tissue biopsies of gastric cancer (GC) patients and are tightly correlated with the tumor differentiation status, nodal metastasis stage, and a poor prognosis [57]. Importantly, shRNA-mediated EphA8 knockdown in cell-based experiments leads to a decreased ADAM10 expression, explained by the interaction of the two proteins. Interaction of ADAM10 and EphA8 could be demonstrated by co-immunoprecipitation and immunofluorescence experiments. There is evidence for the regulation of ADAM10 expression by the PI3K/AKT signaling pathway [58]. Since phosphorylated AKT (p-AKT) levels were reduced in EphA8-shRNA-treated cells, it was speculated that EphA8 acts upstream of ADAM10 [57]. These findings suggest that the ADAM10-EphA8 interaction plays a role in the modulation of this key cellular pathway [58]. On a molecular level, EphA8 overexpression is associated with increased levels of cell proliferation or invasion-associated proteins. The interaction between EphA8 and ADAM10 possibly shapes the tumor biology of GC. Further research defining the cellular pathways and their dependency on the ADAM10-EphA8 complex is required to elucidate the still largely correlative nature of their interplay in GC.

Also, prostate cancer (PCa) has lately been added to the list of ADAM10 overexpressing tumors. In more aggressively progressing forms of PCa, the shedding of ephrin-A5 is part of a molecular pathogenesis [59]. Ephrin-A5 is the primary ligand of the receptor tyrosine kinase EphA3 and undergoes ADAM10-mediated proteolysis (Fig. 2AIII). Mechanistically, ADAM10 promotes PCa metastasis, migration, and invasion through an interaction with the EphA3/ephrin-A5 complex and subsequent release of ephrin-A5, which can be used as a serum marker for the diagnosis of metastatic PCa [59]. The effects upon ADAM10 overexpression in PCa cell lines and xenograft mouse tissue are reversed by applying the ADAM10 inhibitor GI254023X. As an explanation for the decisive regulatory role of ADAM10 in PCa progression and metastasis, a dual effector mechanism was proposed that involves a kinase-independent pro-oncogenic effect and a kinase-dependent antioncogenic effect. ADAM10

mediates the interplay of these two pathways as the postshedding dissociation of ephrin-A5 from the ADAM10/ephrin-A5/EphA3 complex relieves the inhibition of EphA3, caused by ephrin-A5. This ultimately accounts for the pro-oncogenic effect [59].

Apart from malignant diseases, the interaction of ADAM10 and ephrins plays a major role in fibrotic disorders, which are characterized by an extensive deposition of extracellular matrix components and an increased activity of myofibroblasts [60,61]. Soluble ephrin-B2 (sEphrin-B2) is generated through ADAM10-dependent ectodomain shedding and constitutes a key pro-fibrotic mediator in lung and skin diseases [62] (Fig. 2AIII). The release of sEphrin-B2 into the alveolar airspace during lung injury leads to a subsequent increase of fibroblast chemotaxis, followed by an activation of the EphB3/EphB4 signaling axis. Fibroblast ephrin-B2-deficient mice are protected against skin and lung fibrosis, and pharmacological inhibition of ADAM10 reduces sEphrin-B2 levels, protecting mice against fibrosis likewise. Corresponding results were obtained from human tissue samples, derived from patients with idiopathic pulmonary fibrosis, who exhibit an upregulation of the ADAM10-sEphrin-B2 signaling axis in fibroblasts [62]. The underlying signaling mechanisms are complex and reveal a central role of ADAM10. In injured tissue, TGF- $\beta$ -mediated ADAM10 upregulation leads to an increased generation of sEphrin-B2. This possibly provokes an alleviation of the repressive cis inhibitory ephrin-B2-EphB3/B4 complex interaction. On the contrary, it is possible that sEphrin-B2 activates pro-fibrotic EphB3/B4 signaling in an autocrine fashion [62]. Considering the massive antifibrotic effects of the ADAM10 inhibitor GI254023X in mice, its (transient and controlled) administration to human patients might reveal translational potential.

### ADAM10 affects the resistance to PD-(L)1 immune checkpoint inhibitors

Among other surface proteins, the programmed cell death protein-1 (PD-1) on T-cells is a critical regulator for antitumor immunity [63]. The binding of its corresponding ligand, programmed-death-ligand 1 (PD-L1), which is, for example, expressed on tumor cells, results in a massive downregulation of antitumor immune responses and thus acts as a driver for tumor progression. Even though the clinical implementation of PD-(L)1 inhibitors like nivolumab, pembrolizumab, or atezolizumab as monotherapy or in combination with other therapeutic modalities has led to a substantial improvement of patient survival for many different

tumor entities, only few patients with verified PD-L1 expression sufficiently respond to immune checkpoint inhibitors. The underlying mechanisms of resistance remain largely elusive, and there is a huge practical need for biomarkers to predict the drug response before administering inhibitory antibodies [64,65].

ADAM10 and the structurally related ADAM17 protease mediate PD-(L)1 inhibitor resistance *in cellula* by cleaving PD-L1 from the surface of malignant cells, generating an active, soluble fragment (sPD-L1), which compromises antitumor immunity through the induction of apoptosis in CD8+ T-cells. A different cleavage pattern of the two proteases has been reported, but further research is required to evaluate their distinct functions and specificity of each enzyme. However, combined ADAM10/17 inhibition might abrogate inhibitor resistance and a diagnostic co-staining of PD-L1 and ADAM10/17 in immunohistochemical examinations of patient-derived tumor samples could possibly improve the prediction of drug responses in cancer patients [66].

Lymphocyte activation gene-3 (LAG3) is another inhibitory receptor on intratumoral T-cells, whose cell surface expression is regulated by ADAM10/17-mediated ectodomain shedding [67]. LAG3 proteolysis is essential for an effective antitumor immune response and the LAG3/ADAM10 expression ratio on the surface of CD4+ conventional T-cells could serve as a prognostic marker. Since extensive ADAM10-mediated shedding of LAG3 ameliorates the prognosis of certain tumor entities and their sensitivity to immune therapy, the induction of ADAM10/17 could be discussed as a therapeutic strategy. However, such an approach must be carefully considered in each individual tumor entity, given the role of ADAM10/17 as sheddases for other inhibitory receptors, as described above. Therefore, more data are required to assess whether the induction of proteases is beneficial or even harmful for the patient's prognosis upon immune therapy [68].

### Unexpected role of ADAM10 on extracellular vesicles

The presence of proteases on EVs has become a center of attention in search for biomarkers, especially in the context of cancer, so that there are plenty of studies on protease-carrying EVs in different pathophysiological contexts. ADAM10 has been first linked to exosomes in the context of the shedding of the adhesion molecules L1 and CD44 [69]. Here, we will restrict our focus to the best characterized examples where we have a mechanistic understanding of how ADAM10 on EVs can interfere with certain pathophysiological

conditions. Exosomes are a subset of EVs with a diameter of ~ 100 nanometers that are derived from the late endosomal compartment. They are released by most eukaryotic cells and contain, depending on their cellular origin, diverse constituents. Exosomes are found in body fluids what makes them suitable for clinical diagnostics [70].

