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Review article

ADAM10 isoforms: Optimizing usage of antibodies based on protein regulation, structural features, biological activity and clinical relevance to Alzheimer's disease

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ABSTRACT

A Disintegrin and Metalloproteinase 10 (ADAM10) is a crucial transmembrane protein involved in diverse cellular processes, including cell adhesion, migration, and proteolysis. ADAM10's ability to cleave over 100 substrates underscores its significance in physiological and pathological contexts, particularly in Alzheimer's disease (AD). This review comprehensively examines ADAM10's multifaceted roles, highlighting its critical function in the non-amyloidogenic processing of the amyloid precursor protein (APP), which mitigates amyloid beta (Aβ) production, a critical factor in AD development. We summarize the regulation of ADAM10 at multiple levels: transcriptional, translational, and post-translational, revealing the complexity and responsiveness of its expression to various cellular signals. A standardized nomenclature for ADAM10 isoforms is proposed to improve clarity and consistency in research, facilitating better comparison and replication of findings across studies. We address the challenges in detecting ADAM10 isoforms using antibodies, advocating for standardized detection protocols to resolve discrepancies in results from different biological matrices. By highlighting these issues, this review underscores the potential of ADAM10 as a biomarker for early diagnosis and a therapeutic target in AD. By consolidating current knowledge on ADAM10's regulation and function, we aim to provide insights that will guide future research and therapeutic strategies in the AD context.

1. Introduction

A Disintegrin and Metalloproteinase 10 (ADAM10) is a transmembrane protein essential to diverse cellular processes including cell adhesion, migration, and proteolysis (Rosenbaum and Saftig, 2023). However, ADAM10's proteolytic activity extends beyond shedding, encompassing cell adhesion, migration, and proliferation modulation, thereby influencing fundamental cellular behaviors (Seals and Courtneidge, 2003). Dysregulation of ADAM10 activity has been implicated in various pathological conditions, including cancer, inflammatory disorders, and Alzheimer's disease (AD), highlighting its potential as a therapeutic target (Alexandre-Silva and Cominetti, 2024).

Regarding AD, ADAM10 has garnered significant interest for its role as an α-secretase in the non-amyloidogenic processing of the amyloid

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precursor protein (APP) (Lammich et al., 1999). This function potentially mitigates the excessive production of the amyloid beta (Aβ) peptide, a critical factor in developing the disease. Apart from mitigating Aβ production, this non-amyloidogenic cleavage of APP generates a molecule designated sAPPα, which has neurotrophic and neuroprotective effects (Chasseigneaux and Allinquant, 2012). Therefore, ADAM10-mediated shedding regulates synaptic plasticity, neurotransmission, and neuronal survival, implicating its involvement in learning, memory, and neurodegenerative disorders (Rosenbaum and Saftig, 2023).

As a multimodular protein, ADAM10 has distinct domains (Fig. 1). Typically, its amino-terminal (N-terminal) end has a pro-domain (PRO), followed by a metalloproteinase (MTP) domain responsible for catalytic activity. Adjacent to this is the disintegrin domain (DIS), which aids cell adhesion and signaling by interacting with integrins. Further downstream, a cysteine-rich domain (CYS) is located, which contributes to protein-protein interactions and ligand binding. The transmembrane domain (TM) anchors the protein within the cell membrane, and the cytoplasmic tail (CYT) modulates intracellular signaling. This multifaceted structure is essential to ADAM10's participation in the diverse cellular processes mentioned above (Saftig and Lichtenthaler, 2015).

Here, we present a comprehensive review shedding light on

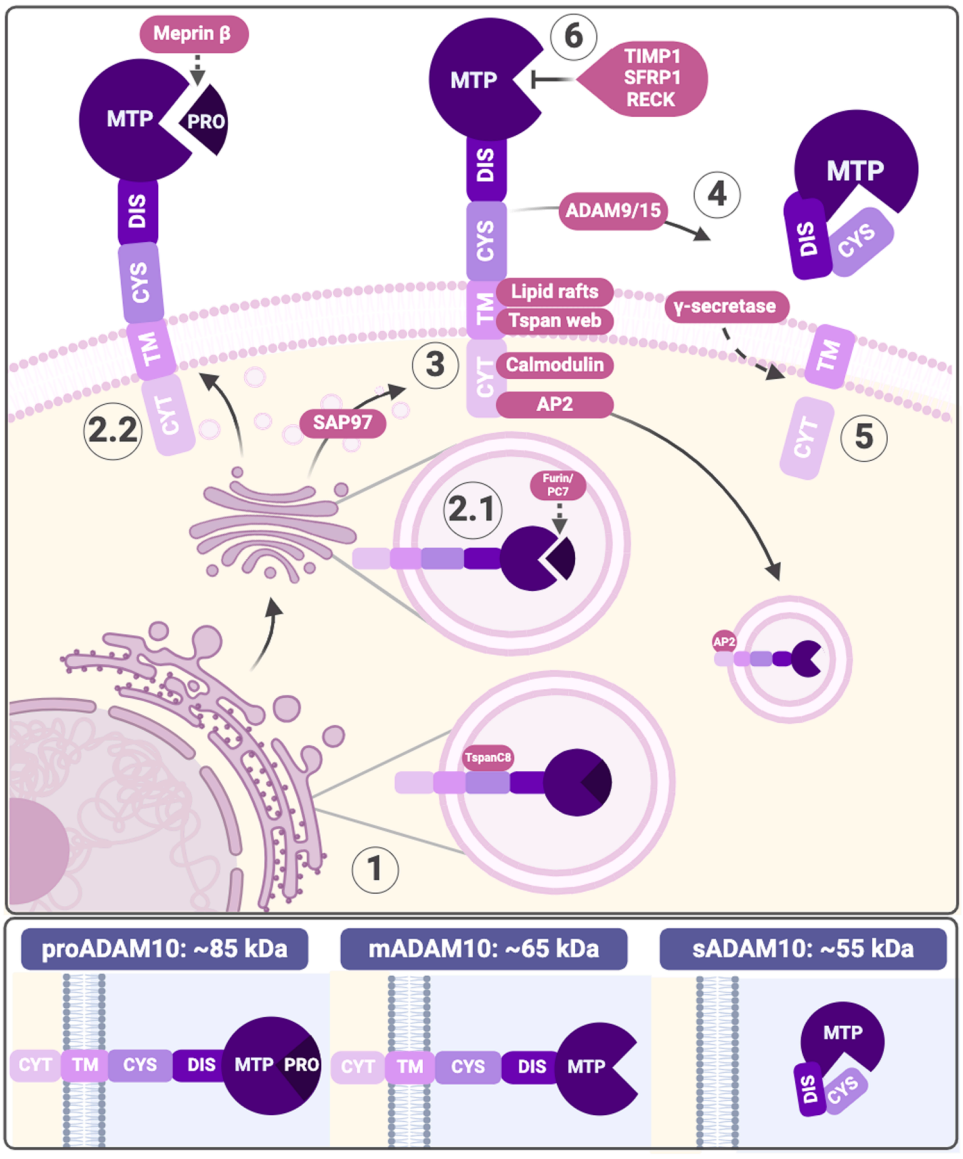

Fig. 1. Upper panel: ADAM10 secretory route to the plasma membrane. (1) After gene transcription, ADAM10 mRNA is processed and translated into a protein in the rough endoplasmic reticulum (ER). TspanC8 mediates its release from this organelle. (2.1) The protein is transported to the Golgi apparatus in its zymogen form and undergoes further modifications, including glycosylation. In this organelle, the inactive ADAM10 zymogen becomes active when its prodomain is cleaved by proprotein convertases such as furin and PC7. (2.2) Immature ADAM10 can also be inserted into the plasma membrane and only then have its pro-domain cleaved by meprin β (3). In neurons, ADAM10 is transported to the cell surface through an interaction with the synapse-associated protein 97 (SAP97). At the plasma membrane, mature ADAM10 (mADAM10) functions as a sheddase, cleaving and releasing the ectodomains of various membrane-bound proteins. Many proteins and lipids interact with the protease and regulate ADAM10's localization and activity at this stage, including the Tspan web, calmodulin, AP2 and lipid rafts. (4) ADAM10 itself can be cleaved by other ADAMs (9 and 15), releasing a soluble form with an autoinhibited conformation in which the cysteine-rich domain masks the active site. (5) The C-terminal fragment that is left is cleaved by γ-secretases, and the cytoplasmic tail is addressed to the nucleus to function as a transcription factor. (6) ADAM10 also possesses endogenous inhibitors, such as TIMP1, SFRP and RECK proteins. Lower panel: ADAM10 isoforms and their respective molecular masses and insertion at the membrane. CYT: cytoplasmic tail; TM: transmembrane domain; CYS: cysteine-rich domain; DIS: disintegrin domain; MTP: metalloproteinase domain; PRO: prodomain. Domains are out of scale. Figure created with BioRender software, publication license: QT272H97ON.

ADAM10's multifaceted roles, deciphering its regulation in several aspects, from gene expression to exosomal release. We will focus particularly on its clinical relevance in AD. We also aim to propose a standardized vocabulary for describing the ADAM10 isoforms, mainly based on their relevance as potential AD biomarkers. This proposed nomenclature will provide greater clarity and consistency in the scientific community's reports on ADAM10, which can have implications for theranostic approaches in future AD research.

Lastly, we will also discuss the experimental aspects concerning the utilization of specific antibodies for detecting ADAM10 isoforms. Given some inconsistencies in results related to ADAM10 detection using particular antibodies in different biological matrices, our review aims to address these issues to clarify discrepancies and support future research. Therefore, this review will assist in understanding the diverse findings reported in the literature regarding detecting ADAM10 in the context of AD.

2. ADAM10 expression and regulation

As a protease in the cell membrane, ADAM10 plays a fundamental role in regulating intercellular communication processes. Therefore, its amounts must be precisely regulated at the transcriptional, epigenetic, translational, and post-translational levels. This extensive regulation ensures a response to immediate disturbances in function and gradual changes associated with aging or specific phases of its maturation (Endres and Deller, 2017). We will initially describe several potential mechanisms of ADAM10 regulation to provide a coherent rationale for the argument proposed in this review.

2.1. Transcriptional regulation

In humans, the ADAM10 gene comprises six exons located on chromosome 15. Nucleotides −508 to −300 have been identified as the core promoter region (Prinzen et al., 2005). ADAM10 expression can be upregulated or downregulated by various factors, which will be summarized in this section (Prinzen et al., 2005; Saftig and Lichtenthaler, 2015).

2.1.1. Retinoic acid pathway

Retinoic acid (RA) is a lipophilic molecule synthesized from vitamin A and is recognized as an inducer of the human ADAM10 promoter activity (Prinzen et al., 2005). The isomers all-trans (atRA) or 9-cis (RA) retinoic acid bind to their respective nuclear receptors, Retinoic Acid Receptor (RAR) and Retinoic X Receptor (RXR). These complexes then interact with RA-responsive elements (RARE) in the ADAM10 promoter region, recruit co-activators, and trigger transcription (Tippmann et al., 2009). Sirtuin 1 (SIRT1), a NAD-dependent deacetylase with anti-aging and anti-stress properties, has been described as a co-activator in RA-mediated ADAM10 expression by promoting deacetylation and subsequent activation of the RAR receptor (Lee et al., 2014; Zhang et al., 2020). The stimulation of ADAM10 expression induced by RA is associated with increased sAPPα secretion and reduced Aβ production, both *in vitro* and *in vivo* (Endres et al., 2014; Koryakina et al., 2009; Reinhardt et al., 2014).

