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ADAM10: α-secretase in Alzheimer's disease and regulator of neurobiology

Introduction

To date, 40 different members of the"a disintegrin and metalloprotease" (ADAM) family have been identified in the genome of mammals. Approximately half of these are thought to be proteolytically active. After synthesis in the endoplasmic reticulum (ER) and transport to the Golgi apparatus, the prodomain of the ADAM is removed by proprotein convertases and the protein undergoes complex glycosylation. The prodomain inhibits the metalloprotease activity and ensures proper folding of the ADAM by virtue of its chaperone function. Most ADAMs reside in the ER and Golgi compartments. However, minor amounts are also found at the plasma membrane, where their actual proteolytic functions have been described.

The process of ectodomain shedding is mainly mediated by membrane-bound proteases. Particularly proteolytically active ADAMs are involved in cleavage of substrates in close proximity to the membrane. Cleavage generates the soluble ectodomains and remaining membrane-bound fragments, both of which are able to induce paracrine and autocrine signaling pathways. Interestingly, ADAM proteases do not share a consensus substrate recognition sequence; rather it is membrane compartmentalization, protease expression patterns and the structure of the substrate that seem to play an essential role in regulating substrate proteolysis. Due to the different expression patterns of ADAMs in tissues, ADAM proteases are involved in physiological and pathophysiological conditions including fertilization, neurogenesis, neurodegenerative diseases, inflammation and development of cancer [11].

Research interest was drawn to ADAM10—a protease with significant expression in the brain—owing to its involvement in developmental processes by cleavage of the Notch-1 receptor. Additionally, ADAM10 is able to cleave the amyloid precursor protein (APP), which is relevant for the molecular pathology of Alzheimer's disease (AD). Both proteolytic events are of importance for developmental processes in embryonic and adult tissues. Compared to other cleavage events, the cascade of Notch-1 receptor proteolysis has been characterized in detail and is well understood. During biosynthesis, the Notch-1 receptor is cleaved in the Golgi apparatus. Subsequently, at the cell surface, ADAM10 generates a membrane-bound Notch-1 fragment which is a substrate for intramembrane proteolysis by the γ-secretase complex. The soluble fragment liberated in the cytosol translocates to the nucleus and regulates expression of Notch-1 target genes.

Cleavage of APP by ADAM10 occurs within the amyloid-β peptide (Aβ) sequence and counteracts the production of Aβ peptides (non-amyloidogenic pathway). Both β-secretase (BACE-1) and the γ-secretase complex are responsible for generation of Aβ peptides, which are found in extraneuronal deposits and contribute to neurodegeneration.

Complete loss of ADAM10 in the mouse leads to an early embryonic lethal phenotype characterized by developmental defects in the central nervous system (CNS), impaired somite development and altered cardiovascular structures, most likely due to a defect Notch-1 signaling pathway. Additionally, 30 other membrane-bound substrates have been identified for ADAM10, some of which have a tremendous impact on CNS function, such as neuronal (N-) cadherin, neuroligin 1, neurexin and the L1 adhesion protein. Due to the multitude of proteins regulated by ADAM10-dependent shedding, this protease also has an important role outside the CNS: ADAM10 plays central roles in inflammation, cancer, skin homeostasis and vascularization ([8], **Fig. 1**). Research based in suitable transgenic mouse models has underlined the pivotal importance of ADAM10-dependent proteolysis in regulating these different processes.

ADAM10 and CNS development

Conditional knockout mouse models offer the opportunity to control the specific deletion of a target protein, due to the fact that the responsible Cre-recombinase is regulated by a tissue- and time point-dependent promoter element. The early embryonic lethality of the classical ADAM10 knockout mouse could be circumvented using a Nestin-Cre deleter strain [2]. The Nestin-Cre-driven deletion of ADAM10 leads to loss of the protease in neuronal progenitor cells, as well as in their neuronal and glial descendants. Under these conditions, deletion of ADAM10 induced a late embryonic and early postnatal lethality of the conditional knockout mice. Morphologically, intracranial bleed-