### ADAM10-containing exosomes contribute to a protection against bacterial toxins

The production of pore-forming toxins that disrupt the integrity of the host cell membrane is a common motif in various bacterial species, among them the 'Methicillin Resistant *Staphylococcus Aureus*, MRSA' which is famous for its problematic role as a hospital germ [71,72]. Recent studies reported immune defense mechanisms that rely on ADAM10-carrying EVs to neutralize pore-forming toxins like the  $\alpha$ -toxin/ $\alpha$ -hemolysin (encoded by certain MRSA strains) [73] (Fig. 2BI). As discussed below, ADAM10 was identified as the  $\alpha$ -hemolysin's cellular receptor in several tissues [74–76]. The autophagy protein ATG16L1 and other ATG proteins are required to protect the host by inducing the release of ADAM10-containing exosomes. Through their function as decoy receptors for soluble  $\alpha$ -hemolysin, these ADAM10-containing exosomes increase the extracellular oligomerization of toxin molecules, thus preventing their binding to cell surface-expressed ADAM10 which halts detrimental pore-forming effects. Moreover, bacterial DNA and CpG DNA are potential triggers for the cellular release of ADAM10-bearing exosomes. In a murine MRSA infection model, the transfer of such exosomes ameliorates the survival of infected animals [73].

### The proteome of extracellular vesicles contains ADAM10

The cellular release of exosomes, a unique subset of EVs that are derived from the endosomal pathway, has attracted the attention of cancer research over the past few years, since exosomes have been mentioned in the context of tumor microenvironment modulation, increased invasiveness, and even chemotherapy resistance [77,78]. Because of their easy accessibility for liquid biopsy and advances in modern mass spectrometry, the analysis of exosomes holds great potential to diagnose or monitor human diseases. TNBC is a particularly aggressive tumor entity with limited treatment options. There is a lack of prognostic markers for TNBC, compared with other breast cancer subtypes. ADAM10 expression positively



correlates with the TNBC tumor grade. ADAM10 is present in cancer cell-derived exosomes, where the upregulation of ADAM10 expression increases upon disease progression [22,79,80]. Profound molecular insights into the functions of protease-bearing exosomes in human cancer remain largely elusive and require further research.

### **An increasing awareness of ADAM10's role in immune regulation, the pathophysiology of inflammatory/immune disorders and metabolic diseases**

Through the ectodomain shedding of various adhesion molecules, chemoattractants, cytokines, and receptors, ADAM10 plays a role in the regulation of both, innate and adaptive immunity, and has been implicated in the activation/suppression, lineage differentiation, intracellular signaling, and maturation of several types of immune cells. The involvement of ADAM10 in many kinds of immune disorders has been recently reviewed [17,43]. Key aspects are also summarized in Table 2 and Fig. 2B. Immunological mechanisms of overriding importance that essentially rely on ADAM10 will be briefly recapitulated (for a more detailed overview, see [81]) to enhance the understanding of more recent aspects of ADAM10's role in immune regulation.

#### **ADAM10-mediated Notch signaling is required for B- and T-cell development**

Physiological cellular differentiation of immune cells, affecting innate and adaptive immunity, largely relies on an undisrupted Notch signaling. Briefly, the binding of a Notch ligand paves the way for ADAM10-mediated ectodomain shedding of the Notch receptor. The subsequent  $\gamma$ -secretase-mediated RIP ultimately releases the Notch intracellular domain (NICD) which translocates to the nucleus, forms a complex with the transcription factor RBP-J $\kappa$ , and differentially regulates the expression of target genes [32,82,83].

ADAM10 deficiency drastically alters B-cell development, resulting in a complete loss of the marginal zone B-cell compartment (MBZ) due to a defective Notch2 signaling [84]. Interestingly, also the overexpression of ADAM10 has detrimental effects on hematopoietic processes since it results in a deletion of the whole B-cell lineage, accompanied by a myeloid expansion [82]. The maintenance of a certain expression level of ADAM10 is critical to regulate substrates such as Notch, ICOSL, CD23, and many more, which exert key functions for B-cell development and activation

[82]. In the lineage differentiation of T-cells, ADAM10-dependent Notch signaling affects the differentiation between CD4<sup>+</sup>/CD8<sup>+</sup> and  $\alpha\beta/\gamma\delta$  T-cell subpopulations [85–87]. Moreover, the activation of Notch1 on antigen-presenting cells constitutes a proliferative signal for T-cells and sustains the survival of memory T-cells (CD4<sup>+</sup>) [88,89]. Other ADAM10 substrates also regulate T-cell migration (CD44), modulate apoptosis (FASL) or serve as biomarkers for T-cell exhaustion in the microenvironment of tumors (LAG3 and TIM3) [67,90–92].

#### **Thrombocyte ADAM10 plays a central role in the regulation of immune responses**

Thrombocytes are disk-shaped, akaryote platelets in the peripheral blood that are derived from megakaryocytes in the bone marrow. Their function goes far beyond hemostatic maintenance and clot formation. By coating circulating tumor cells, supplying growth factors, and enhancing endothelial adhesion, thrombocytes make malignant cells hardly targetable for immune cells, thus increasing their survival and their ability to metastasize [93]. Interestingly, ADAM10 is among the most abundant proteins in thrombocytes and its substrate spectrum has important implications for platelet biology [94]: The glycoprotein V, a collagen receptor involved in the activation of thrombocytes, and glycoprotein VI, which exerts as part of the GPIb-IX-V complex important functions in platelet activation upon von Willebrand factor (vWF) binding, are established ADAM10 substrates [95]. A recent review outlines the great variety of confirmed and putative ADAM10 substrates on thrombocytes [96]. Platelet-derived EVs contain catalytically active ADAM10 and possibly influence immune responses, for example, in the context of rheumatoid arthritis (RA) where they aggravate joint inflammation owing to an immune reaction of synovial fibroblasts. The modulation of regulatory T-cells was likewise reported to be shaped by platelet-derived EVs. Despite a lack of knowledge with regard to precise molecular mechanisms, T-cell regulation occurs in a P-selectin-dependent manner [97,98]. Moreover, thrombocyte ADAM10 cleaves NKG2D ligands (MICA, MICB, and ULBP2) on the surface of tumor cells in trans and thus reduces their cell surface levels, which drastically impairs the ability of natural killer (NK) cells to attack malignant cells [99–101]. Apart from ADAM10-containing EVs, soluble ADAM10 or the transfer of ADAM10 from the thrombocyte cell membrane to tumor cells (trogonocytosis) may explain the increased shedding of ADAM10 substrates on the surface of