2.1.2. Other transcriptional regulators

The X-box binding protein (XBP)-1 transcription factor has been identified as an efficient regulator for increasing ADAM10 expression (Reinhardt et al., 2014). XBP-1 acts as a transcriptional regulator activated by inositol-requiring enzyme 1 (IRE1), an endoplasmic reticulum (ER)-stress sensor specifically involved in the unfolded protein response (UPR). Deregulation of this transcription factor has been observed in persons living with AD (Reinhardt et al., 2014).

The activation of N-methyl-D-aspartate (NMDA)-type glutamatergic receptors plays crucial roles in modulating ADAM10 expression, leading to increased ADAM10 mRNA and protein levels via a Wnt/extracellular signal-regulated kinase (ERK)1/2/β-catenin signaling pathway in mouse primary cortical neurons (Wan et al., 2012).

On the other hand, the T-box family member 2 (TBX2) acts as a transcriptional repressor, reducing ADAM10 expression in SH-SY5Y cells. The repression is mediated by two functional TBX2 binding sites within the ADAM10 core promoter sequence. Analysis of cortical brain samples from AD patients, which showed reduced ADAM10 mRNA levels, revealed a 2.5-fold increase in TBX2 levels, while TBX3 and TBX21 levels remained unaffected (Reinhardt et al., 2019).

2.1.3. Hormonal regulation

Studies have demonstrated the significant impact of hormonal regulation on ADAM10 transcriptional activity. Melatonin regulates various physiological functions, such as circadian rhythm, antioxidant activity, and neuroprotection (Shukla et al., 2017). This hormone can activate the −1193/-555 region of the human ADAM10 promoter through its receptors on the plasma membrane and ERK phosphorylation. This leads to elevated levels of ADAM10 mRNA and protein, increased ADAM10 catalytic activity and production of sAPPα, favoring the non-amyloidogenic pathway of APP processing in neuronal and non-neuronal cells (Nopparat et al., 2022; Panmanee et al., 2015; Shukla et al., 2020). In aged mice, melatonin upregulates ADAM10 expression in the hippocampus by increasing SIRT1, a key regulator of ADAM10 transcription (Mukda et al., 2016).

Although understanding epigenetic modifications affecting ADAM10 expression remains limited, evidence suggests a potential regulatory role for methylation processes (Endres and Deller, 2017). SIRT1 has been identified to increase ADAM10 expression and is involved in histone deacetylation and methylation, promoter CpG island methylation, and inactivation of non-histone transcription factors (Lim et al., 2024; Zhang and Kraus, 2010). Melatonin can increase deacetylase levels in primary neurons in an *in vitro* neuronal aging model (Tajes et al., 2009). Thus, the observed induction of ADAM10 by melatonin may also be related to deacetylase activation (Panmanee et al., 2015; Shukla et al., 2020). This interplay of various regulatory mechanisms underscores the complexity of ADAM10 expression regulation and its responsiveness to diverse signaling cues in different cellular contexts.

2.2. Translational regulation

Human ADAM10 mRNA is 4.4 kb in size, with a nucleotide sequence that features an unusually GC-rich 5'-untranslated region (5'-UTR) (Lammich et al., 2010). Within this region, a motif spanning nucleotides 66–94 forms a parallel and intramolecular G-quadruplex secondary structure stabilized by potassium ions (Lammich et al., 2011). This motif likely promotes translational repression by inhibiting the formation of initiation complexes (Vincent, 2016). Moreover, mRNA production can be regulated by binding proteins, microRNAs (miRNAs), and circular RNAs (circRNAs).

2.2.1. Regulation by proteins

Translational inhibition by the 5'-UTR can be modulated by protein binding, such as fragile-X mental retardation protein (FMRP), which is implicated in the development of Fragile X syndrome (Lammich et al., 2011; Pasciuto et al., 2015). This interaction disrupts the G-quadruplex secondary structure, affecting translational regulation and leading to the ADAM10 upregulation (Pasciuto et al., 2015). A similar upregulation effect can be induced by neuronal embryonic lethal abnormal Vision (nELAV) RNA-binding protein, which regulates gene expression in memory formation (Amadio et al., 2009). The putative binding site of nELAV is a conserved AU-rich element (ARE) motif in the 3'-UTR of ADAM10 mRNA. Furthermore, $A\beta_{1-42}$ treatment reduces nELAV levels in the SH-SY5Y cells (Amadio et al., 2009).

ADAM10 translational regulation can also occur by the binding of kenpaullone (KEN) to its 5′UTR. KEN is a small molecule that targets serine hydroxymethyltransferase (SHMT2). This interaction mediates

KEN-induced ADAM10 translation *in vitro* and *in vivo*, alleviating amyloidogenesis in APP/PS1 mice (Song et al., 2024).

2.2.2. Regulation by miRNAs

The translation of ADAM10 is tightly regulated by miRNAs, which serve as crucial "gatekeepers" of ADAM10 expression (Vincent, 2016). MiRNAs are short, non-coding RNA molecules typically consisting of around 22 nucleotides capable of regulating gene expression at the post-transcriptional level (Bartel and Chen, 2004). The interaction of miRNA and target mRNA requires base pairing between the miRNA seed sequence (positions 2–8) at the 5′ end and a sequence most frequently found in the 3′-UTR of the target mRNA (Augustin et al., 2012).

Many miRNAs have been studied and found to be involved with regulating ADAM10. These miRNAs play pivotal roles in numerous aspects of neuronal function, facilitating neurite outgrowth, orchestrating the development of dendritic spines, promoting neurogenesis in specific brain domains, and regulating the differentiation of human neurons in the central nervous system (CNS) (Cheng et al., 2013).

Computational strategies and experimental validation proposed potential miRNAs regulating ADAM10 expression. It was shown that miR-144 and miR-122 can bind to ADAM10 mRNA, reducing this protein's levels upon overexpression (Bai et al., 2009; Cheng et al., 2013). Three miRNAs (miR-103, miR-107, and miR-1306), identified as associated with AD, were found to have conserved binding sites for ADAM10 across different species. These three miRNAs exhibited notable inhibitory effects on ADAM10 expression levels in SH-SY5Y cells (Augustin et al., 2012). Additionally, the upregulation of miR-144 and miR-451 in SH-SY5Y cells results in elevated $A\beta_{1-42}$ levels (Cheng et al., 2013).

Moreover, miR-144 exhibits increased expression in the cortex of individuals with AD (Persengiev et al., 2011). In contrast, miR-107 expression is reduced in the initial phases of AD, and computational analysis suggests its potential role as a suppressor of the β-site amyloid precursor protein cleaving enzyme 1 (BACE1) (Wang et al., 2008). MiR-221 is another potential regulator of ADAM10, as its overexpression in SH-SY5Y cells reduced ADAM10 protein levels, whereas its inhibition increased these levels (Manzine et al., 2018).

2.2.3. Regulation by circular RNAs (circRNAs)

A new class of non-coding RNAs, circular RNAs (circRNAs), has been identified as regulators of miRNA activity. They are circular single-stranded RNA molecules, lacking 5' and 3' ends due to forming a covalent bond after the transcription (Memczak et al., 2013). It has been shown that some circRNAs regulate ADAM10 translation by acting as molecular sponges for specific miRNAs. For instance, it has been reported that circ_0006867 regulates oxidized low-density lipoprotein (ox-LDL)-induced endothelial injury by acting as a molecular sponge of miR-499a-3p, leading to changes in the downstream target gene ADAM10, affecting cell apoptosis and migration in the context of atherosclerosis (Hong et al., 2023).

2.3. Post-translational regulation

Due to its crucial role as a molecular scissor, ADAM10 also undergoes various post-translational regulatory processes that encompass its expression in an inactive pro-form, endoplasmic reticulum (ER) retention, trafficking, activation by prodomain removal at the Golgi apparatus, position at the plasma membrane, and cleavage by other ADAMs (Fig. 1).

2.3.1. Maturation

Proteins belonging to the ADAM family commonly undergo glycosylation. This significant post-translational modification process alters newly synthesized proteins by adding high-mannose and complex-type glycan groups. This modification facilitates proper folding and regulates protein quality within the ER. The glycosylation sites feature a conserved amino acid sequence motif NXS/T, in which X cannot be proline. ADAM10 possesses four glycosylation motifs: ^{267}NIS, ^{278}NTT, and ^{439}NIS at the metalloprotease domain and ^{551}NFT at the disintegrin domain (Escrevente et al., 2008) (Fig. 2). Incorporating high-mannose, hybrid, and complex-type N-linked glycans contributes approximately 9 kDa to the ADAM10 mature form. Studies on bovine ADAM10 suggest potential roles for these motifs. For instance, ^{278}NTT prevents ER accumulation, aiding ADAM10 processing and likely facilitating its correct folding through interaction with the chaperone calnexin. Additionally, ^{439}NIS safeguards ADAM10 from proteolysis (Escrevente et al., 2008).

An inherent structural mechanism within ADAM10 itself might govern its trafficking through the secretory pathway and surface expression. Within its carboxy-terminal (C-terminal) tail, ADAM10 possesses a three-arginine motif (^{723}RRR) that facilitates a rate-limiting step in its release from the ER. It has been demonstrated that the second arginine within this motif is adequate for retaining ADAM10 within the ER. This mechanism is shared by other transmembrane proteins, such as ADAM12 and 22, to prevent the release of faulty proteins and regulate protein maturation (Marcello et al., 2010). The bond of a protein called tetraspanin C8 (TspanC8) with ADAM10 (discussed further) likely masks this arginine motif through steric effects exerted by the polypeptide chain. This regulation mechanism ensures that only functional proteins are released from the ER (Teasdale and Jackson, 1996).

After being released from the ER, ADAM10 transitions to the Golgi compartment in its proenzyme form (Fig. 1). This latency of ADAM10 is facilitated by its pro-domain, which utilizes a cysteine residue conserved within the ADAM family to occupy the active site, coordinating the zinc ion at the metalloprotease domain. This regulation type is called the "cysteine switch," a well-known activation mechanism used by the members of the matrix metalloproteinases (Van Wart and Birkedal-Hansen, 1990). The ADAM10 pro-domain prevents inappropriate activities and aids in proper ADAM10 folding, functioning in a chaperone-like manner (Fahrenholz et al., 2000).

In the trans-Golgi compartment, cleavage of the ADAM10 pro-domain is mediated by proprotein convertases (PCs), like furin and PC7. Within the ADAM proteins, a conserved RXXR motif is recognized by PCs for cleavage, typically positioned at the boundary between the pro-domain and catalytic domain (Fig. 2). In ADAM10 specifically, this motif is located at ^{210}RKKR, and there is an additional motif at ^{48}RAKR position (upstream to the PC cleavage region). Interestingly, only the pro-domain cleavage at the upstream PC motif (^{48}RAKR) generates an active, mature ADAM10 at the cell surface. Mutations in this domain impair ADAM10's function as a sheddase. However, the PC consensus motif (^{210}RKKR) is not required for ADAM10 maturation (Anders et al., 2001; Wong et al., 2015). Eventually, immature ADAM10 can undergo pro-domain cleavage by meprin β upon reaching the plasma membrane. This zinc-dependent metalloprotease cleaves the pro-domain through the interaction site at residues ^{198}QEE of ADAM10 (Jefferson et al., 2013; Wichert et al., 2019) (Fig. 2).