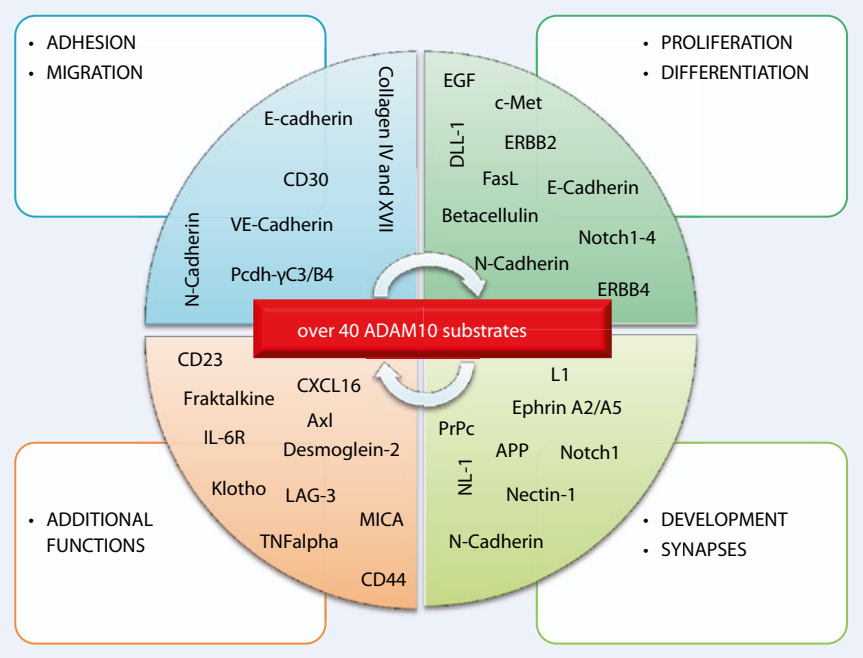

Fig. 1 ▲ Summary of some of the characterized ADAM10 substrates involved in physiological and pathophysiological conditions of the organism

ings and premature differentiation of neuroepithelial stem cells and radial glial cells into neuronal stages were observed in regions of the ventricular zone. This led to a pronounced reduction in the number of neuronal cells and a decrease in the size of the ganglionic eminence. The ganglionic eminence is a morphological structure observed during CNS development, where neuronal progenitors proliferate and from which different subtypes of neuronal cells originate, e.g. gamma-aminobutyric acid (GABA)-dependent neurons. Additionally, immunoblot analysis of conditional knockout mouse brains revealed an altered processing of the Notch-1 receptor and altered Notch-1-dependent target gene expression. The ADAM10-modulated canonical Notch-1 signaling pathway is responsible for lateral inhibition, which regulates preservation of the stem cell state and neuronal differentiation during neurogenesis. The proliferation and migration of neuronal cells was followed in control- and ADAM10-deficient mice by staining of actively proliferative embryonic cells. In ADAM10-deficient animals, postmitotic cells were already detected in actively proliferative zones. These studies led to the conclusion that ADAM10 deficiency led to disturbed radial migration. The process of radial migration mainly regulates the development of versatile laminated regions, such as the cerebral hemispheres. Early neurons build up in layers near to the ventricular zone of the cortical plate; whereas later-appearing neurons find their positions in the overlying layers. Analysis of the conditional knockout mice revealed that ADAM10 specifies the differentiation of multipotent neuronal precursor cells into glial and neuronal precursor states in a Notch-1-dependent manner. At early time points, the activity of ADAM10 inhibits premature differentiation of neuronal precursors; whereas at later time points, gliogenesis is induced. ADAM10 deficiency leads to an increase in neuronal precursors and subsequently to more postmitotic neurons. Additionally, ADAM10 deficiency also decreases glial differentiation, thus leading to a reduced number of glial cells and oligodendrocytes (◘ **Fig. 2**).

ADAM10 and Alzheimer's disease

In 1990, the proteolytic processing of APP within the Aβ sequence by a protease—whose identity was unknown at the time—named "α-secretase" was described. The availability of this non-amyloidogenic processing of APP, as an alternative pathway to processing by BACE-1, has led to this mechanism being considered as an interesting therapeutic target. Extensive studies have since been initiated to identify the responsible protease(s). The activation of α-secretase represents another option for modulating APP processing. Overexpression of ADAM10 in a murine model of AD led to an increase in the secretion of soluble APPα [4]. Moreover, the impaired cognitive skills of the mice were partially restored.