**Table 2.** Summary of ADAM10's role in immune disorders and inflammation.

Disease	Pathogenesis	Role of ADAM10	Therapeutic potential	References
Psoriasis	<ul style="list-style-type: none"> <li>Chronic inflammatory skin disease characterized by hyperproliferative lesions</li> <li>Promoted by immune response dysregulation and disrupted keratinocyte differentiation</li> <li>Regulated by EGF-, Wnt and Notch signaling</li> </ul>	<ul style="list-style-type: none"> <li>ADAM10 regulates Notch signaling: ADAM10 and subsequent <math>\gamma</math>-secretase cleavage ultimately release the transcriptionally active NICD</li> <li>Notch signaling suppresses the proliferative activity of keratinocytes</li> <li>A decreased expression of NICD-responsive genes was correlated with psoriatic lesions</li> <li>ADAM10 deficiency in keratinocytes in mice mimics the hyperproliferative phenotype of human psoriatic lesions</li> <li>Growth factors such as amphiregulin, HB-EGF and TGF<math>\alpha</math> are increased in psoriasis and their release is ADAM10-dependent</li> <li>Increased ADAM10 expression in hyperproliferative lesions</li> <li>Increased ADAM10 levels in endothelial cells and leukocytes promote leukocyte diapedesis to psoriatic lesions due to CX3CL1-shedding</li> </ul>	<ul style="list-style-type: none"> <li>Acitretin, an oral retinoid, is used for the treatment of psoriasis and induces the expression of ADAM10</li> <li>Stimulating the expression/activity of ADAM10 will be useful for the normalization of keratinocyte proliferation and differentiation</li> </ul>	[192–195]
Systemic lupus erythematosus (SLE)	<ul style="list-style-type: none"> <li>Common, multisystem organ inflammation caused by autoantibodies directed against nuclear antigens</li> <li>Antibody–antigen immune complexes form deposits in tissues that progressively lead to organ dysfunction</li> <li>The pharmacological suppression of B-cells is the primary treatment option to limit the production of autoantibodies</li> </ul>	<ul style="list-style-type: none"> <li>ADAM10 expression is increased in SLE splenocytes and ADAM10 is responsible for the shedding of Axl, TACI and fractalkine (CX3CL1)</li> <li>The Axl receptor is an important tyrosine kinase in immune regulation, its surface expression is reduced by ADAM10-mediated ectodomain shedding</li> <li>The binding of the ligand Gas6 (expressed on macrophages) to Axl triggers anti-inflammatory signaling by suppressing the NF<math>\kappa</math>B-pathway</li> <li>The reduction of Axl on the cell surface drives the progression of SLE through an increased release of pro-inflammatory cytokines (TNF<math>\alpha</math> and IL-6)</li> <li>Soluble Axl also indirectly impairs anti-inflammatory signaling since sAxl acts as a decoy receptor for Gas6</li> <li>The inhibition of ADAM10 restores the anti-inflammatory capabilities of the immune system</li> </ul>	<ul style="list-style-type: none"> <li>The current state-of-the-art therapy (systemic immunosuppressive agents) carries the burden of severe side effects, which may alter life quality</li> <li>The modulation of ADAM10 appears as a favorable therapeutic target</li> <li>The effects of ADAM10 in SLE progression seem to point at different directions, so that the role of ADAM10 in SLE is very likely to be dependent on the disease stage</li> <li>Inhibiting ADAM10 would reduce the shedding of TACI, leading to an increased T-cell-independent activation of B-cells because of a lack of the decoy receptor sTACI to bind BAFF and APRIL</li> <li>The inhibition of ADAM10 would decrease the shedding of ICOSL, increase the internalization of ICOS on T-</li> </ul>	[196–199]

**Table 2.** (Continued).

Disease	Pathogenesis	Role of ADAM10	Therapeutic potential	References
		<ul style="list-style-type: none"> <li>TACI (transmembrane activator and CAML interactor) is a member of the TNFR family that plays a key role in the regulation of B-cell homeostasis.</li> <li>The binding of ligands such as B-cell activating factor (BAFF) and a proliferation promoting ligand (APRIL) upon B-cell activation stimulate TACI and lead to prolonged mature B-cell survival</li> <li>The ADAM10-mediated generation of soluble TACI, which acts as a decoy receptor for soluble BAFF and APRIL, might prevent T-cell-independent B-cell activation and thus alleviate the progression of SLE</li> <li>ICOSL is an ADAM10 substrate on the surface of B-cells</li> <li>Impaired ectodomain shedding of ICOSL promotes the internalization of ICOS on T-cells which suppresses T helper cell maturation and subsequently reduces antibody production</li> <li>Soluble fractalkine/sCX3CL1 (generated by ADAM10) acts as a chemoattractant for immune cells and was found to be increased in SLE</li> </ul>	<ul style="list-style-type: none"> <li>cells and thus reduce antibody production</li> <li>The inhibition of ADAM10 would restore the surface levels of Axl and prevent the generation of sAxl, so that anti-inflammatory signaling could predominate</li> <li>Therapeutic potential of ADAM10 modulation in SLE needs to be studied</li> </ul>	
Bullous pemphigoid (BP)	<ul style="list-style-type: none"> <li>BP is a severe autoimmune disease that interferes with the integrity of the dermo-epidermal junction due to autoantibodies directed against collagen XVII (BP182).</li> <li>Separation of the epidermis from the dermis, accompanied by blistering.</li> <li>Pathological B-cell activation.</li> </ul>	<ul style="list-style-type: none"> <li>Semaphorin 4D, whose release from CD15+ granulocytes, is ADAM10- dependent, is elevated in BP and increases the production of anti-BP180 antibodies <i>in vitro</i></li> </ul>	<ul style="list-style-type: none"> <li>Because of the central role of semaphorin 4D and its ADAM10-dependent release from granulocytes, the pharmacological inhibition of ADAM10 possibly suppresses the production of autoreactive antibodies in BP patients</li> </ul>	[200,201]
Rheumatoid arthritis (RA)	<ul style="list-style-type: none"> <li>Chronic inflammatory disease that affects mainly synovial joints and features synovitis, cartilage loss and joint ankylosis</li> <li>RA pathogenesis is mainly driven by autoreactive antibodies directed against neoantigens,</li> </ul>	<ul style="list-style-type: none"> <li>ADAM10-mediated ectodomain shedding of JAM-A/C, CXCL16 and CX3CL1 in synovial tissues seems to be a key driver of RA disease progression: CXCL16 and CX3CL1 act as chemoattractants for immune cells after being proteolyzed</li> <li>Both, ADAM10 and CXCL16 levels, are increased in tissue</li> </ul>	<ul style="list-style-type: none"> <li>The variety of pathophysiological processes that are dependent on ADAM10 makes its inhibition a promising therapeutic target</li> <li>ADAM10 might also serve as a biomarker for the responsiveness to targeted therapies such as the anti-IL-6 receptor mab Tocilizumab,</li> </ul>	[202–206]

**Table 2.** (Continued).

Disease	Pathogenesis	Role of ADAM10	Therapeutic potential	References
	<p>derived from post-translational modifications, such as carbamylation or citrullination of peptides</p> <ul style="list-style-type: none"> <li>• A hallmark is the formation and subsequent deposition of immune complexes in articular surfaces that locally induce inflammatory responses</li> <li>• An early histological feature is an increased angiogenesis that allows excessive infiltration of immune cells to maintain inflammation</li> <li>• RA often leads to bone erosion</li> </ul>	<p>biopsies from RA patients, the two proteins co-localize on the surface of macrophages</p> <ul style="list-style-type: none"> <li>• Downregulation of ADAM10 in patient-derived fibroblasts reduces the levels of pro-inflammatory cytokines (IL-6, IL-8, and TNF<math>\alpha</math>)</li> <li>• ADAM10 exerts pro-angiogenic effects as it was found to be upregulated in endothelial cells</li> <li>• <i>In vitro</i> and <i>in vivo</i> ADAM10 knockdown decreases angiogenesis by suppressing the release of VEGF and alleviates RA symptoms</li> <li>• ADAM10 influences the activation of osteoclasts and thus constitutes an important factor for bone erosion</li> <li>• CD23, an IgE receptor on B-cells, is an ADAM10 substrate and soluble CD23 induces the release of pro-inflammatory cytokines from macrophages</li> </ul>	<p>whose therapeutic success positively correlates with the patient's expression level of ADAM10</p>	
Chronic liver inflammation	<ul style="list-style-type: none"> <li>• The chronic exposure to noxae and subsequent injury induce wound healing and inflammatory processes in the liver that result in the deposition of extracellular matrix</li> </ul>	<ul style="list-style-type: none"> <li>• The expression of bile acid transporters in hepatocytes relies on the presence (but not the catalytic activity) of ADAM10, so that bile acids accumulate in the absence of the protease</li> <li>• This chronic irritant leads to the formation of necrotic plaques and the activation of liver progenitor cells (LPC)</li> <li>• ADAM10 acts as a negative regulator of proliferative signaling in LPC and was identified as the sheddase of c-Met, the receptor for the hepatic growth factor</li> <li>• ADAM10 expression is increased during chronic liver disease and ADAM10-dependent generation of sCX3CL1 is essential for the attraction of immune cells</li> <li>• The activation of hepatic stellate cells which express both, ADAM10 and CX3CL1, on their surface plays a central role</li> </ul>	<ul style="list-style-type: none"> <li>• Liver fibrosis is a major complication of chronic liver injury and is caused by a sustained proliferation of LPC, which could be suppressed by stimulating ADAM10</li> <li>• A dysregulation of the bile acid homeostasis and other side effects must be carefully considered</li> </ul>	[135,207,208]
Atherosclerosis	<ul style="list-style-type: none"> <li>• Atherosclerosis is a common inflammatory disorder of the blood vessel wall</li> <li>• A hallmark of the disease is the pathological</li> </ul>	<ul style="list-style-type: none"> <li>• ADAM10 was found in atherosclerotic plaques and its presence influences plaque composition and stability with trends toward increased collagen</li> </ul>	<ul style="list-style-type: none"> <li>• The pharmacological inhibition of ADAM10 might enhance the plaque stability due to increased fibrosis and less inflammation</li> </ul>	[209–211]