Interestingly, there are notable exceptions to these regulatory mechanisms. For instance, the predominant isoform identified in colon tumor tissues was the ADAM10 zymogen (proADAM10), which unexpectedly exhibited activity (Atapattu et al., 2016). The proADAM10 showed a higher affinity for the anti-ADAM10 monoclonal antibody (mAb) 8C7 in these cells compared to mature ADAM10 (mADAM10). This interaction is likely mediated by the CXXC motif (^{594}CHVCC), also present in ADAM17 (Atapattu et al., 2016). The mAb 8C7 interacts explicitly with the cysteine-rich region within ADAM10 that binds to the Ephrin A (EphA) receptor (Janes et al., 2005), an ADAM10 substrate (Atapattu et al., 2012). Therefore, the interaction between the anti-ADAM10 mAb 8C7 and proADAM10 suggests that this region is not occluded by the pro-domain as anticipated. This indicates that proADAM10 may undergo conformational changes through the potential rearrangement of disulfide bonds in its cysteine residues under oxidative conditions, such as those found in tumor environments, thus activating this isoform (Atapattu et al., 2016). Moreover, this finding implies that,

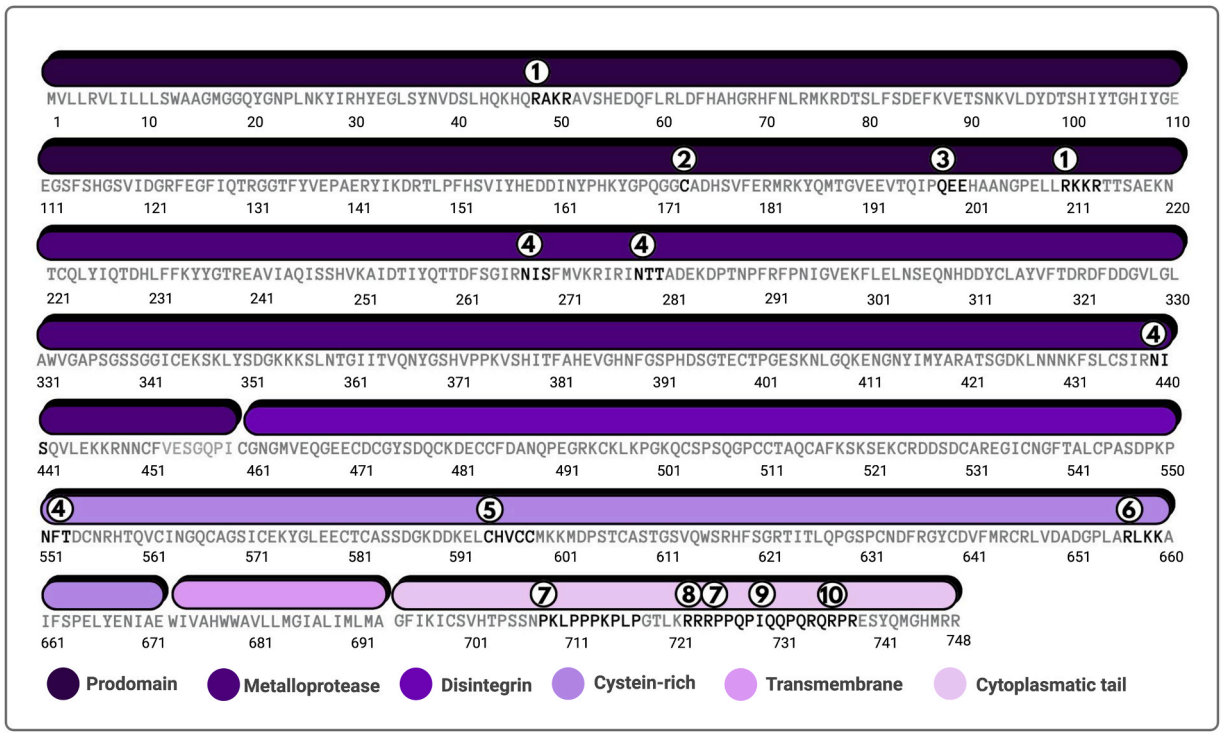

Fig. 2. ADAM10 motifs involved in post-translational regulatory processes: (1) PC cleavage site. (2) cysteine-switch. (3) Meprin β cleavage site. (4) Glycosylation sites. (5) Thioredoxin motif. (6) PS binding site. (7) SH3 binding site. (8) ER retention motif. (9) Calmodulin binding site. (10) AP2 binding site. The numbers below each amino acid represent their order sequence. Figure created with BioRender software, publication license: CR26VLQ78I.

depending on the tissue, ADAM10 processing may not be essential for its functionality.

The observation of immature ADAM10 at the plasma membrane (Atapattu et al., 2016) and its maturation solely through the cleavage upstream to the PC motif prompted the proposal of two cleavage mechanisms involving the ADAM10 pro-domain. In the first mechanism, cleavage upstream of the PC motif releases mature ADAM10 (Wong et al., 2015). The second mechanism proposes that after cleavage, the pro-domain continues interacting with the active site region of ADAM10's ectodomain through intermolecular interactions. This interaction results in an unstable intermediate complex between ADAM10 and its pro-domain. In this scenario, ADAM10 maturation occurs through interaction with meprin β at the cell surface (Wichert et al., 2019; Wong et al., 2015). The hypothesis of the second mechanism is supported by the observation that the isolated pro-domain selectively interacts with its corresponding mature ADAM10, leading to protease inhibition (Moss et al., 2007).

2.3.2. *Localization and binding partners*

Following its synthesis and release from the ER, ADAM10 undergoes trafficking along the secretory pathway (Fig. 1), with its localization regulated by various factors. Notably, ADAM10 has two proline-rich stretches in its C-terminal tail, located at positions ^{708}PKLPPPKPLP and ^{722}RRRPPQP, that can be characterized as binding motifs for Src homology 3 (SH3) domain-containing signaling molecules (Ebsen et al., 2014; Kleino et al., 2015; Wild-Bode et al., 2006). These SH3 domains, typically comprising 50–70 amino acid residues, specifically recognize proline-rich sequences within target proteins and are commonly found in eukaryotic signal transduction and cytoskeletal proteins (Kay et al., 2000).

2.3.2.1. Interaction with lipids. Once positioned at the membrane, ADAM10 can interact with different partners. The literature extensively addresses the interplay of cell membrane changes, phosphatidylserine (PS) exposure, insertion, and proteolytic activity of ADAM10. Besides previously shown processes, motifs present in the membrane-proximal region of ADAM10 (^{648}VDADGPLARLKKAIFSP) can bind to PS liposomes (Dusterhoft et al., 2015). Changes to these residues (^{657}R/^{659}K/^{660}K) markedly reduce this protein's activity despite its mature isoform on the cell surface. These data indicate that surface-exposed PS can control the biological function of ADAM10 (Bleibaum et al., 2019).

The scramblase-dependent externalization of the negatively charged PS also plays an essential role in the ADAM10 activation regulation (Reiss et al., 2022). PS is typically confined to the inner leaflet of the plasma membrane in healthy cells. However, in response to certain stimuli or cellular signaling events, scramblases can facilitate the translocation of PS from the inner to the outer leaflet of the membrane. Once PS is exposed on the outer leaflet of the membrane, it serves as a docking site for ADAM10, promoting its interaction and subsequent activation. This activation process may involve conformational changes in ADAM10, enabling it to cleave its substrates or undergo shedding from the membrane (Bleibaum et al., 2019; Reiss et al., 2022). Accordingly, deficient PS externalization is linked to dysregulation of ADAM10 shedding activity in naked mole-rat fibroblasts (Urriola-Munoz et al., 2023). The involvement of Anoctamin-6 (ANO-6), a scramblase proficient in translocating PS from the inner to the outer membrane, underscores the critical role of PS surface exposure for the sheddase activity of ADAM10 and ADAM17 (Leitzke et al., 2022).

Cholesterol levels were also shown to regulate ADAM10 levels. Cholesterol-rich lipid rafts retain a minor fraction of the proADAM10. When cholesterol is depleted, ADAM10 moves out of these rafts, increasing α-secretase activity and promoting non-amyloidogenic APP processing. Conversely, high cholesterol levels reduce this activity by

keeping ADAM10 in the lipid rafts, thereby regulating its maturation and transport in the secretory pathway (Kojro et al., 2001). Accordingly, targeting ADAM10 to lipid rafts in neuroblastoma SH-SY5Y cells using a glycosylphosphatidylinositol (GPI) anchor reduces amyloidogenic processing of APP. This targeted ADAM10 competes with β-secretase for APP within lipid rafts, lowering Aβ production (Harris et al., 2009).

2.3.2.2. Interaction with proteins. Other interactions between ADAM10 and specific interaction partners were identified by interactome analyses. Most potential protein partners interacting with ADAM10 through the SH3 region are non-receptor tyrosine kinases and adaptor proteins involved in membrane localization, trafficking, and endo- and exocytosis. Among the putative interactors of ADAM10 are endophilins, zinc finger DHHC-type palmitoyl transferase 6 (ZDHHC6), the Grb2 family, sorting nexins, and protein kinase C and casein kinase substrate in neurons (PACSINs) (Ebsen et al., 2014; Kleino et al., 2015). Interestingly, the ADAM10 motif at positions ^{708}PKLPPPKPLP contains two essential amino acids that deviate from the commonly observed di-hydrophobic residues in proline-rich motifs (^{716}LP) (Fig. 2) (Wild-Bode et al., 2006). However, ADAM10's SH3-binding motif does not exhibit high selectivity toward any specific SH3 domain, unlike observed patterns in other members of the ADAM family (Kleino et al., 2015).

Another ADAM10 partner, the synapse-associated protein 97 (SAP97), was identified in hippocampal neurons, specifically at postsynaptic density (PSD) where it is involved in the trafficking of ionotropic glutamate receptors (iGluRs). SAP97 is a protein that binds to ADAM10 through its SH3 motif, facilitating its trafficking to the postsynaptic membrane after NMDA receptor activation (Marcello et al., 2007). Consequently, SAP97 positively modulates ADAM10 activity, resulting in increased sAPPα release. Furthermore, SAP97 is crucial in trafficking ADAM10 to the postsynaptic membrane, particularly upon long-term depression (LTD) induction, when ADAM10 activity contributes to spine remodeling (Marcello et al., 2013). Protein kinase C (PKC) phosphorylation of the SAP97 SH3 domain is essential for ADAM10 trafficking from the Golgi outposts to the synapse (Saraceno et al., 2014). Notably, in the hippocampus of individuals with AD, an impairment in the binding capacity of SAP97 and a reduction of PKC-dependent SAP97 phosphorylation were observed, limiting its ability to bind to ADAM10 and, thereby affecting its synaptic localization (Marcello et al., 2012; Saraceno et al., 2014). As proof of concept of the relevance of ADAM10 trafficking in AD, blocking SAP97-mediated ADAM10 trafficking allows the reproduction of initial phases of sporadic AD (Epis et al., 2010) Interestingly, the motif ^{708}PKLPPPKPLP (Fig. 2) proved to be sufficient to promote the localization of ADAM10 to the basolateral membrane under conditions of cell-cell contact, thereby enabling it to facilitate E-cadherin processing in madin-darby canine kidney (MDCK) cells (Wild-Bode et al., 2006). However, further studies must determine how the two proline-rich motifs may influence ADAM10 activity and localization differently.

Tetraspanins (Tspans) are also recognized ADAM10 partners. Tspans constitute a superfamily characterized by four distinct transmembrane regions arranged in a conical structure, creating a cavity where a cholesterol-binding pocket capable of inducing conformational changes can be observed (Zimmerman et al., 2016). These four-pass integral membrane proteins are vital in regulating ADAM10 in the membrane (please see session 2.3.6).