The generation of primary neuronal cultures deficient in ADAM10 showed that soluble APPα production was drastically reduced. In support of these findings, knockdown experiments reducing ADAM10 expression and activity in primary neurons led to comparable results [3]. The non-amyloidogenic APP processing pathway that liberates soluble APPα is thought to excerpt neuroprotective functions. It has been shown that soluble APPα stimulates neurite outgrowth in chick and mouse neurons. In addition, it influences growth of dendrites and axons in embryonic cortical neurons. Interestingly, patients carrying familial mutations in the *APP* gene close to the α-secretase cleavage site show severe AD progression associated with hereditary cerebral angiopathy. These mutations not only enhance $A\beta_{42}$ release, but also reduce liberation of the P3 fragment, which is produced by α-secretase and γ-secretase complex activity (◘ **Fig. 3**). A recently published study described mutations in the ADAM10 prodomain. These mutations lead to AD and a reduction in α-secretase activity, which also increased the production of Aβ peptides in vivo [9].

ADAM10 and prion diseases

The glycosylphosphatidyl (GPI)-linked cellular prion protein (PrPC) fulfills dual functions in CNS biology. On one hand it is a substrate for the pathological isoform of the prion protein (PrPSc) and on the other hand, it influences myelinization and neurogenesis. An experimental study identified PrPC as a substrate for ADAM10 using the ADAM10-(Nestin-Cre)-knockout mouse model described above [1]. It could be shown that upon deletion of ADAM10 in neuronal progenitor cells, PrPC

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Abstract
Proteolytic and amyloidogenic processing of amyloid precursor protein (APP) by β- and γ-secretases are pathological hallmarks of Alzheimer's disease (AD). These proteolytic activities lead to release of the amyloid-β peptides believed to cause neurological pathology and be linked to pathological progression in AD. Due to its capability to cleave APP within the toxic peptide sequence, the metalloproteinase ADAM10 ("a disintegrin and metalloprotease") is a known antagonist of the disease-causing pathway. ADAM10 also plays a major role in the ectodomain shedding of a number of important cell surface proteins. In addition, ADAM10 is involved in the proteolytic activation cascade of the Notch receptor, which is of crucial function in developmental processes. The study of ADAM10-deficient mice also revealed that ADAM10 regulates synaptic function and synaptogenesis. Pharmacological activation of ADAM10 is postulated to represent a valuable strategy for prevention of AD. However, due to the multiple roles of ADAM10 in the brain, it will be challenging to find a suitable therapeutic window.

Keywords
Development · Notch receptor · Amyloid precursor protein · Ectodomain shedding · Proteolysis

accumulates at early time points in the secretory pathway and at the plasma membrane. Simultaneously, it could be proven that ADAM10 mediates the shedding of PrPC close to the membrane. The impact of PrPC accumulation on neuronal function is still unclear. Analyzing conditional knockout mice deficient for ADAM10 in the adult CNS showed an increased expression of PrPC in regions of the hippocampus and cortex. The increase in PrPC expression in cellular model systems has been postulated to induce p53-dependent apoptosis. Regulation of the level of PrPC at the cell surface by ADAM10 potentially influences the conversion of prion proteins to the pathological PrPSc isoform.

ADAM10 in the adult CNS

To characterize the role of ADAM10 in regulation of the integrity and function of the adult CNS, the protease was deleted in adult neurons using a calcium/calmodulin-dependent protein kinase II (CamKII) α-Cre deleter strain [5]. The conditional knockout mice are characterized by an increased lethality during weaning, which is partially associated with epileptic episodes. Additionally, the mutant mice showed a reduced long-term potentiation (LTP), a disturbed fear-associated behavior (passive avoidance tests) and impaired visual spatial memory (Morris water maze). Histologically, a reactive astrogliosis was detected. Immunoblot analysis revealed reduced APP processing and decreased expression of the N-methyl-D-aspartate (NMDA) receptor subunit 2A. The NMDA receptor is a glutamate-dependent ion channel that is essential for synaptic plasticity and is a basis for learning and memory formation. Calcium influx through NMDA receptors is a prerequisite for synaptogenesis, experience-driven synaptic modulation and long-term changes in synaptic regions. The transport of NMDA receptor 2A subunits to the postsynaptic surface plays an important role during the induction of LTP in the hippocampus. The observed reduction in NMDA receptor 2A expression is thought to be partially responsible for the reduction of LTP induction and impaired spatial memory formation in the conditional ADAM10 knockout mice.