**Table 2.** (Continued).

Disease	Pathogenesis	Role of ADAM10	Therapeutic potential	References
	deposition of lipids, foam cells and extracellular matrix that form atherosclerotic plaques	<ul style="list-style-type: none"> <li>deposition and less macrophages in the absence of ADAM10</li> <li>The protease also plays a central role in orchestrating anti-inflammatory responses, the attraction of leukocytes and the degradation of extracellular matrix</li> <li>Macrophages that lack ADAM10 reveal increased levels of IL-10, whereas TNF<math>\alpha</math>, IL-12 and nitric oxide production are decreased</li> </ul>	<ul style="list-style-type: none"> <li>The exact molecular mechanisms of ADAM10's involvement in atherosclerosis remain elusive</li> </ul>	

tumor cells [96]. Functions of ADAM0 in the regulation of the CXCR1/CX3CL1-axis, FasL, RANKL, and E-/VE-cadherin also regulate thrombocyte biology. Tetraspanin C8 family members Tspan10, Tspan15, and Tspan33 are found in thrombocytes. Tspan14 is a negative regulator of ADAM10-dependent GPVI ectodomain shedding [102,103]. A mechanistic explanation for the mentioned involvement of platelets in tumor cell migration and metastasis refers to the release of thrombin from thrombocytes or the tumor cell itself, which activates the PAR-1 receptor, increasing ADAM10 activity and the subsequent cleavage of adhesion molecules to pave the way for tumor cells to spread [104].

### ADAM10's implications in a rare and severe autoimmune disease: Pemphigus vulgaris

Pemphigus vulgaris (PV) is a rare, severe autoimmune disease driven by autoantibodies directed against the desmosomal cadherins desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1). Pemphigus is characterized by intraepithelial blistering of the skin and mucous membranes. The binding of autoantibodies to their corresponding antigens triggers signaling events that involve kinases such as p38MAPK, ERK, Src, and PLC. These events culminate in a loss of keratinocyte cell adhesion, disruption of the keratin cytoskeleton, and the internalization of adhesion proteins [105–108]. In a PV mouse model, ADAM10 impacts acantholysis, that is, a loss of intercellular connections. The modulation of downstream Src-dependent intracellular signaling pathways upon autoantibody binding was suggested as an explanation. Moreover, ADAM10-mediated suprabasal acantholysis in PV is linked to the proteolytic release of epidermal growth factor (EGF) and BTC [109]. In cell-based assays, the inhibition of ADAM10 exerts protective effects by preventing the autoantibody-induced loss of

intercellular adhesion in human keratinocytes. These results were limited to certain autoantibody profiles (antibodies against Dsg1 and Dsg3, but not Dsc3) and do not seem to hold true for every subtype of the disease [110]. ADAM10 is also involved in the direct regulation of Dsg2 turnover since it cleaves the desmosomal protein [111] (Fig. 2BIV). The inhibition of ADAM10 creates a hyperadhesive cellular phenotype, which possibly withstands mechanical stress and is less prone to develop blistering skin diseases [112]. Altogether, high Dsg3 and low Dsg1 autoantibody levels constitute a constellation where an inhibition of ADAM10 might be a favorable intervention to decelerate PV progression, even though there is still a lack of *in vivo* or even clinical data. Other autoantibody profiles have presented themselves as nonresponsive to ADAM10 inhibition [110].

### Skin homeostasis and hair follicle integrity rely on faultless ADAM10-dependent Notch signaling

Hair follicles (HF) are immunological hubs that play an important role in orchestrating immune responses in the skin and feature a very specific follicular microbiome. Bilateral interactions between the host and commensal microorganisms, as well as signaling pathways like the ADAM10-Notch axis, are crucial to maintain the physiological symbiosis of the skin [91,113] (Fig. 2BIII). The expression of ADAM10 in the upper part of HFs is indispensable to regulate the skin microbiome and to prevent the onset of inflammatory processes and the subsequent destruction of HFs together with their stem cell niche [114]. A disruption of ADAM10-dependent Notch signaling leads to an altered microbiome composition with a predominance of *Corynebacterium mastitidis*, resulting in skin dysbiosis and an impaired epithelial barrier [114]. Mechanistically, IL-7R, CCR6, and S1P1R are activated during skin dysbiosis and trigger group 2 innate

lymphoid cell-mediated (ILC2) inflammation, which ultimately culminates in pyroptosis and irreversible hair loss (alopecia). The contribution of an intact ADAM10-Notch axis to skin symbiosis and innate immunity was related to the expression of  $\beta$ -defensin-6, which is induced by type I interferon responses [114]. It should be noted that most data were obtained from mouse models, so that suggestions about clinical implications in human alopecia might seem premature, which does not reduce their relevance or translational potential, but requires further research.

### First insights into the role of ADAM10 in metabolic diseases: Diabetes mellitus type 2

Diabetes mellitus type 2 (T2DM) is among the most severe burdens to global health. Even if sufficiently treated, chronic complications are often hardly avoidable. Microvascular (neuropathy, nephropathy, retinopathy, etc.) and macrovascular (myocardial infarction, stroke, peripheral vascular disease, etc.) are concomitant diseases and characterized by a complex pathophysiology, which involves the formation of 'Advanced Glycation End Products (AGEs)' [115]. AGEs exert their detrimental effects, for example, by binding to a multiligand receptor belonging to the immunoglobulin superfamily (RAGE), which results in increased cell proliferation, migration, altered gene expression and overall pro-inflammatory intracellular signaling [116]. RAGE exists as a cell surface receptor or as a soluble form (sRAGE), which can be generated either by alternative splicing or by proteolytic cleavage of the membrane-bound form. Since sRAGE acts as a decoy receptor for AGEs and thus prevents their binding to cell surface RAGE with its detrimental downstream effects, details about the generation of sRAGE and possible use as a biomarker in diabetes patients are of great clinical interest. RAGE undergoes ADAM10-mediated ectodomain shedding [117] (Fig. 2CII). ADAM10 might therefore serve as a predictive marker for sRAGE levels in diabetes patients [117]. A recent study analyzing T2DM patients suffering from acute coronary syndrome (ACS, a macrovascular complication of T2DM) found lower sRAGE serum levels and a decreased expression of ADAM10, compared with T2DM patients without ACS. It was also demonstrated that the proteolytic release of the membrane-bound RAGE, and not alternative splicing, accounts for the vast majority of sRAGE in patient-derived sera. A reduced expression of ADAM10 in peripheral blood mononuclear cells is causative for the reduced sRAGE levels in patients with ACS and statistical analysis proved sRAGE levels and ADAM10

expression as sensitive and specific markers for ACS among T2DM patients. A poor control of blood sugar levels in T2DM patients was also associated with lower sRAGE levels, so that an interplay between the glycemic status and the expression of ADAM10 is an interesting topic of research [118].