2.3.3. Endo and exocytosis processes

ADAM10 endo- and exocytosis processes have also been proposed as physiological mechanisms of negative regulatory impact on protease activity. An excess of substrate or the inactivation of ADAM10 led to a reduction in its levels on the cell surface. This regulation occurs through synthetic and physiological inhibitors but not in inactive ADAM10 cell mutants. In the absence of inhibitors, surface levels of ADAM10 were restored (Seifert et al., 2021). The effect of ADAM10 loss on the surface was coincident with its accumulation in extracellular vesicles. Furthermore, the internalization and degradation of these inhibited ADAM10 molecules in lysosomes were also shown to be involved. The endocytosis inhibitor prevented the induced downregulation while blocking acidification prevented the decrease in total mature ADAM10 in the cell lysates (Seifert et al., 2021).

ADAM10 activity can be modulated through exosome production, particularly during bacterial infections. Crucially, the infection led to the release of ADAM10 on exosomes, likely as a protective response mechanism (Aljohmani et al., 2022; Keller et al., 2020). Moreover, the engagement of the β-2 adrenergic receptor (β2AR) on primed B cells increased ADAM10 expression and promoted its localization to exosomes (Padro et al., 2013).

Regarding ADAM10 endocytosis, this process was dynamin-dependent in human embryonic kidney (HEK) cells. Dynamin plays a critical role in endocytic membrane fission events; thus, inhibiting internalization by a nonfunctional dynamin mutant led to increased levels of mature ADAM10 at the cell surface, while immature ADAM10 accumulated intracellularly (Carey et al., 2011). Additionally, this inhibition potentiated the generation of the ADAM10 C-terminal fragment (CTF), suggesting that under conditions of endocytosis-regulated inhibition, ADAM10 may undergo regulation through proteolysis (as discussed below). This implies that modulation of internalization could serve as a regulatory mechanism for ADAM10 (Carey et al., 2011).

Indeed, at synapses, ADAM10 endocytosis is facilitated by the clathrin adapter protein AP2, a heterotetrameric assembly complex that allows the formation of clathrin-coated pits. This interaction promotes ADAM10 downregulation and is part of a bidirectional mechanism that counteracts SAP97-induced ADAM10 membrane exposure (Marcello et al., 2013). The interaction with AP2 occurs through the C-terminal end of ADAM10 at position ^{735}RQR (Fig. 2), where two arginine residues have been demonstrated to be crucial. This motif does not overlap with the SH3 motif responsible for SAP97 interaction, indicating that, despite promoting opposing mechanisms, there is no competition between SAP97 and AP2 for ADAM10 binding.

Furthermore, unlike SAP97, ADAM10-AP2-dependent endocytosis was upregulated by Long Term Potentiation (LTP). Thus, the bidirectional mechanism for regulating ADAM10 localization involves clathrin-dependent endocytosis and trafficking by SAP97 and is modulated by synaptic plasticity in hippocampal cells (Marcello et al., 2013). Short-term exposure to Aβ oligomers reduces the interaction between ADAM10 and AP2 (Marcello et al., 2019), which is increased in the hippocampus of AD patients despite the unchanged protein levels. This observation was mainly associated with early and sporadic AD (Marcello et al., 2013).

2.3.4. Proteolysis of ADAM10

As part of its regulatory processes that occur by changing the location of ADAM10, it was observed that the protease undergoes cleavage mediated by other ADAMs, specifically ADAM9 and ADAM15, in a process called regulated intramembrane proteolysis (RIP). This cleavage generates the already mentioned soluble ectodomain of ADAM10, with approximately 55 kDa (sADAM10), and the cell-bound ADAM10 CTF (Moss et al., 2011; Shackleton et al., 2017; Tousseyn et al., 2009). Interestingly, these cleavage events appear to occur through distinct mechanisms; cleavage by ADAM9 leads to an accumulation of cell-bound C-terminal ADAM10, whereas ADAM15 does not. However, the mechanisms underlying these cleavages have not yet been fully elucidated. Furthermore, other intricate mechanisms governing ADAM10 regulation ensure that the absence of ADAM9 and ADAM15 does not lead to full ADAM10 accumulation. Notably, even in the absence of ADAM9 and ADAM15, ADAM10 cleavage was observed in specific tissues (Tousseyn et al., 2009), suggesting the involvement of additional mechanisms.

Furthermore, like its substrates, the ADAM10 CTF undergoes RIP by

the γ-secretase complex, which includes presenilin 1 (PS1) and presenilin 2 (PS2). The PS1 gene has been identified as prevalent for processing in mouse brain and lung tissues, while the PS2 gene predominates in liver tissue. The liberation of the ADAM10 CTF fragment via γ-secretase cleavage suggests a potential role for ADAM10 in controlling gene transcription. However, further investigations are necessary to elucidate the possible functions of these two ADAM10 fragments released through cleavage and RIP processes (Tousseyn et al., 2009).

Supporting this notion, proA9, an inhibitor of ADAM9 corresponding to its prodomain (24−204), increases membrane-bound ADAM10 and promotes the cleavage of various substrates, including APP, epidermal growth factor (EGF), human epidermal growth factor receptor 2 (HER2), osteoactivin, and CD40 ligand (Moss et al., 2011). However, a proteomic assay conducted in chondrocyte-like cells showed that silencing ADAM15 did not significantly alter membrane levels of ADAM10 (Calligaris et al., 2023). This suggests that although ADAM15 functions as a protease acting on ADAM10, its shedding can be compensated by other regulatory mechanisms, which may involve other proteases. This highlights the need for future studies to understand these mechanisms better and identify novel proteases that target ADAM10 as a substrate (Tousseyn et al., 2009).

2.3.5. *Autoregulation*

The crystal structure of the ADAM10 ectodomain reveals an autoregulatory mechanism. In the resolved structure, the catalytic site is partially obscured by the C-terminus of the cysteine-rich domain, forming an "arrowhead"-like conformation (Seegar and Blacklow, 2019). This mechanism prevents inappropriate activity of the ADAM10 ectodomain after proteolytic release into the extracellular environment. Additionally, the crystal structure of the ADAM10-Tspan15 complex demonstrates that this ectodomain conformation is also present in mature ADAM10 at the cell surface, potentially serving as a mechanism to limit access to the catalytic site and allowing for substrate selectivity by partners such as TspanC8 (Lipper et al., 2023). This notion is supported by the observation that the disintegrin and cysteine-rich domains exert an inhibitory effect on well-known ADAM10 substrates, such as Notch and APP (Seegar et al., 2017), likely due to regions of interaction with TspanC8, as previously demonstrated (Noy et al., 2016) (discussed further).

2.3.6. *Substrate selectivity*

In addition, to facilitate the release of ADAM10 from the ER, Tspans are recognized as the primary partners that regulate the substrate selectivity of this protease and provide it with a platform on the membrane through their nanodomains (Harrison et al., 2021; Matthews et al., 2017; van Deventer et al., 2021) since ADAM10 is not predominantly found in lipid rafts (Kojro et al., 2001).

In addition to the transmembrane domains, Tspans possess two extracellular loops of different sizes: a large extracellular loop (LEL) containing the Cys–Cys–Gly motif and a small extracellular loop (SEL) (Harrison et al., 2021). Four, six, or eight cysteine residues facilitate the formation of disulfide bonds, stabilizing the LEL and conferring flexibility, enabling it to adopt several crucial conformations for binding various partners (Charrin et al., 2014; Oosterheert et al., 2020). Additionally, Tspans have N- and C-terminal regions as intracellular tails (Zimmerman et al., 2016).

Polar amino acids, conserved in the transmembrane region of tetraspanins, are stabilized by hydrogen bonds between polar residues. This characteristic allows these proteins to form extensive interaction networks, creating nanodomains with other partners, such as ADAM10. Consequently, this forms a platform capable of temporally and spatially influencing its components (Charrin et al., 2014; Matthews et al., 2017; van Deventer et al., 2021). These interactions lead to "tetraspanin networks", which play pivotal roles in intracellular trafficking, function, lateral mobility, and clustering of associated molecules on the cell surface. Joint partners of tetraspanins include integrins, immunoreceptors, signaling molecules, cell adhesion proteins, growth factors, cytokine receptors, and membrane-embedded enzymes such as metalloproteases (van Deventer et al., 2021; Yanez-Mo et al., 2009).

Specifically, a subset of six Tspans, known as TspanC8, distinguished by the presence of eight cysteine residues in the LEL region (including Tspan5, Tspan10, Tspan14, Tspan15, Tspan17, and Tspan33), interacts directly with ADAM10 (Haining et al., 2012; Noy et al., 2016; Prox et al., 2012). Notably, TspanC8 exhibits specificity for ADAM10, as its expression does not affect the levels of ADAM17 (Dornier et al., 2012).

The interaction between the TspanC8 family and ADAM10 initiates at the ER, facilitating the exit of ADAM10 from this cellular compartment (Dornier et al., 2012; Prox et al., 2012). Although Tspan10 and Tspan17 promote the exit of ADAM10 from the ER, they do not induce the accumulation of ADAM10 at the cell surface, underscoring their importance in the intracellular redistribution of ADAM10 (Dornier et al., 2012; Noy et al., 2016). Experiments demonstrated that the interaction between TspanC8 and ADAM10 occurs through distinct molecular mechanisms (Noy et al., 2016). Regions of the TspanC8 LEL mediate this interaction. Specifically, the 26-amino acid stalk region of ADAM10, located at the membrane-proximal region after the cysteine-rich domain, is sufficient for interaction with Tspan15. In contrast, the stalk and cysteine-rich domains are required for interaction with Tspan14, Tspan10, and Tspan17. However, the interaction with the latter is destabilized by the disintegrin domain of the protease. Tspan5 and Tspan33 do not interact with the stalk, but they do with the cysteine-rich and disintegrin domains (Noy et al., 2016).

The different complexes between ADAM10 and TspanC8 facilitate the diversification and regulation of substrates to be cleaved, promoting the cleavage of some substrates while inhibiting others. Tspan15 emerges as ADAM10's primary partner in the N-Cadherin cleavage (Prox et al., 2012; Seipold et al., 2018). However, in conjunction with Tspan33, it acts as a negative regulator of ligand-induced Notch activity (Jouannet et al., 2016). Conversely, Tspan5 and Tspan14 are activators of the Notch signaling (Harrison et al., 2021). The regulation of TspanC8 over ADAM10 is also influenced by its distinct distribution in various cell types. While Tspan5 and Tspan14 exhibit higher expression in precursor oligodendrocytes, astrocytes, and neurons, Tspan15 is predominantly expressed in myelinating oligodendrocytes, where Tspan33 is absent (Matthews et al., 2017; Zhang et al., 2014).

To understand how TspanC8 can influence ADAM10 activity, a recent study elucidated the structure of a complex between ADAM10 and Tspan15 (Lipper et al., 2023). In this structure, the authors observed that the ADAM10 ectodomain adopts an open conformation induced by the interaction with the Tspan15 LEL through two interfaces. The first interface, necessary for interaction between proteins, occurs in a loop region conserved among members of TspanC8 that binds to the cysteine-rich domain of ADAM10. The second occurs in another loop region (distinct from TspanC8) that interacts with the catalytic domain of ADAM10, which is not crucial for complex formation. This last interface determines the diverse selectivity of ADAM10 for substrates (Lipper et al., 2023). Variation in this region between different TspanC8 molecules results in distinct distances between the membrane and the catalytic site, effectively acting as a gauge, allowing only a certain length of amino acids to enter. This experiment elucidates why ADAM10 substrates, such as GVPI and N-Cadherin, positioned 5 and 12 amino acid residues from the membrane, respectively, are cleaved by Tspan14 and Tspan15 (Lipper et al., 2023; Matthews et al., 2017; Reiss et al., 2005). These findings underscore the six-scissors concept, indicating that different TspanC8 molecules induce ADAM10 to adopt various conformations, allowing it to target different substrates (Matthews et al., 2017).