Ectodomain cleavage of N-cadherin was also inhibited in adult neuronal ADAM10-deficient mice. Cadherins are calcium-dependent adhesion molecules which regulate the recognition/adhesion of neurites via homophilic interactions, thereby affecting formation of synapses. In the adult CNS, N-cadherin is expressed in the cerebellum, in the neocortex and within the hippocampus. At postsynaptic regions, N-cadherin regulates surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, thus modulating synaptic plasticity. Interestingly, studies have revealed that blockage of ADAM10 postsynaptic transport by inhibition of the interaction with the synapse associated protein 97 (SAP97) led to morphological changes in dendritic spine structures and an altered AMPA receptor level as a function of N-cadherin proteolysis at the postsynaptic surface.

Synaptogenesis and ADAM10 activity

The development and modulation of synapses is an essential process for maintenance of CNS function, as it is for the differentiation of different neuronal and glial cell types. At synapses, multiprotein complexes integrated in pre- and postsynaptic structures are key elements for the regulation of neuronal activity in neuronal networks. The development of synapses is strictly dependent on protein complex formation between receptors, signaling molecules and scaffold proteins. At the presynaptic site, soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) proteins modulate synaptic vesicle fusion and recycling to control the release and uptake of neurotransmitters. In the postsynaptic region, dendritic spines and electron-dense regions are found (postsynaptic density, PSD) at the border to the synaptic cleft. Components of the PSD are receptors (AMPA, NMDA and ephrin receptors), cell adhesion molecules (N-cadherins, protocadherins and neuroligins), signaling molecules (CamKIIs and phosphatases), scaffold and adaptor proteins (PSD95, SAP102 and SAP97), cytoskeletal proteins (actin), as well as motor proteins and regulators of the cytoskeleton, which regulate functions of the synapse by integration into or association with the membrane.

After the release of glutamate in the synaptic cleft, the neurotransmitter binds to glutamate-dependent receptors (NMDA and AMPA) at the postsynaptic surface and triggers opening of the channels, leading to influx of sodium and calcium, and membrane depolarization. Depolarization of the membrane induces structural and functional changes in pre- and postsynaptic structures, which, after a repeated stimulus, lead to a more efficient synapse. During LTP, changes in receptor composition, AMPA receptor phosphorylation status, the surface of dendritic spines and the amount of neurotransmitter released at the presynaptic membrane are observed. Many of these processes are