### ADAM10 regulates the expression of the antiaging protein Klotho

Klotho is considered an important antiaging protein as its deficiency in mice leads to a premature aging phenotype including atherosclerosis, cardiac hypertrophy, osteoporosis, and cognitive decline [119]. The beneficial effects of Klotho that consist, that is, in an increased life span and an ameliorated resistance to oxidative stress are causally linked to its synthesis in the kidney and the subsequent proteolytic release of a soluble Klotho extracellular domain (sKlotho) into the circulation [120,121]. Based on cell culture studies including inhibitor and siRNA experiments, ADAM10 and ADAM17 were revealed as sheddases of Klotho [122]. Interestingly, insulin increased the shedding of Klotho by the two ADAM proteases in a PI3K-dependent manner, leaving the ADAM10/17 mRNA and protein levels unchanged arguing for their increased availability and activity at the plasma membrane [122]. Insulin initiates intracellular signaling events that also result in an increased trafficking of ADAM10/17 to the cell surface and/or a stimulation of their proteolytic activity. An impaired phosphorylation of the insulin receptor substrate (IRS) upon Klotho's influence was reported [123]. This in turn leads to a disruption of the signaling events downstream of the insulin receptor (PI3K and Akt activation). However, the exact mechanism how proteolytically generated Klotho fragments modulate insulin signaling remains an interest of ongoing research.

Interestingly, a recent study substantiates the central importance of the kidney as the main source of soluble Klotho and reports about a renal Calcium-sensing receptor (CaSR)-ADAM10-Klotho axis as a key physiologic pathway to regulate levels of soluble Klotho. CaSR, Klotho, and ADAM10 co-localize in the mouse distal convoluted tubule (DCT) and the activation of the CaSR by calcium, allosteric activators or alkaline pH augments ADAM10-mediated shedding of membrane-bound Klotho. Based on experiments using the ADAM10 inhibitor GI254023X and ADAM10-specific siRNA, ADAM10 turned out to be the major Klotho sheddase, whereas siRNA directed against ADAM17-mRNA had no effect on the cleavage of

Klotho [124]. These findings partially contrast with other studies, so that further research is required to elucidate the distinct functions of the closely related ADAM family members regarding the proteolytic generation of soluble Klotho.

### ADAM10 as a 'receptor protease' in bacterial infections

An exciting and already briefly mentioned aspect of ADAM10 biology has been first reported in 2010 where the protease was described as a receptor for the best understood bacterial virulence factor, the pore-forming  $\alpha$ -hemolysin (H1 $\alpha$ ) toxin from *Staphylococcus aureus* [125]. *S. aureus* infections are clinically relevant and frequently observed in sepsis, pneumonia, and severe skin infection in human patients. ADAM10 was identified as an interacting protein in a biochemical approach using binding analysis to recombinant H1 $\alpha$ , followed by mass spectroscopy as a readout [125]. On account of siRNA experiments, it could be shown that ADAM10 is required for the  $\alpha$ -hemolysin cytotoxicity, which was explained by an impact of the  $\alpha$ -hemolysin complex on integrin signaling and subsequent disruption of focal adhesions [125]. This study could be extended by presenting evidence that conditional ADAM10 knockout mice, with a deletion of the protease in lung epithelial cells, are resistant toward *S. aureus*-induced lethal pneumonia. Mechanistically, this was explained by a  $\alpha$ -hemolysin triggered upregulation of ADAM10 expression in alveolar epithelial cells and an increased ectodomain shedding of E-cadherin. This leads to a defective barrier, enabling massive bacterial invasion [126]. *S. aureus* infection also induces the expression of the G-protein-coupled platelet-activating-factor receptor, which triggers an activation of ADAM10 leading to shedding and activation of pro heparin-binding epidermal growth factor [127]. ADAM10 acts as a  $\alpha$ -hemolysin receptor at the plasma membrane, together with tetraspanin 33 which binds cytosolic pleckstrin homology domain-containing, family A member 7 (PLEKHA7). This complex allows the clustering of ADAM10 at adherens junctions leading to  $\alpha$ -hemolysin-induced pore formation [128].

### ADAM10 in viral infections

A specific type of infection is mediated by viruses and also here ADAM proteases and more specifically ADAM10 plays a role. This is not completely surprising, since many viruses require binding to cell surface proteins followed by endocytosis. Many viruses also

express some of their viral gene products at the surface of the host cell and also here the modulation of the cell surface protein configuration by ectodomain shedding is of potential relevance. An example for the shedding of proteins, which viruses use to enter cells, is the angiotensin-converting enzyme 2 (ACE2), serving as a receptor for coronaviruses. ACE2 is shed from human airway epithelia, and both ADAM17 and ADAM10 have been implicated in the ACE2 cleavage (Fig. 2BII). In part, this is dependent on induction by calcium ions and phorbol ester activation of kinases and endotoxins. Interestingly, soluble ACE2 partially inhibited virus entry into target cells [129]. More recent work implicated the collectrin-like extracellular, membrane proximal part of ACE2 to be essential for this shedding event [130]. Jocher *et al.* [131] also reported that both ADAM10 and ADAM17 are implicated in SARS-CoV-2 cell entry and spike protein-mediated lung cell fusion. Here, ADAM10 was found more important as a host factor for lung cell syncytia formation, whereas ADAM17 served as a facilitator of virus entry. *In vitro* both proteases are able to cleave the spike protein of SARS-CoV2. Importantly, an inhibition of both ADAM proteases reduced SARS-CoV2 infection of primary human lung cells [131] making both ADAMs attractive targets for antiviral therapies. In an independent study, it was confirmed that ADAM10 and ADAM17 play distinct roles in SARS-CoV-2 infection [85]. In experiments using small interfering RNAs (siRNAs) and ADAM10/17 selective inhibitors, a contribution of ADAM10 for a metalloproteinase-dependent entry of SARS-CoV-2 was revealed. It was suggested—despite a lack of a clear mechanistic explanation—that furin and metalloproteinases, including ADAM10, are essential for the spread of the virus and disease development [85].

Interestingly, myeloid-expressed ADAM10 protects against influenza virus infection and pneumonia [132] and ADAM10 was suggested as a therapeutic target. In earlier studies and based on ADAM10 silencing experiments in human monocyte-derived macrophages and CD4<sup>+</sup> cell lines, an involvement of ADAM10 in human immunodeficiency virus type-1 replication was suggested [133,134]. Overexpression of ADAM10 increased HIV-1 replication. The mechanisms of how ADAM10 exerts these effects were not revealed in both studies [133,134], but it was suggested to occur before nuclear entry of HIV-1 [134].