Moreover, two other tetraspanins, Tspan3 and Tspan12, belonging to the TspanC6 subgroup, seem to influence ADAM10 maturation and APP clearance (Seipold et al., 2017; Xu et al., 2009). However, the interaction between Tspan12 and ADAM10 requires the persistence of the

palmitoylation process. This suggests that this interaction is likely indirect, possibly occurring through the "tetraspanin web" (Haining et al., 2012). Experiments involving Tspan3 (TspanC6), prominently expressed in neurons and astrocytes, suggest that its expression is increased approximately twofold in the brain tissue of individuals with AD and that it interacts with ADAM10, serving as a scaffold in the complex formed by ADAM10, APP, and γ-secretase at the membrane (Seipold et al., 2017).

2.3.7. Extracellular signaling

The activity of ADAM10 can also be influenced by extracellular signals, as demonstrated by the modulation caused by the influx of Ca^{2+} ions, which have been associated with cellular process movements (Tosetti et al., 2021). Ca^{2+} influx has also been associated with the regulation of ADAM10 cleavage of enteropathogenic *Escherichia coli*-induced ADAM10-mitogen-activated protein kinase (MAPK) signaling by mitochondria-associated protein (Map) (Ramachandran et al., 2020); CD44 (Nagano and Saya, 2004); N-Cadherin (Reiss et al., 2005); betacellulin (BTC) (Sanderson et al., 2005); and sortilin (Evans et al., 2011).

The regulation of ADAM10 activity by the influx of extracellular Ca^{2+} ions may occur through modulation of calmodulin (CaM) activity (Nagano and Saya, 2004). CaM interacts with the C-terminus of ADAM10, which conserves the general IQ motif (^{729}IQXXXRXXXXR) among different species in its C-terminus, a motif widely found in proteins that bind to CaM (Bahler and Rhoads, 2002). CaM can switch between an active conformation without binding to the Ca^{2+} ion or an inactive conformation, Ca^{2+}-CaM. Thus, the concentration of Ca^{2+} can regulate the activity of CaM, acting as a limiting factor in the regulation pathway (Persechini and Stemmer, 2002; Tran et al., 2003). However, mutations in the IQ residues of ADAM10 did not prevent its interaction with Ca^{2+} (Horiuchi et al., 2007). Further studies are needed to investigate the essential residues for this interaction.

In addition, a recent study demonstrated that Ca^{2+} influx can activate anoctamin 6 (ANO-6). This scramblase is responsible for PS exposure, allowing ADAM10 interaction with the ^{657}RLKK motif. This interaction stimulates substrate cleavage by ADAM10. The authors proposed that the negatively charged PS could draw out a small loop in the region of the ADAM10 stalk that occludes its active site (Bleibaum et al., 2019).

2.3.8. Endogenous inhibitors

Tissue inhibitors of metalloproteinases (TIMPs) constitute a family of four mammalian proteins that inhibit ADAMs, ADAMs with thrombospondin motifs (ADAMTSs), and other metalloproteinases. Through this inhibition, they regulate extracellular matrix (ECM) remodeling by controlling the release of substrates by proteases into the extracellular environment. Moreover, although less studied, TIMPs also function as signaling molecules (Murphy, 2011). TIMPs are small globular proteins comprising two lobular subdomains at the N- and C-termini. The N-terminus contains a netrin module (NTR) characterized by six conserved cysteines and blocks of conserved hydrophobic amino acid residues (Banyai and Patthy, 1999). These residues enable the NTR domain to adopt a wedge-shaped fold, facilitating a pair of conserved cysteine residues in a Cys-X-Cys motif to chelate the Zn^{2+} ion and a threonine or serine residue to interact with the nucleophilic glutamate of the catalytic cleft of the ADAM10 protease domain (Murphy, 2011; Seegar and Blacklow, 2019).

TIMP1 and TIMP3 inhibit ADAM10 (Amour et al., 2000). However, it has been shown that this inhibition requires additional interactions with the C-terminal domain of TIMPs. The N-terminus of TIMP1 and TIMP3 alone did not promote ADAM10 inhibition (Rapti et al., 2008). TIMP3 is widely recognized as an inhibitor of ADAMs, acting on ADAM10, ADAM12, ADAM17, ADAM19, ADAM28, and ADAM33 (Murphy, 2011; Seegar and Blacklow, 2019). TIMP3 levels were increased in the brains of persons with AD and in AD animal models (Hoe et al., 2007). Additionally, overexpression of this inhibitor leads to an increase in Aβ levels in cultured primary cortical neurons (Hoe et al., 2007). This suggests that TIMP3 could modulate APP processing, potentially playing a role in the AD pathological molecular mechanisms (Dewing et al., 2019).

Contrarily to TIMP3, TIMP1 demonstrates selective inhibition of ADAM10 (Seegar and Blacklow, 2019). Interestingly, while TIMP1 is widely expressed in mammalian tissues, in the CNS, it is restricted to regions associated with neuronal plasticity, such as the hippocampus, olfactory bulb, and cerebellum (Rivera et al., 2010). Furthermore, TIMP1 levels are increased in cancer patients and correlated with a poor prognosis (Murphy, 2011; Schelter et al., 2011). Studies indicate that the inhibition of ADAM10 by TIMP1 prevents the cleavage of the hepatocyte growth factor receptor (Met) (Schelter et al., 2011). Increased levels of this receptor on the surface promote tumor development and aggressive cellular invasiveness, highly related to metastatic events (Cecchi et al., 2011).

Like TIMPs, the family of secreted-frizzled-related proteins (SFRP) retains an NTR module in its structure (Banyai and Patthy, 1999). This motif was found in the C-terminal domain of these proteins and allows SFRP1 and SFRP2 to inhibit ADAM10 by a mechanism like that observed with TIMPs (Esteve et al., 2011). Furthermore, SFRP1 shows increased levels in extracts from the entorhinal cortex of AD individuals in early and intermediate disease stages. These levels positively correlate with Aβ concentrations in these extracts. SFRP1 also increases the cerebrospinal fluid (CSF) of persons living with AD (Esteve et al., 2019). Immunohistochemical analysis revealed that SFRP1 can bind to Aβ, hindering the formation of Aβ protofibrils and promoting aggregation. Consequently, SFRP1 accumulates in amyloid plaques (Esteve et al., 2019).

ADAM10 is also inhibited by Reversion-Inducing Cysteine-Rich Protein with Kazal Motifs (RECK) (Muraguchi et al., 2007). This inhibitor is a membrane protein anchored by the C-terminus through a glycosylphosphatidylinositol (GPI) (Takahashi et al., 1998). Furthermore, RECK has an ectodomain residue/ moiety consisting of a signal peptide at its N-terminus and an intermediate portion with two epidermal growth factor (EGF)-like motifs and three Kazal motifs (Russell et al., 2021; Takahashi et al., 1998). The molecular mechanism by which RECK promotes ADAM10 inhibition remains unclear. However, it is known that RECK regulates the Notch signaling pathway by inhibiting ADAM10 (Hong et al., 2014; Muraguchi et al., 2007). Furthermore, a study showed elevated membrane-bound RECK in the brains of persons with AD (Nakamura et al., 2021).

3. Clinical significance of ADAM10 in Alzheimer's disease

Having elucidated the intricate regulatory mechanisms governing ADAM10 activity, this review will now focus on its role in different aspects of AD. ADAM10 cleavage of APP positions it as a key player in this disease. AD is a progressive neurodegenerative condition, and its typical clinical manifestation is characterized by cognitive decline - typically with memory loss - and impairment of daily functioning (Arvanitakis and Bennett, 2019). Critically, AD is the most common cause of neurocognitive disorders, accounting for approximately 60–80 % of all dementia cases worldwide (Association, 2023). The AD pathological hallmarks include accumulating extracellular Aβ plaques and intracellular neurofibrillary tangles derived from hyperphosphorylated tau protein (Self and Holtzman, 2023). These pathological changes lead to synaptic dysfunction, neuronal loss, and ultimately, brain atrophy, resulting in the clinical manifestations of AD (Fan et al., 2019).

No etiology has been identified as responsible for sporadic AD (Das et al., 2021); however, the amyloid hypothesis posits that aberrant APP processing and subsequent accumulation of Aβ peptides play a central role in AD pathogenesis (Self and Holtzman, 2023; Selkoe and Hardy, 2016). In this process, known as the amyloidogenic pathway, on the one hand, β- and γ-secretases, respectively, cleave APP (Fan et al., 2019). On the other hand, through the non-amyloidogenic pathway, Aβ production is mitigated (Khezri et al., 2023). ADAM10 emerges as the main

α-secretase that, under physiological conditions, naturally cleaves APP as long as they are close to the membrane (Anders et al., 2001; Lammich et al., 1999).

In support of that, research suggests that dysregulation of ADAM10 is associated with AD pathology. For instance, in individuals with AD, levels of ADAM10 in platelets are reduced (Bram et al., 2019; Fu et al., 2023; Manzine et al., 2013a), and the quantity of platelet-associated ADAM10 diminishes with disease progression (Manzine et al., 2013b). In plasma and CSF, in contrast, such levels seem to be higher in persons with AD compared to healthy controls (de Oliveira et al., 2020, 2024; Pereira Vatanabe et al., 2021; Vatanabe et al., 2021). Notably, changes in plasma ADAM10 levels have also been detected in individuals with mild cognitive impairment (MCI) preceding the onset of AD (de Oliveira et al., 2020; Pereira Vatanabe et al., 2021).

ADAM10 levels have also been investigated as a predictor of cognitive worsening. A 3-year longitudinal cohort study found that higher plasma levels of ADAM10 predict worse performance, evaluated by the mini mental state examination (MMSE) scores, even among those cognitively healthy at baseline (Oliveira Monteiro et al., 2024). In another study involving older adults with fewer years of education, plasma ADAM10 levels were associated with 4.5-fold more chances of being diagnosed with MCI and 5.9-fold more chances of being diagnosed with AD (Pelegrini et al., 2024).

Altogether, these pieces of evidence support the potential utility of ADAM10 as a biomarker for AD risk assessment, early diagnosis, and monitoring of disease progression. However, further validation studies are warranted to establish its clinical utility in routine practice (Oliveira Monteiro et al., 2024).

Another exciting perspective regarding ADAM10 is its association with AD risk factors, such as the apolipoprotein E (APOE) gene. APOE, particularly the ε4 allele (APOEε4), represents the strongest genetic risk factor for late-onset AD (Frisoni et al., 2022). Available evidence suggests a complex interplay between APOEε4 and ADAM10 in AD pathogenesis. APOEε4 carriers exhibit alterations in ADAM10 expression and activity, potentially contributing to the dysregulation of APP processing and increased Aβ production observed in AD (Shackleton et al., 2017). Accordingly, AD patients had lower expression of ADAM10 in the cerebral cortex and being an APOEε4 carrier contributed to this (Nyarko et al., 2018).

Also, APOEε4 contributed to downregulating ADAM10 mRNA levels (Theendakara et al., 2016). Moreover, evidence suggests that APOEε4 also influences the expression of SIRT1, a known inducer of ADAM10 transcription (Theendakara et al., 2018), as mentioned in the first part of this review. Consequently, the combined effect of APOEε4 interference on both SIRT1 and ADAM10 may reduce the levels of the neuroprotective sAPPα (Theendakara et al., 2016). This suggests the intricate interplay between APOEε4, SIRT1, and ADAM10, highlighting the potential for further investigation to advance the evidence on a potential molecular pathway underlying AD pathology.