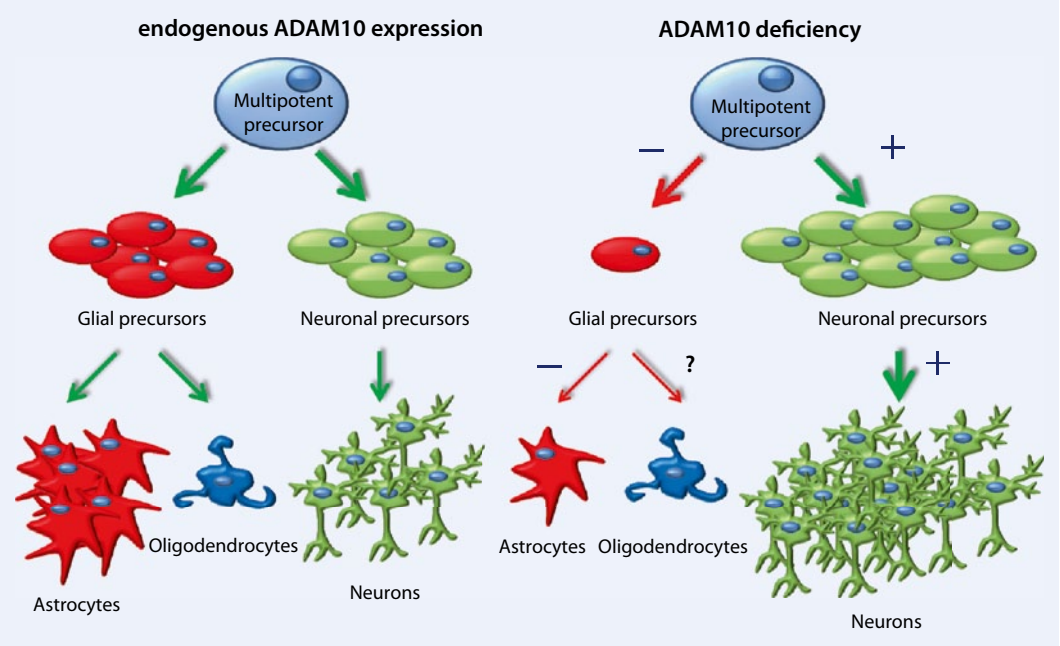

Fig. 2 ◀ Simplified presentation of the role of ADAM10 during central nervous system (CNS) development, focusing on neuronal and glial differentiation

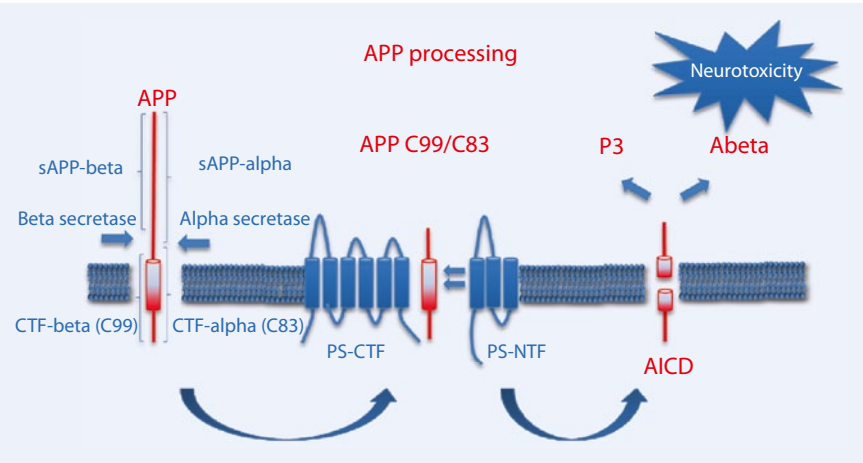

Fig. 3 ▲ Proteolytic cascade of amyloid precursor protein (*APP*) processing by different secretases and intramembrane proteases which leads to the production of the amyloid beta (*Abeta*) peptide. *CTF, C* C-terminal fragment, *NTF* N-terminal fragment, *s* soluble, *AICD* APP intracellular domain, *PS* presenilin. Figure modified from [6]

controlled by PSD protein complexes and perturbance of their composition has significant effects on glutamate-dependent synapse function.

Blocking the postsynaptic transport of ADAM10 by SAP97 in cell culture showed that this had effects on structural rearrangements and synapse function. It became apparent that by inhibition of postsynaptic transport, uncleaved N-cadherin accumulated. Furthermore, this accumulation led to an increase in the GluR1 subunits of the AMPA receptor. It was also detected that the dendritic spines of hippocampal neurons were increased in size and an altered AMPA receptor-dependent current was revealed, showing that ADAM10 is important for the modulation of glutamate-dependent synapses.

Conditional CamKII α-Cre-ADAM10 knockout mice are characterized by impaired learning capacity and an altered neuronal network activity in the CA1 region of the hippocampus, which underscores the role of ADAM10 during synapse formation. An altered synaptic function could apparently also be linked to morphologically changed spine structures. The detected reduction in NMDA receptor expression is explained by this altered morphology. The impaired development of spines after ADAM10 deletion was also detected in an independent study, after induced misstrafficking of the protease in postsynaptic cells. The ADAM10-mediated ectodomain shedding processes are most likely responsible for the observed morphological and functional changes. Upon deletion of ADAM10, it has been found that the nectin-1 adhesion molecule shows reduced ectodomain shedding. Together with its adaptor protein Afadin, nectin-1 colocalizes in cadherin/catenin structures at the postsynaptic membrane, where it regulates the size and structure of the developing synapse. Neuroligin 1 (NL1) has a similar effect on synaptogenesis. It has also been identified as an ADAM10-specific substrate [10]. Ectodomain cleavage of NL1 is triggered by synaptic activity or interaction with neurexins. This, in turn, leads to a reduction of surface NL1 expression and reduced synaptic activity. ADAM10 functions as a central molecular switch for this regulatory circle.