### ADAM10 and myocardial infarction

Inflammatory processes and infiltrating leucocytes also play a central role in the pathology of myocardial

infarction, which represents a major cause of cardiac death. An involvement of ADAM10 in leucocyte recruitment has been appreciated some time ago. Here, the CX3C chemokine fractalkine (CX3CL1) appears of central importance. CX3CL1 mediates cell–cell adhesion, and after ectodomain shedding, it can also act as a soluble protein mediating chemotaxis. ADAM10 inhibition, overexpression, and experiments using ADAM10-deficient cells confirmed that the constitutive cleavage of the chemokine regulates adhesion and detachment of monocytic cells [135]. Targeting cytokines and chemokines after myocardial infarction to reduce leucocyte infiltration has turned out as an attractive, but side-effect-prone, preclinical approach [136]. The idea to reduce CX3CL1 levels to affect leucocyte recruitment in cardiac tissue after myocardial infarction was recently addressed by Klapproth and coworkers [136] (Fig. 2CI). They could demonstrate that the expression of the CX3CL1 sheddase ADAM10 is increased already early on in patients with ischemic cardiomyopathy. Administration by mini-pumps for 14 days, but also for only 3 days, of the ADAM10 inhibitor GI254023X in mice that underwent an experimental infarction revealed a therapeutic potential, that is, an improved survival and augmented cardiac function after ADAM10 inhibition [136]. The inhibition of the protease caused decreased CX3CL1 serum levels and a reduced neutrophil recruitment postinfarction. Importantly, the findings were also confirmed in a conditional knockout of ADAM10, where the protease was specifically deleted in cardiomyocytes. In the conditional knockout mice, a protection from ischemic injury was observed [136]. The authors speculate that modulating the ADAM10/CX3CL1 axis may also be useful in short-term therapeutic interventions, aiming to reduce scar size and improve cardiac function after infarction [136]. Importantly, reducing ADAM10-mediated shedding of CX3CL1 may also be beneficial for other injury-induced diseases with a harmful leucocyte infiltration and inflammation. As a note of caution, it cannot be excluded that also other cardiomyocyte- or immune cell-specific ADAM10 substrates or/and modifiers contribute—next to CX3CL1—to the pathology in myocardial infarction and future research will address these open questions.

## ADAM10 in neurodegeneration and neurological disorders

The pivotal role of ADAM10 in the development and homeostasis of the central nervous system has been underlined following the in-depth analysis of

conditional ADAM10 knockout mice with a brain-specific deletion of the protease at different time points [11,137]. A variety of neuronal ADAM10 substrates such as the APP, the cellular prion protein, neuroligin, NCAM, nectin 1, LRP1, L1, ephrin-A2 and ephrin-A5, and N-cadherin, to name only a few, have been identified [138]. Physiological brain functions in development and network regulation have been linked to ADAM10 such as neuron vs. glia cell decisions, synaptic plasticity and learning, synaptogenesis, axon formation, neuronal differentiation, and neurite outgrowth. It is therefore not surprising that dysregulated ADAM10 is also involved in neurological diseases and neurodegeneration [16] as it has been observed in prion disease, AD, autism, bipolar disorders, and fragile X-syndrome (reviewed in [16]).

An interesting example for the involvement of ADAM10 in a neurological disease is Huntington's Disease, a fatal neurodegenerative disorder. A modified huntingtin gene with an expansion of CAG repeats to translate into elongated polyglutamine amino acid residues is responsible for disease development. Among other functions, huntingtin can affect neurulation through the homotypic interaction between neuroepithelial cells. It was suggested that huntingtin decreased ADAM10 activity and the ectodomain shedding of N-cadherin. ADAM10 inhibition led to a rescue of the neural tube developmental defect in huntingtin knockdown zebrafish [139]. In this study, ADAM10 was proposed as a new target in the treatment of HD. ADAM10 was later also recommended as a target of interest in HD since it has an essential function in the connectivity of synapses. In HD patients and mouse models, an increased expression and activity of ADAM10 toward N-cadherin at synaptic sites was found, which was linked to excitatory synapse loss and cognitive dysfunction [140]. The data of this study suggested that targeting, that is, inhibition of ADAM10 by different means can be neuroprotective in HD [140]. The disease-causing role of ADAM10 at HD synapses was further investigated in molecular detail by Cozzolino and coworkers [141]. Using proteomics of immunoprecipitated ADAM10 derived from the striatum of wild-type vs HD knockin mice, endogenous ADAM10 interactors were identified. Interestingly, many presynaptic proteins were revealed as interactors and active ADAM10 was increased at the presynaptic terminal in HD mice [141]. As the most interesting ADAM10 interactor, piccolo (PCLO), a large protein at the active zone involved in synaptic vesicle organization, was identified. In the HD brain, a defective synaptic function is caused by the mutated huntingtin acting on the



formation of a functional ADAM10/PCLO complex within the presynaptic site [141]. This causes an altered distribution of synaptic vesicles and synaptic transmission. It remains open if ADAM10 has a dual role in HD at pre- and postsynaptic sites through modulation of N-cadherin shedding and formation of the ADAM10/PCLO complex. Targeting of ADAM10 seems to be, however, still a very attractive approach to normalize synaptic function in HD disease models and maybe at some point in HD patients.

### Pharmacological modulation of ADAM10 and its suitability as a drug target

From the description of ADAM10's involvement in various human diseases, the modulation of the protease evidently emerges as a therapeutic option. However, the question whether an inhibition or an increase in ADAM10's activity is a favorable therapeutic approach varies drastically between different pathophysiological conditions, so that the value of an ADAM10 modulation must be carefully considered. It should be noted that most efforts to pharmacologically exploit the modulation of ADAM10 have been made around AD to increase the nonamyloidogenic  $\alpha$ -secretase activity and thus reduce the production of plaque forming, neurotoxic A $\beta$ -species (Tables 3 and 4). In general, proteases are difficult therapeutic targets since their individual modulation (activation or inhibition) may affect a large number of substrates and even other proteases (and their respective substrates) embedded in a specific protease network. Despite these hesitations, it may well be suitable that under certain topic administration or within a well-defined therapeutic window protease modulation will avoid unwanted side effects. As pointed out in this review, it may also well be that targeting ADAM10 modulators such as tetraspanins is a better strategy to modulate ADAM10 in a substrate-specific way.