In the last years, more sensitive and refined analysis methodologies are being introduced in this research field (Li and Mielke, 2019). A study demonstrated the feasibility of measuring sADAM10 levels in plasma for early AD diagnosis using a low-cost, high-sensitivity and disposable microfluidic platform (de Oliveira et al., 2020, 2024). Receiver operating curves showed that ADAM10 levels distinguished between cognitively healthy individuals and those living with MCI with a sensitivity of 70 % and specificity of 80 % at a cut-off threshold of 1765 pg/mL (de Oliveira et al., 2020). Additionally, when distinguishing between healthy controls and patients mildly affected by AD, the sensitivity and specificity were 78 % and 80 %, respectively, at the same ADAM10 cutoff. These assays were also replicated using immunoenzymatic assays to confirm the findings, designed for specific detection of the sADAM10 isoform (de Oliveira et al., 2024). Although the study evaluated a limited number of samples, it pointed to a promising new direction for diagnosing and monitoring AD (de Oliveira et al., 2020, 2024). Besides, these technologies can detect very low concentrations of sADAM10 in the sample – in the order of picograms/mL – and offer a less invasive resource and low sample volume required for the analysis. In addition, as the sample can be highly diluted, it reduces possible nonspecific binding signals. This method has advantages over traditional methods, such as speed, lower cost, and lower sample volume required, making it a promising alternative for early diagnosis of AD (de Oliveira et al., 2020, 2024). Altogether, these data strongly suggest that detecting ADAM10 in blood samples has significant clinical implications for diagnosing individuals, including those with MCI. This underscores ADAM10's potential as a biomarker for AD, either alone or as part of a diagnostic panel.

In addition, the clinical significance of ADAM10 modulation in the context of AD must be recognized. Upregulation of its secretase activity using different strategies (Manzine et al., 2019) is a promising therapeutic approach. Despite the limited scope of research on the impact of specific techniques to enhance ADAM10 expression and activity in individuals with AD, the findings are notably interesting. For instance, acitretin has demonstrated the potential to boost α-secretase activity, as evidenced by elevated levels of CSF sAPPα (Endres et al., 2014).

The use of AD medication has proven to interfere with ADAM10 modulation. Bianco and co-workers (Bianco et al., 2016) found that serotonergic medication positively affected platelet ADAM10 protein expression in AD patients. Additionally, others have demonstrated that APP metabolism improved in persons with AD after 30 days of cholinesterase inhibitor (ChEI) treatment (Zimmermann et al., 2005). This was evidenced by increased levels of ADAM10 activity and reduced β-secretase activity in platelets. These changes suggest a beneficial rebalancing of APP processing pathways.

Moreover, postmortem brain samples from AD patients treated with rivastigmine showed increased sAPPα levels and decreased sAPPβ and $A\beta_{1-42}$ levels compared to non-medicated AD patients (Ray et al., 2020). It seems rivastigmine shifts APP processing towards the alpha-secretase pathway, potentially through the upregulation or preservation of ADAM10. However, brain Aβ levels were higher in AD patients than non-AD controls, and there was no significant difference in Aβ levels between rivastigmine-treated and untreated AD patients (Ray et al., 2020).

Reduced melatonin levels in persons with AD are linked to decreased ADAM10 expression and Aβ accumulation (Shukla et al., 2017). In preclinical studies, melatonin induced ADAM10 transcription by directly affecting promoter regions, thus increasing ADAM10 expression, as mentioned earlier in this review (Shukla et al., 2015).

The interference with ADAM10 endocytosis is a notable approach to upregulating its postsynaptic localization and activity (Musardo et al., 2022). In AD, ADAM10 endocytosis increases in the hippocampus, reducing the enzyme's postsynaptic localization. Researchers developed a cell-permeable peptide (PEP3) with a safety profile designed to interfere with ADAM10 endocytosis to address this disruption. When administered at an early disease stage, PEP3 administration effectively rescued cognitive deficits in APP/PS1 mice. Although further studies are needed to assess the long-term efficacy and safety of PEP3, these results provide preclinical evidence supporting its therapeutic potential in AD.

The structure of ADAM10 can be a model for innovative bioengineering strategies, as exemplified a previous work (Hershkovits et al., 2023). The authors proposed a new approach using an engineered soluble form of mature ADAM10 to develop a potential novel strategy for AD treatment. This truncated ADAM10, solely based on its catalytic metalloprotease domain, demonstrated the ability to shed both overexpressed and endogenous APP, to increase sAPPα levels, and to hydrolyze Aβ42, thereby inhibiting its aggregation in neuronal cells.

Another strategy was proposed in another study (Pastore et al., 2023) in which a series of engineered ADAM10 analogs containing a Tobacco Etch Virus protease (TEV) cleavage site (TEVcs) was generated, rendering ADAM10 cleavable by TEV. This strategy revealed that, without other stimuli, the TEV-mediated removal of the prodomain could not activate ADAM10. However, the TEV-mediated cleavage of

the cytosolic domain significantly increased ADAM10 activity. Subsequently, ADAM10 with minimal constitutive catalytic activity was generated, which increased substantially in the presence of TEV or after activating a chemically activatable TEV. The results demonstrated a bioengineering strategy for controlling ADAM10 activity in living cells, paving the way for spatiotemporal control of ADAM10. Furthermore, it was proven that this approach promoted α-secretase activity and the non-amyloidogenic cleavage of APP, thereby increasing the production of the neuroprotective sAPPα.

Advances in ADAM10 structural studies enabled the generation of the 8C7 mAb that specifically binds to a particular ephrin (Eph) substrate-binding pocket in the ADAM10 cysteine-rich domain, differently from the traditional antibodies that target the metalloproteinase domain (Atapattu et al., 2012). Although this antibody acts as an inhibitor of ADAM10-mediated Eph cleavage, it can relieve the autoinhibitory mechanism and restore ADAM10 ectodomain activity through exposure to the active site (Atapattu et al., 2012; Seegar et al., 2017). Furthermore, the mechanism by which TspanC8 regulates ADAM10 has different interfaces for the complex formation and substrate selectivity, enabling the development of antibodies that could direct ADAM10-TspanC8 complex for APP cleavage while inhibiting the unregulated activity of ADAM10 about other substrates (Lipper et al., 2023). Therefore, the advances in structural technical methods and recent artificial intelligence tools that can accurately predict antibody structures are promising for designing specific therapeutic and diagnostic molecules (Ruffolo et al., 2023).

Physical exercise is recognized as a potent modulator of brain health, enhancing cognitive function and neural plasticity (Fernandes et al., 2017). Allied with brain-derived neurotrophic factor (BDNF) treatment, 8-week exercise sessions increased ADAM10 activity in mice's prefrontal cortex and hippocampus, indicating a shift in APP processing (Baranowski et al., 2023). Similarly, after an acute protocol (2 h treadmill running), mice injected with interleukin-6 (IL-6) showed increased ADAM10 activity in the prefrontal cortex. In contrast, reduced activity was found in the hippocampus administration, highlighting brain regional differences in the response to acute IL-6 (Marko et al., 2023). Comparable findings were observed in an AD mouse model, with treadmill exercise upregulating the peroxisome proliferator-activated receptor alpha (PPARα) to stimulate the transcription of ADAM10 in the mice hippocampus, leading to the reduction of endogenous Aβ production (Rangasamy et al., 2023).

The results above suggest that exercise can activate various pathways, stimulating the secretion of peripheral factors capable of crossing the blood-brain barrier and potentially affecting APP processing. Exercise may promote non-amyloidogenic APP processing by increasing ADAM10 activity and reducing Aβ production. However, confirming whether these effects will clinically impact ADAM10 levels in humans requires more extensive and controlled trials.

The potential of these pharmacological and non-pharmacological interventions in AD treatment is captivating, with ADAM10 modulation holding promise as a therapeutic strategy for AD. However, it is crucial to consider its potential positive and negative effects, particularly related to its association with other diseases, such as cancer. ADAM10's involvement in cancer progression with stimulation of cell proliferation and migration is a significant concern (Alexandre-Silva and Cominetti, 2024). Therefore, future research should focus on the specific targeting of ADAM10 to substrates in AD, which may be necessary to mitigate potential adverse effects and ensure the safety of this therapeutic approach. It is imperative to conduct further investigation through clinical trials to ascertain whether these interventions would be efficacious alone or combined with other strategies. This emphasis on the need for ongoing research underscores the potential of ADAM10 modulation as a promising therapeutic avenue for AD treatment. Still, caution and thorough investigation are also needed, considering the various ADAM10 isoforms identification peculiarities presented in this review.

4. Recommendations for ADAM10 isoforms detection by commercial antibodies

Given ADAM10's critical role in AD pathogenesis, we will now focus on some studies that have evaluated this protein as a blood-based biomarker for the disease. By examining the outcomes of these studies, we aim to call attention to some aspects that require consideration when detecting ADAM10's different isoforms and cleavage products using commercial antibodies or antibody-based detection kits. Presenting a comprehensive guideline for investigating ADAM10's different isoforms tailored to the specific biological matrices being evaluated and clarifying key aspects may be helpful for future research.

The role of ADAM10 roles in AD has been reported since 1999 (Lammich et al., 1999). During this long journey, several new pieces of information were grouped, helping to construct the current scientific knowledge in the field over the years. Simultaneously, commercially available antibodies targeting specific regions of ADAM10 were introduced and have been used in several studies (Table 1, Fig. 3).

In the initial works measuring ADAM10 levels in platelets of AD patients, a reduction was found compared to cognitively unimpaired individuals. This reduction became more pronounced as the disease progressed (Colciaghi et al., 2002, 2004). These studies employed antibodies targeting the ADAM10 C-terminal region, detecting a band with a molecular mass of around 65 kDa, representing the mADAM10 isoform (Table 1, Fig. 3). Subsequently, other studies replicated these findings, reporting similar results (Manzine et al., 2013, 2013ba, 2014; Manzine et al., 2013, 2013b) (Table 1, Fig. 3). Notably, these studies were carried out with antibodies specific to the N-terminal region of the protein (1−300), which can detect both pro- (proADAM10), mature (mADAM10) and soluble (sADAM10) isoforms. As expected, however, only proADAM10 and mADAM10 were identified in platelet lysates (Manzine et al., 2013b).

The following studies corroborated these findings (Sarno et al., 2017; Vinothkumar et al., 2018; Yu et al., 2021) or presented contrary results (Bermejo-Bescos et al., 2013) (Table 1). It is important to emphasize that the reported divergences in ADAM10 levels may arise from the distinct targets recognized by the antibodies (C-terminal, N-terminal or ectodomain detection regions) between studies. Moreover, in some cases, for example, in the findings of Bermejo-Bescos et al. (2013), no information is provided about the specific recognition target of the anti-ADAM10 antibody used or the molecular masses it recognizes. Notably, the manufacturers' datasheets for the ADAM10 detection antibodies used in some studies often lack detailed information about the specific region of the protein targeted by the antibody (Table 1).

This methodological gap has raised new concerns regarding the precise protein region detected and which isoforms are being examined. Additionally, it is important to note that the presence of comorbidities (Lee et al., 2015), the degree of dementia (Manzine et al., 2013b), and especially the use of medications (Bianco et al., 2016; Zimmermann et al., 2005) can alter mADAM10 levels and activity, which might also result in contradicting study outcomes. Further research is needed to determine whether these factors also affect sADAM10 levels.

Platelet lysates contain membrane portions abundant in proteins, lipids, and other molecules (Chatterjee, 2020). Upon lysis, these membrane components, including membrane-bound proteins such as pro- and mADAM10, are present in the lysate. Consequently, both N-terminal and C-terminal antibodies can be employed to detect these isoforms. However, N-terminal targeting antibodies detect proADAM10, mADAM10, and sADAM10, while C-terminal antibodies specifically target only the membrane-associated ADAM10 isoforms (Fig. 3). Therefore, it is crucial to ensure that any potential contamination of platelet lysates, such as from plasma, does not compromise the detection and analysis. This can be achieved by performing several washing steps to thoroughly remove plasma proteins and other contaminants from the platelet lysates. Careful sample preparation and antibody specificity validation are essential to distinguish between the different ADAM10

Table 1
Results from previous studies showing the levels of ADAM10 in different biological sources and the commercial antibodies used to recognize the protein.