Aside from the aforementioned substrate proteins that are modulated by ADAM10, there are additional substrates—such as ephrin ligands, PrPC and adhesion molecules (NCAM and L1)—which may contribute to the observed synaptic

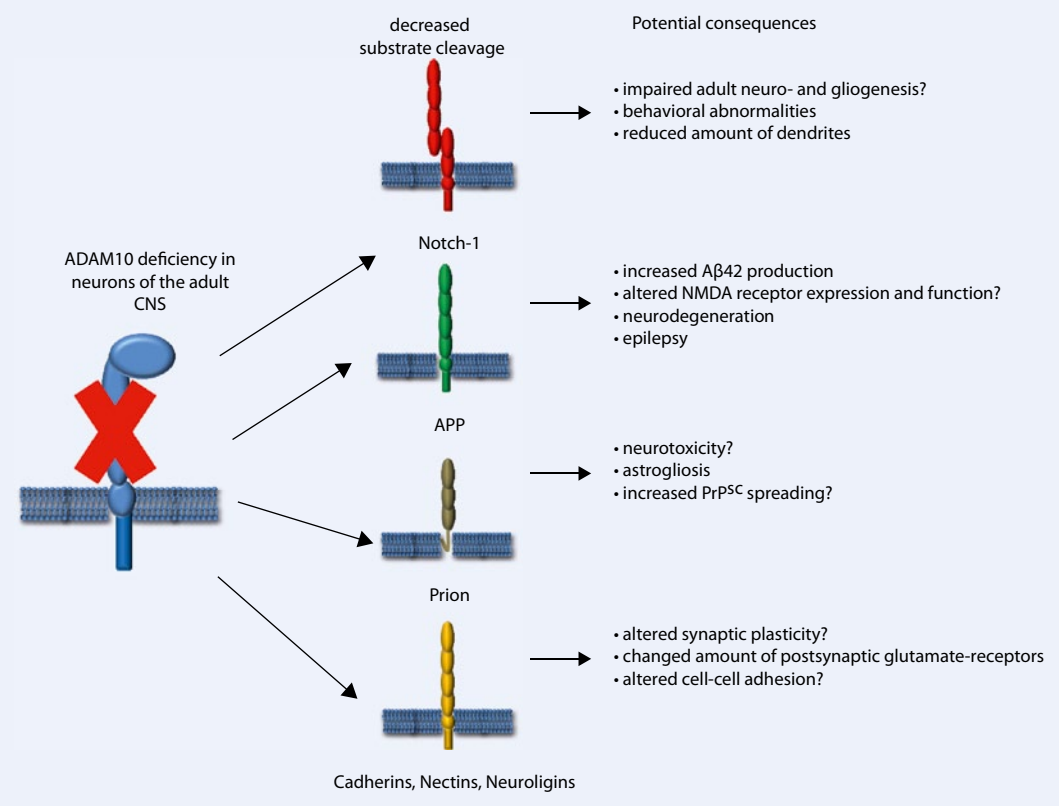

Fig. 4 ◀ Postnatal neuronal deletion of ADAM10 leads to altered processing of ADAM10 substrates, which can explain the phenotypes of conditional knockout mouse models. *CNS* central nervous system, *APP* amyloid precursor protein, *NMDA* N-methyl-D-aspartate

defect in the ADAM10-deficient animals. Moreover, APP and its proteolytic fragments generated by ADAM10 are thought to be involved in synapse reorganization.

The prominent role of ADAM10 in synapse biology questions the applicability of some novel therapeutic approaches which aim to stimulate ADAM10. However, a moderate upregulation of ADAM10 activity in postmitotic neurons is well tolerated, as shown in studies with transgenic animal models of ADAM10 [4]. To what extent this may be exploited therapeutically in humans in the future remains open. A neuron-specific modulation of ADAM10 activity is most likely difficult to realize.