Overall, ADAM10 inhibitors (Table 4) can be assigned to the following categories: small molecules, including the dominant group of hydroxamate inhibitors, inhibitory antibodies as well as natural compounds. The mode of action of hydroxamate inhibitors, like the first-generation inhibitor GI254023X, is the chelation of Zn<sup>2+</sup> ions in ADAM10's active site [142]. Being still in use for cell-based or mouse model experiments, the application of GI254023X in humans would raise the problem of insufficient selectivity (ADAM17, MMP 2/9 are also targets) making it prone to unwanted off-target effects. Moreover, related hydroxamate compounds failed in clinical trials resulting in

their discontinuation in phase I/II due to hepatotoxic effects and/or a lack of efficacy when administered systemically as it was pointed out by previous reviews [142–145]. Despite these problems, the development of hydroxamate inhibitors continued in search of selectivity and came up with some new, improved candidates. INCB3619 has been tested in tumor xenograft models where it revealed some promising effects and INCB7839 presented itself as a promising alternative to first-generation inhibitors because of the absence of severe side effects in preliminary results obtained from breast cancer patients. Even though these new substances exclude a broad spectrum of MMPs from their inhibitory spectrum, they still do not meet the goal to distinguish between the close homologue family members ADAM10 and ADAM17 [146,147]. Furthermore, it should be noted that INCB3619, despite excluding many MMPs from its target spectrum, inhibits MMP2 and MMP12 at low IC<sub>50</sub> values [146], which does not exclude the risk for off-target effects (e.g., musculoskeletal) at therapeutic doses in humans even if such effects were not observed in mice. INCB8765 and LT4 are next-generation substances that feature an improved ADAM10 specificity, at least *in cellula* [144,148,149]. However, it needs to be considered that INCB8765, despite its advantage in efficiently excluding MMPs from its inhibitory spectrum, only presents a 20-fold difference in IC<sub>50</sub> values for ADAM10 and ADAM17, which is a rather poor difference in selectivity compared with the 'classical' ADAM10 inhibitor GI254023X that displays a 100-fold difference in favor for a more selective inhibition of ADAM10 [147].

Apart from the mentioned classical hydroxamate inhibitors, the murine monoclonal inhibitory antibody 8C7 (mAb 8C7) has been designed to target ADAM10's substrate-binding cleft, making it sterically inaccessible for putative shedding substrates (described for the Eph-A/Ephrin complex) [150]. Interestingly, 8C7 selectively targets cancer stem cells binding to an activated conformation of ADAM10 that is particularly present on malignant cells. 8C7 inhibits Notch activation and the ectodomain shedding of various cell surface receptors in a mouse model for colorectal cancer without exhibiting any dose-limiting toxicity [151]. 8C7-based drug conjugates containing cytotoxic agents were designed to selectively kill tumor cells overexpressing an active ADAM10 conformer [152]. Recently, the generation of a novel, fully human anti-ADAM10 monoclonal antibody (1H5) targeting the protease outside of its catalytic domain was reported. The antibody binds to the cysteine-rich substrate-binding domain and recognizes ADAM10 in an activated conformation on the surface of malignant cells, comparable to mAb

**Table 3.** Modulation of ADAM10's expression, activity, and maturation. Information was obtained from [clinicaltrials.gov](https://clinicaltrials.gov).

Substance	Molecular mechanism	Disease context	Clinical trial status
<i>ADAM10 expression</i>	The expression of ADAM10 is positively regulated by a retinoid acid receptor (RAR) which is part of the ADAM10 promotor. The binding of retinoid acids to the RAR induces the formation of a RAR/RXR heterodimer that binds to the DNA [18,193,212]		
Am80 (Tamibarotene)	As a synthetic retinoid acid, Am80 directly binds to the RAR with a high selectivity for RAR $\alpha$ / $\beta$ , thereby preventing unwanted side effects [213]	AD	Phase 2 (NCT01120002) Approved drug in Japan to treat promyelocytic leukemia
Acitretin	Indirect stimulation of the RAR through a competitive interaction with retinoid acid binding proteins to increase the release of bound retinoid acids, which in turn stimulates the RAR and subsequently ADAM10 expression. Acitretin has the ability to penetrate the blood–brain barrier [214,215]	AD	Phase 2 (NCT01078168) Approved for psoriasis treatment
Resveratrol	Sirtuin 1 (Sirt1) is a deacetylase that promotes the transcription of ADAM10 in a RAR $\beta$ -dependent manner. Sirt1 induces the deacetylation of RAR $\beta$ , thus abrogating the inhibition of RAR $\beta$ [216]	AD	Phase 2 (NCT01504854)
Fibrates (Gemfibrozil)	Peroxisome proliferator-activated receptors (PPARs) also interact with RXR and the PPAR $\alpha$ /RXR heterodimer induces the expression of ADAM10. Gemfibrozil is a PPAR $\alpha$ agonist that also decreases cholesterol levels, which is thought of as beneficial for ADAM10 activation [19,217]	AD	
Pholganantholide C	Diterpene lactone that increases ADAM10 expression through an unknown mechanism [218]		
<i>ADAM10 maturation and activity</i>			
(–)-epigallocatechin-3-gallat (EGCG)	EGCG from green tea was reported to enhance ADAM10 maturation and activity <i>in cellula</i> [219]. The EGCG-induced increase in the nonamyloidogenic APP processing relies on two independent mechanisms. An estrogen receptor $\alpha$ (ER $\alpha$ )/PI3K/Akt involving mechanism as well as an upregulation of furin in a MAPK/ERK-dependent manner was suggested. These observations can be linked to the postmenopausal increased AD risk due to a depletion of physiological estrogens [220]	AD	Phase 2/3 (NCT00951834)
Etazolate	The pyrazolopyridine etazolate displays anxiolytic effects due to its selective agonism at the GABA $_A$ receptor and increases ADAM10's $\alpha$ -secretase activity toward APP. These effects are neither transcriptional nor related to maturation [221]	AD	Phase 2 (NCT00880412)
Bryostatin-1	Bryostatin-1 is a protein kinase c (PKC) agonist downstream of the G-protein-coupled mACh receptor. Promoting acetylcholin signaling is beneficial for the treatment of AD. However, direct M1 agonists display severe systemic side effects due to a parasympathetic overstimulation. The direct activation of PKC increases ADAM10 activity with less unwanted side effects [222,223]	AD	Phase 1/2 (NCT02221947)
PACAP	Pituitary adenylate-cyclase-activating polypeptides (PACAP) stimulate the PACAP type 1 receptor (PAC1) and enhance ADAM10 activity. Their poor bioavailability upon systemic administration can be avoided by an intranasal administration [214,224]		

8C7's mode of action. Using the 1H5 antibody, Notch shedding and Notch-dependent proliferation were suppressed in colon cancer cell lines and in an *in vivo* mouse model. The combination with the classic cytostatic drug Irinotecan revealed an outstandingly effective attenuation of tumor growth (> 80% growth inhibition), thus presenting a promising finding that bears translational potential [153]. Remarkably, 1H5

was hypothesized to selectively inhibit oncogenic Notch signaling, as cell-based studies revealed no effect on the cleavage of APP, highlighting the great potential in the search for selectivity that lays within the research on ADAM10's substrate-binding domains [153]. Another innovative approach to target tumor cells that overexpress members of the ADAM family was perused by generating a bispecific single-chain