Authors, (year); country	Source	Antibody	Main results	Reference
Colciaghi et al., (2001); Italy	platelets	C-terminal ADAM10 antibody – (Prosci Inc.)	↓ mADAM10 in vmAD and mAD	Alpha and beta secretase activity in platelets of Alzheimer's disease patients. J Neurochem, 77:21, 2001.
Colciaghi et al., (2002); Italy	platelets	C-terminal ADAM10 antibody – (Prosci Inc.)	↓ mADAM10 in AD	α-Secretase ADAM10 as Well as αAPPs Is Reduced in Platelets and CSF of Alzheimer Disease Patients. Mol Med 8, 67–74, 2002
Manzine et al., (2003); Brazil	platelets	N-terminal ADAM10 antibody (sc−48400, Santa Cruz Biotechnology)	↓ mADAM10 in AD; ↓ mADAM10 according to the severity of the dementia; Positive correlation between mADAM10 and Clock Drawing Test	Platelet a disintegrin and metallopeptidase 10 expression correlates with clock drawing test scores in Alzheimer's disease. International Journal of Geriatric Psychiatry, v. 30, 2013
Manzine et al., (2003); Brazil	platelets	N-terminal ADAM10 antibody (sc−48400, Santa Cruz Biotechnology)	↓ mADAM10 in AD; ↓ mADAM10 according to the severity of the dementia; Positive correlation between mADAM10 and MMSE.	Correlation Between Mini-Mental State Examination and Platelet ADAM10 Expression in Alzheimer's Disease. Journal of Alzheimer's Disease, 36(2), 253–260, 2013
Manzine et al., (2003); Brazil	platelets	N-terminal ADAM10 antibody (sc−48400, Santa Cruz Biotechnology)	↓ mADAM10 in AD and according to the severity of the dementia	ADAM10 as a Biomarker for Alzheimer?s Disease: A Study with Brazilian Elderly. Dementia and Geriatric Cognitive Disorders, v. 35, p. 58–66, 2013
Tang et al., (2006); USA	platelets	ADAM10 antibody, NR (Chemicon, Temecula, CA)	↓ ADAM10 in mild AD and severe AD	Platelet amyloid precursor protein processing: a biomarker for Alzheimer's disease. J Neuro Sci, 240 (1−2):53–8, 2006
Bermejo et al., (2013); Spain	platelets	ADAM10 antibody, NR (Santa Cruz Biotechnology, Santa Cruz, CA, USA)	↑ ADAM10 levels in MCI and AD	Processing of the platelet amyloid precursor protein in the mild cognitive impairment (MCI). Neurochem Res, 38(7):1415–23, 2013
Sarno et al., (2017); Brazil	platelets	C-terminal ADAM10 antibody (Abcam)	↓ mADAM10 in AD	Protein expression of BACE1 is downregulated by donepezil in Alzheimer's disease platelets. J Alzheimers Dis; 55(4):1445–5, 2017
Sogorb-Esteve et al., (2018); Spain	CSF	Ectodomain ADAM10 antibody - OAGA02442, Aviva; N-terminal ADAM10 antibody (ab39153, Abcam) and C-terminal ADAM10 antibody (ab124695, Abcam)	↓ mADAM10 and sADAM10 levels in AD	Levels of ADAM10 are reduced in Alzheimer's disease CSF. J Neuroinflamm, 15(1):1–9, 2018
Vinothkumar et al., (2018); India	platelets	Ectodomain ADAM10 antibody (bs−3574R, Bioss Inc)	↓ ADAM10 in AD	Therapeutic impact of rHuEPO on abnormal platelet APP, BACE 1, presenilin 1, ADAM 10 and AJ3 expressions in chronic kidney disease patients with cognitive dysfunction like Alzheimer's disease: a pilot study. Biomed Pharmacother, 104:211–22, 2018
Bram et al., (2019); Brazil	platelets, leukocytes	ADAM10 antibody, NR (ab124695, Abcam)	↓ mADAM10 in AD (in platelets). No differences (leukocytes)	Protein levels of ADAM10, BACE1, and PSEN1 in platelets and leukocytes of Alzheimer's disease patients. Eur Arch Psychiatry Clin Neurosci, 269 (8):963–72, 2019
Oliveira et al., (2020); Brazil	plasma, serum, CSF	N-terminal ADAM10 antibody (ab39180, Abcam); ADAM10 ELISA kit (Cloud-Clone Corp, SEA766Hu)	↑ sADAM10 in AD and MCI	Early diagnosis of Alzheimer?s disease in blood using a disposable electrochemical microfluidic platform. ACS Sensors, v. 1, p. 1, 2020
Agüero et al., (2020); Spain	CSF	Ectodomain ADAM10 antibody - OAGA02442, Aviva	↓ mADAM10 and sADAM10 levels in AD	a-Secretase nonsense mutation (ADAM10 Tyr167*) in familial Alzheimer's disease. Alzheimers Res Ther,12(1):1–9, 2020
Vatanabe et al., (2021); Brazil	platelets, plasma, CSF, SH−5YSY cells	N-terminal ADAM10 antibody (ab39153, Abcam); C-terminal ADAM10 antibody (2051, Prosci Inc.)	↑ sADAM10 in AD; sADAM10 presented no activity; mADAM10 detected only in platelets and SH−5YSY cells	ADAM10 Plasma and CSF Levels Are Increased in Mild Alzheimer's Disease. International Journal of Molecular Sciences, v. 22, p. 2416, 2021
Yu et al., (2021); China	platelets	ADAM10 antibody, NR (AF5294, Affinity Biosciences)	↓ ADAM10 in MCI and AD	Platelet biomarkers for a descending cognitive function: a proteomic approach. Aging Cell, 20(5): e13358, 2021
Vatanabe et al., (2021); Brazil	platelets, plasma	C-terminal ADAM10 antibody (ProSci 2051) and N-terminal ADAM10 antibody (ab39153, Abcam)	↓ mADAM10 and ↑ sADAM10 in MCI	ADAM10: Biomarker of mild cognitive impairment but not of cognitive frailty, Experimental Gerontology, 149, 111303, 2021
Oliveira et al., (2024); Brazil	plasma	N-terminal ADAM10 antibody (ab39180 Abcam); ADAM10 ELISA kit (Cloud-Clone Corp, SEA766Hu)	↑ sADAM10 in AD and MCI	Electrochemical magneto-immunoassay for detection of ADAM10 Alzheimer's biomarker using gold nanoparticles as label. TALANTA, v. 266, p. 125042–8, 2024

AD: Alzheimer's disease; MCI: mild cognitive impairment; CSF: cerebrospinal fluid; MMSE: Mini-Mental State Examination; NR: Epitope not reported; mADAM10: mature isoform; sADAM10: soluble isoform.

isoforms and to obtain precise and reproducible data.

Regarding human CSF, previous studies described the presence of different ADAM10 isoforms and a reduction of what was called mADAM10 (~ 55 kDa) and sADAM10 (~ 50 kDa) levels in persons with AD, compared to cognitively unimpaired participants (Aguero et al., 2020; Sogorb-Esteve et al., 2018). Other studies have shown that sADAM10 levels – within samples probed against the N-terminal ADAM10, which recognized a sADAM10 55 kDa isoform - are increased in the CSF and plasma of people with mild AD (Vatanabe et al., 2021). This sADAM10 found in blood and CSF is possibly released from the membrane by other metalloproteases, as described in this review. Using a fluorogenic peptide as the sADAM10 substrate, very low activity was

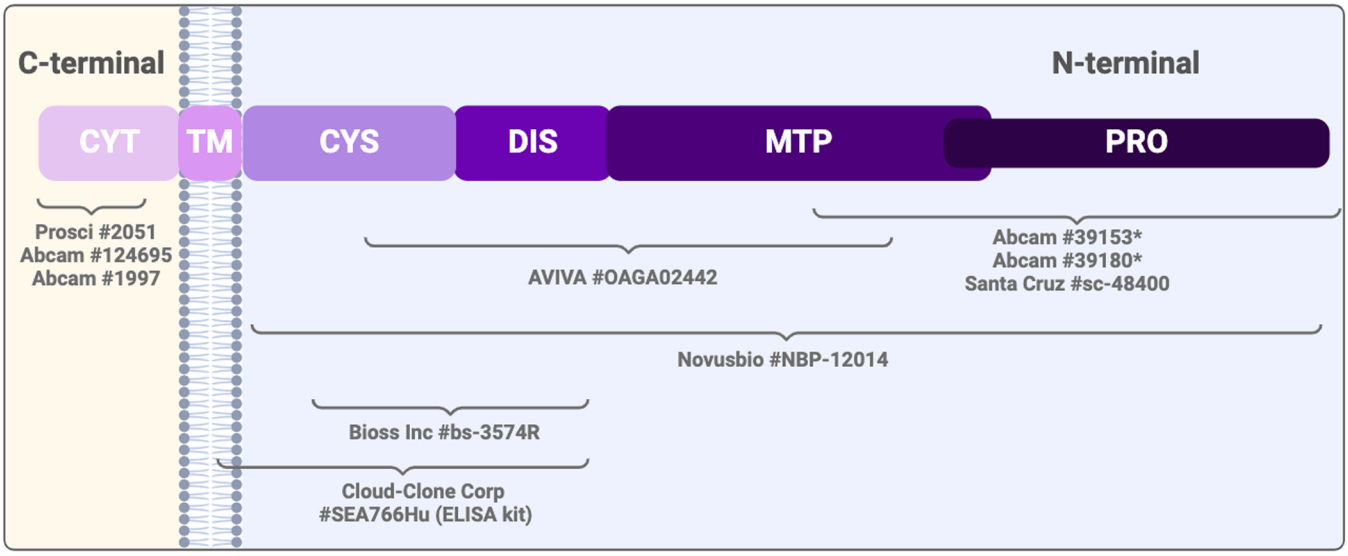

Fig. 3. Recognition sites of commercially available antibodies against ADAM10. Available antibodies recognizing the C-terminal region of ADAM10 are Prosci #2051, Abcam #124695, and Abcam #1997, and they can recognize the zymogen proADAM10 and membrane-bound ADAM10. Antibodies Abcam #39153 and Abcam #39180, which bind to the N-terminal portion of ADAM10, and the ADAM10 ELISA kit from Cloud-Clone Corp #SEA766Hu (binds to amino acids Gln457 to Leu682), besides detecting the mature and immature isoforms, can also detect the soluble isoform. Furthermore, according to their datasheets, the antibodies Santa Cruz #sc-48400 (binds to amino acids 1–300 of ADAM10), Novusbio #NBP-12014 (binds to the extracellular domain of ADAM10), AVIVA #OAGA02442 (binds to the middle region of ADAM10), and Bioss #bs-3574R (amino acids 501–600/748) should also be able to detect sADAM10. Antibodies without known epitopes (see Table 1) are not integrated into the scheme. *Antibodies have been discontinued by their producer. Figure created with BioRender software, publication license: PC272GN7I0.

detected in serum and CSF, compared to platelet and SH-SY5Y cell lysates and recombinant ADAM10, which presented greater secretase activity (de Oliveira et al., 2020).