**Table 4.** Pharmacological ADAM10 inhibition.

ADAM10 inhibitor	Substance class	Molecular mechanism	Comments
GI254023X	Synthetic, Hydroxamate	ADAM10/ADAM17 active site inhibitor	100-fold more potent inhibitor for ADAM10 than for ADAM17, discontinued clinical trials for related hydroxamate compounds due to hepatotoxic effects, insufficient selectivity (targets MMP2 and MMP9)
INCB3619		ADAM10/ADAM17 active site inhibitor	Improved selectivity for ADAM proteases, ADAM17-inhibition-related side effects
INCB7839		ADAM10/ADAM17 active site inhibitor	
INCB8765		ADAM10/ADAM17 active site inhibitor	Specificity for ADAM10 over ADAM17 and MMPs
LT4		ADAM10 active site inhibitor	
mAb 8C7	Murine monoclonal antibody	Steric inaccessibility of the substrate-binding cleft	Best characterized for the Eph-A/Ephrin complex, targets an activated ADAM10 conformation on malignant cells
mAb 1H5	Human monoclonal antibody	Similar epitope and mode of action as mAb 8C7	Inhibits oncogenic Notch signaling in a substrate-selective manner and targets and activated ADAM10 conformation on malignant cells
Rapamycin (Sirolimus)	Natural, macrolide	Inhibited maturation – overall, not fully understood	Clinically widespread and well-established
Triptolide	Natural, diterpenoid epoxide	Enhances ADAM10 degradation by metalloproteinases – overall, mechanism not fully understood	Used to treat ADAM10-related pathologies like RA or SLE in traditional Chinese medicine

antibody directed against ADAM17 and CD3, which induces the lysis of PCa cells in a T-cell-dependent manner [154]. Such antibodies belong to the class of bispecific T-cell engager antibodies (BiTEs) that on the one hand target tumor-cell-specific cell surface proteins and on the other hand bind/activate CD3 to attract cytotoxic T-cells [155,156]. Since there are various tumor entities that overexpress ADAM10, the generation of a bispecific antibody for ADAM10 and, for example, CD3 using an ADAM10-specific single-chain variable fragment (scFv) fused to a CD3-specific scFv might be of clinical interest.

Another option to achieve a specific inhibition of ADAM10 is the use of its prodomain. Recombinant murine ADAM10 prodomain is a potent and selective competitive inhibitor of the human protease that leaves other ADAM family members as well as MMPs unaffected [157]. The effector mechanism of a prodomain-mediated metalloproteinase inhibition was initially described for MMPs. Here, a ‘cysteine switch’ was suggested involving the replacement of zinc-bound water by cysteine residues in the protease’s active center [158]. However, the ADAM10 prodomain seems to act through a distinct mechanism since the introduction of a mutation leading to an exchange of cysteine to serine does not affect its inhibitory potency [157]. Interestingly, for the close family member ADAM17 a novel bispecific recombinant fusion protein was developed that consists of the protease’s inhibitory

prodomain and an EGFR-targeting/inhibiting protein in order to achieve an enrichment of the compound in EGFR-positive cells, for example, in EGFR overexpressing cancer cells [159]. A similar approach may be attractive for an inhibition of ADAM10 to direct ADAM10 inhibitors conjugated with other compounds to a specific subset of cells that overexpress a certain cancer-associated protein on their cell surface.

Alongside toxicity and limited selectivity of small molecule compounds, a major problem of the systemic application of ADAM10 inhibitors, to possibly prevent them from being translated into the clinic, is caused by the partially opposing biological functions of ADAM10 substrates. To overcome this obstacle, research efforts were made to identify novel ADAM10 inhibitors that display a to date unique substrate-selective inhibition. These exosite modulators target ADAM10 beyond its active site by addressing secondary substrate-binding sites (exosite) in a nonzinc binding manner [160]. Different ADAM10 substrates interact with distinct subsets of exosites determining a specific substrate-exosite interaction. A recent review discusses the lead compound of this new group (CID 3117694) as a substrate-selective competitive ADAM10 inhibitor with potentially low *in vivo* off-target toxicity. A glycosylated TNF $\alpha$ -based exosite binding substrate was used to identify new nonzinc chelating inhibitors of ADAM10. It was hypothesized that the inhibitory selectivity of CID 3117694 is determined by

a competition with the carbohydrate moieties of glycosylated ADAM10 substrates, preventing their binding and subsequent shedding, whereas nonglycosylated substrate variants are unaffected. However, the glycosylation status of many identified ADAM10 substrates and the possibly altered glycosylation patterns in disease states remain largely elusive to date so that more research is required to achieve selectivity and to avoid toxic off-target effects [161].

A clinically already well-established immunosuppressant, the mTOR inhibitor Rapamycin (Sirolimus), also displays ADAM10 inhibitory effects [162]. Another natural compound that was found to inhibit ADAM10 in terms of a downregulated expression (probably an increased degradation) is the diterpenoid epoxide triptolide that is already in use for the treatment of ADAM10-related pathologies such as RA or systemic lupus erythematosus (SLE) in traditional Chinese medicine [163]. Further naturally occurring and well-established ADAM10 inhibitors are found within the family of tissue inhibitors of MMPs (TIMPs) or the class of secreted Frizzled-related proteins (Sfrps). TIMPs were originally described as endogenous inhibitors of MMPs. They are now considered to be in control of diverse metalloproteinases, among them ADAM family members, regulating their proteolytic activity. TIMPs play a central role in the onset of many hallmarks of cancer, their expression profile correlates with the prognosis of certain tumor entities, and they have been shown to regulate signaling pathways what raised a substantial research interest for this group of proteins [164]. While TIMP-1 displays inhibitory effects on ADAM10 activity *in vitro*, it leaves its close homologue ADAM17 unaffected indicating its high specificity and affinity to ADAM10. These differences can most likely be explained by structural differences between the two proteases. The differing susceptibility to TIMP-1 can be used to distinguish ADAM10 and ADAM17 in cell-based experiments, whereas both proteases were reported to be prone to TIMP-3-mediated inhibition. [165].

Sfrps form a family of secreted proteins that possess two domains. Their C-terminal domain contains a netrin-related motif (NTR) that is also found in the TIMPs. Due to their homology to the extracellular domain of the Fzd receptor, the function of Sfrps was originally attributed to their capability to bind and sequester Wnt ligands making them potent inhibitors of Wnt signaling [166]. However, a Wnt-independent role of Sfrps, for example, in the regulation of Notch signaling was demonstrated. Srfp1 can bind and down-regulate the activity of ADAM10. Sfrps should bind

to the cysteine-rich motif of ADAM10 bringing the Sfrp-NTR domain close to the protease's catalytic center so that Srfp1 and Srfp2 most likely inhibit ADAM10 by competing for substrate binding. The inhibition of Srfp1 is a potential mechanism to enhance the nonamyloidogenic  $\alpha$ -secretase activity of ADAM10 in order to decrease the production and subsequent accumulation of the neurotoxic A $\beta$  species in AD. The role of Srfp1 and Srfp2 was extensively studied in the context of impaired retinal neurogenesis of mouse embryos that were deficient for the two proteins leading to an upregulated Notch signaling. This is due to the lack of the Srfp1/Srfp2-mediated ADAM10 inhibition and could be partially rescued using pharmacological ADAM10 inhibitors [167]. The transmembrane protein reversion-inducing cysteine-rich protein with kazal motifs (RECK) also exerts a potent inhibitory effect on ADAM10 through a to date poorly characterized mechanism [168,169].

Owing to the biological diversity of ADAM10-mediated mechanisms in the human body, one should always carefully consider the time point and duration of delivery as well as the option of local targeting of ADAM10. This might include the local application of compounds (e.g., via inhalation), coupling them to implanted materials, for example, stents or fusing them with suitable membrane linkers to exclusively target them to the cell surface.

## Conclusions

ADAM10 emerged as one of the most important proteases with specific cell surface protein-modulating activity. Expression, localization, and activity of ADAM10 are tightly regulated, and any dysfunction may be associated with its contribution in different types of diseases. It is still largely unexplored if ADAM10 is, from a therapeutic perspective, a suitable drug target. The ubiquitous expression, its localization in cells and EVs as well as its broad spectrum of substrates will most likely represent a challenge for the clinical use of ADAM10-modulating drugs. We also rely on future research to better understand ADAM10's regulation and proteins interfering with its function.

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## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

DR and PS made the concept of this review. Both wrote and edited the review. DR designed the figures and tables.

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