The above-described discrepancies must be analyzed from the viewpoint of methodological aspects concerning, e.g., normalization. In the works of Aguero et al. (2020) and Sogorb-Esteve et al. (2018), the authors did not standardize the protein concentrations of CSF samples loaded onto the gels. Instead, they used the ADAM10 isoforms ratio (50 kDa+55 kDa/80 kDa) for the analyses. The authors justified these procedures with a non-significant trend towards a decrease in the CSF/serum albumin ratio in AD compared to non-AD participant samples. However, the reported decline in albumin levels in AD may not reflect an actual reduction. Still, it could stem from unequal protein loading into the gel from these participants' CSF samples, as the same protein concentration was not consistently loaded onto gels.

Given that CSF is a matrix with low protein content (0.3–1.3 mg/mL) (Collins et al., 2015), selecting a specific endogenous control such as albumin presents challenges. However, employing Ponceau staining could offer a viable solution for this purpose. Prior studies have demonstrated the accuracy and precision of this method as an alternative loading control technique when working with brain homogenates (Thacker et al., 2016) or CSF (Suon et al., 2010). Furthermore, considering albumin's prominent presence as the most abundant protein in the CSF (Conly and Ronald, 1983; Zappaterra and Lehtinen, 2012), some studies have employed a methodological approach utilizing albumin detected by Ponceau staining as the endogenous control to normalize ADAM10 levels in these samples (Pereira Vatanabe et al., 2021). Without these controls, it is impossible to determine whether the ADAM10 levels differ among the participants, thereby compromising the validity of any comparative analysis (Ghosh et al., 2014).

Indeed, in the assays detecting higher sADAM10 levels in plasma and CSF, a 66 kDa band visualized with Ponceau S staining, corresponding to albumin, was used as the endogenous control. This protein is abundant in the plasma and present in the CSF (Collins et al., 2015). Ponceau S normalization techniques are popular for normalization in western blotting due to their simplicity, reproducibility, and cost-effectiveness. It can ensure that observed differences in protein levels are due to genuine biological variations rather than technical artifacts (Helbing et al., 2022). Ponceau S is a reversible stain that detects proteins on nitrocellulose or polyvinylidene fluoride (PVDF) membranes after transfer from gels. It binds non-specifically to proteins, producing a visible red stain, which allows for the visualization of the total protein content on the membrane. Unlike other stains, Ponceau S can be removed entirely from the membrane, enabling subsequent immunodetection without interference. The staining and destaining process is quick and straightforward, typically taking only a few minutes. Ponceau S is inexpensive compared to other protein stains and antibodies for housekeeping proteins. It provides a view of the entire protein content on the membrane, offering a more comprehensive normalization approach compared to single housekeeping proteins, which may vary under different experimental conditions.

In addition to the serum albumin endogenous control, a sample called "young control", consisting of a suspension prepared from a pool of plasma from young, healthy volunteers, was added to each gel to control analytical differences between blotted membranes prepared on different days (inter-assay variation) (Pereira Vatanabe et al., 2021). Therefore, in these assays, it is imperative to ensure precise quantification and consistent protein loading, accompanied by normalization using appropriate endogenous controls, to achieve reliable and reproducible results. Complementing these findings, ELISA experiments, which precisely detect a region of the ADAM10 ectodomain (^{457}Gln~^{682}Leu), also found increased levels of sADAM10 in the plasma and CSF of people with AD (de Oliveira et al., 2020) (Table 1).

The elevated sADAM10 soluble levels in plasma and CSF of AD individuals may be associated with reduced overall enzymatic activity. While the reasons for increased ectodomain shedding have not been thoroughly investigated, one hypothesis is that diminished sADAM10 activity leads to the removal of mADAM10 from the cell membrane via internalization or secretion, thereby raising extracellular levels (Seifert et al., 2021). Given that mADAM10 primarily operates at the cell

membrane to cleave the proximal target (Hitschler and Lang, 2022), the observed activity levels in plasma and CSF may indicate a reduced presence of functionally active mADAM10 at the plasma membrane, which could explain the decreased mADAM10 seen in platelets from persons with AD.

Since plasma samples are more accessible and require a more simple processing than CSF or platelet samples, sADAM10 emerges as a promising biomarker for cognitive changes, including pre-dementia conditions (Pereira Vatanabe et al., 2021) or even a predictor of cognitive worsening in older adults (Oliveira Monteiro et al., 2024). This highlights its relevance for clinical purposes and the development of new point-of-care technologies.

Regarding the different western blotting result outcomes in recognizing ADAM10 isoforms across different research groups, it is crucial to underscore the necessity of validating antibodies for detecting specific ADAM10 isoforms in various biological matrices (see Box 1). This would be crucial for ensuring the accuracy and reliability of experimental results. Validation ensures that the antibodies are specific to the target isoform and do not cross-react with other proteins, reducing the likelihood of false-positive or false-negative results. This is particularly important in complex biological matrices, where numerous proteins can complicate detection.

Moreover, future studies must provide increasingly detailed information about the antibodies (specific detection regions, C-terminal, N-terminal) and consider them according to the isoform (proADAM10, mADAM10 or sADAM10) and biological material under analysis (plasma, platelets, cell lysates or CSF). Various techniques have embraced this practice, including quantitative polymerase chain reaction (PCR) studies (Bustin, 2010), mass spectrometry (Taylor et al., 2008), and microscopy image analysis (Nelson et al., 2021). These fields have introduced specific guidelines to standardize procedures, ensuring experimental consistency and reliability. Adopting this additional practice in the context of blood-based AD biomarkers, besides those already recommended (Zeng et al., 2024), would be essential to establish minimal reporting standards for western blotting experiments to ensure data reliability and reproducibility. Adhering to a comprehensive set of guidelines, such as the 10-point requirement outlined in the western blotting minimal reporting standard (WBMRS), will facilitate robust scientific documentation and enhance the integrity of experimental findings (Gilda et al., 2015).

The data underscore the critical need for standardizing experimental protocols and sample processing methodologies. Additionally, selecting the appropriate antibodies for protein detection is essential to ensure reproducibility and facilitate accurate comparison of ADAM10 isoforms across different studies. Box 1 presents detailed recommendations for investigating ADAM10's isoforms.

5. Future directions

Although we have shown that sADAM10 levels are altered in AD (Manzine et al., 2013b; Oliveira Monteiro et al., 2024), the mechanisms behind the increased ectodomain shedding of this α-secretase are not fully known. Considering ADAM9 and 15 are responsible for this process (Tousseyn et al., 2009), future research regarding the levels and activity of those proteins is needed since their functionality could be impaired under AD pathology. Interestingly, previous *in vitro* studies have shown that ADAM9 activity modulation could either increase ADAM10 ectodomain shedding upon stimulation or decrease this process after inhibition (Moss et al., 2011; Parkin and Harris, 2009; Ray et al., 2020). Thus, ADAM9's possible role in AD must be investigated since it could favor the amyloidogenic pathway through increased ADAM10 ectodomain shedding.

Furthermore, a better understanding of the different isoform levels of ADAM10 in AD is needed since it is unknown if the increased levels of sADAM10 and decreased mADAM10 are seen in the brain. In brain samples derived from persons with AD, immunohistochemistry experiments showed a slight but significant decrease in the number of immunoreactive neurons for ADAM10 compared to age-matched controls, corroborating how ADAM10 levels are decreased in AD (Bernstein et al., 2003). Furthermore, ADAM10 immunoreactivity was also seen around amyloid plaques, i.e., in the ECM, which, considering our hypothesis, could be interpreted as soluble ADAM10 that was shed from the plasma membrane (Bernstein et al., 2003). Considering these results, ADAM10 central levels and activity need further investigation. AD cellular models could be helpful in this process.

A comprehensive investigation of sADAM10 activity is warranted,

Box 1
Comprehensive guidelines for investigating ADAM10's different isoforms.

- Carefully collect, process and store samples according to the investigated matrix protocols;
- Choose which ADAM10 isoform(s) will be analyzed;
- Check the recognition target of the anti-ADAM10 antibody or the molecular masses it recognizes (C-terminal, N-terminal or middle region);
- Seek for detailed information about the specific region of the protein targeted by the antibody in the manufacturers' datasheets or inquire the manufacturers' technical support services;
- Ensure that any potential contamination of different isoforms and/or matrices do not compromise the detection and analysis;
- Whenever available, validate antibodies for the detection of specific ADAM10 isoforms in the biological matrix under study (ideally by using a knockout cell lysate or cell lines overexpressing ADAM10 isoforms);
- Validate the results through different laboratory techniques, wherever possible;
- Consider the presence of influencing factors (such as morbidities, medication, age and degree of dementia) for analysis;
- Adopt a comprehensive set of guidelines to standardize procedures, ensuring experimental consistency and reliability;
- Regard the principles of quality and reproducibility of laboratory techniques;
- Use biological and technical triplicates or more;
- Standardize protein concentration using consistent techniques and reagents from reliable suppliers;
- Minimize inter-assay variation by using identical handling procedures for all samples, the same batch of reagents for all assays when possible, and regularly calibrating pipettes, plate readers, and other equipment to ensure accuracy and precision;
- Normalize assays using appropriate loading controls or Ponceau S staining according to sample matrices;

given the conflicting results regarding the magnitude of the proteolytic activity of this isoform (Hershkovits et al., 2023; Moss et al., 2011; Vatanabe et al., 2021). Additionally, the findings indicating elevated sAPPα levels in the CSF of individuals with AD, compared to cognitively unimpaired, require further clarification (Fellgiebel et al., 2009; Sennvik et al., 2000). These contradictory results might be due to experimental procedures, such as using non-physiological substrates for the activity assays and different interpretations of what domains comprise the soluble isoform of ADAM10. Thus, as previously mentioned, future research needs to consider the presence of different isoforms, which may vary according to the specimen under investigation, i.e., platelets, plasma, cells, CSF, and the ECM (Pereira Vatanabe et al., 2021). It is also important to consider that ADAM10 detected in plasma may originate from exosomes released by the brain. This represents a potential source of contamination, but it also offers an opportunity to gain insights into brain ADAM10 levels through blood samples.

In addition, these different samples must be carefully separated to avoid confounding results. Importantly, as previously mentioned, the different isoforms of ADAM10 need to be detected through specific antibodies targeting either their C- or N-terminal. They can be distinguished experimentally by their different molecular weights, i.e., 85 kDa, 65 kDa and 55 kDa for proADAM10, mADAM10 and sADAM10, respectively. Lastly, it is crucial to uphold appropriate methodological standards when detecting ADAM10 isoforms through experiments involving specific antibody recognition techniques.

6. Conclusion

This comprehensive review illuminates the multifaceted roles of ADAM10, spanning its pivotal regulation processes, with a particular focus on its clinical relevance in AD. Through our exploration, we advocate for standardized terminology to describe ADAM10 isoforms, aiming to enhance clarity and consistency in scientific literature, especially concerning its potential as an AD biomarker. By exploring the experimental considerations surrounding antibody utilization for protein detection, we aim to reconcile diverse findings in ADAM10 detection within the context of AD research. Our investigation provides a nuanced understanding of ADAM10's regulation at different levels and its mechanisms of action, substrate repertoire, and significance in cellular homeostasis and disease pathogenesis. It underscores its potential as a pivotal player in theranostics for AD.

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CRediT authorship contribution statement

L.N.C.P. and M.R.C. conceptualized the review. S.D.O., V.A.S., C.P. P., D.B.S., M.M.G., L.N.C.P. and P.R.M. conducted the literature search, writing, reviewing, and editing of the manuscript. V.A.S. created the figures. E.M., K.E. and M.R.C. assisted with the literature search and manuscript writing, reviewed, and edited. M.R.C. provided financial support for the project leading to this publication. All authors approved the final manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT to improve language and readability. After using this tool, they reviewed and edited the content as needed and took full responsibility for the publication's content.

Declaration of Competing Interest

The authors report no declarations of competing interests.

Data Availability

No data was used for the research described in the article.

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