Regulation of ADAM10

The prominent role of ADAM10 in the finely tuned control of the cellular mechanisms and processes of healthy organisms is further supported by studies of ADAM10 deficiency in skin and the hematopoietic system. For a detailed characterization of ADAM10 it is essential to analyze regulation, transport and activity of the ADAM10 protein, due to its broad substrate spectrum and possibly overlapping substrate specificity with the closely related metalloprotease ADAM17.

The aforementioned SAP97 protein was initially identified as a shuttle molecule, shuttling glutamate-dependent receptors to postsynaptic areas of excitatory synapses. In addition, ADAM10 was shown to be transported to the postsynapse via interaction of its C-terminal Src homology (SH3) domain with SAP97. This process is regulated by NMDA receptor activation and controls the α-secretase activity at postsynaptic membranes. Furthermore, analysis of a mouse model in which the postsynaptic transport of ADAM10 was blocked revealed phenotypes which partially reflect early AD events in humans.

Following analysis of the promoter region of the human *ADAM10* gene, binding elements of retinoic acid responsive elements (RAREs) were identified that regulate the expression of *ADAM10*. Cell culture-based functional studies showed that the vitamin A metabolite all-trans retinoic acid (atRA) affected ADAM10 mRNA and protein expression via the activation of retinoic acid receptors (RARs). The induced increase in ADAM10 expression correlated directly with enhanced APP proteolysis via the α-secretase pathway. Clinical trials using acitretin (a synthetic vitamine A analog) are currently being performed in psoriasis and AD patients. Acitretin does not bind directly to RARs, but it displaces atRA from cellular retinoid-binding proteins (CRAPs) and enriches the amount of free atRA, which subsequently leads to higher RAR activity.

Deacetylation is another regulatory mechanism by which the activity of histones and transcription factors are controlled. The transcriptional activity of the RA receptor β (RARβ) and its activation are controlled by a NAD-dependent deacetylase (SIRT1), which directly influenced the α-secretase pathway in an animal model. After crossing a mouse model of AD with brain-specific SIRT1 knockout mice, accelerated AD-associated symptoms (plaque formation and behavioral abnormalities) were observed, which were accompanied by lethality in the animals at 3–5 months of age. Additionally, transgenic overexpression of SIRT1 in the murine model decreased plaque formation and reduced the behavioral abnor-

malitie—an effect which could be attributed to enhanced APP processing through the α-secretase pathway.

Tetraspanins (TSPAN12, TSPAN15, CD9 and CD81) were identified as important modulators of ADAM10 activity. Tetraspanins make up a family of multimeric transmembrane proteins that span the membrane four times and are structurally characterized by a small and a large extracellular loop (SEL and LEL). They are found in different species. Due to their largely ubiquitous expression patterns in the body, as well as their number, tetraspanins are involved in a multitude of cellular processes, including cell migration and cell fusion. Tetraspanins have also been described as functional organizers of multimolecular membrane and signaling complexes which are influenced by their integration in the "tetraspanin-web". The tetraspanins CD9 and CD81 have been identified as ADAM10 interaction partners. The application of antibodies against CD9 and CD81 led to an increase in ADAM10-dependent shedding of substrates (epithelial growth factor, EGF; tumor necrosis factor α, TNFα) in cell culture experiments. TSPAN12 and TSPAN15 have also been identified as ADAM10 interaction partners.

The physical interaction of ADAM10 with TSPAN15 has been demonstrated using different approaches (yeast two-hybrid interaction screening and coimmunoprecipitation) [7]. ADAM10 and TSPAN15 colocalized in ER regions and at the plasma membrane. Overexpression of TSPAN15 increased the maturation of ADAM10 and simultaneously led to enriched ADAM10 plasma membrane localization. The increase in plasma membrane expression of ADAM10 elicited by TSPAN15 overexpression increased the proteolysis of "neuronal" substrates (APP, N-cadherin). This increase in substrate proteolysis correlated with a prolonged half-life of the active form of ADAM10, which was revealed by pulse-chase experiments. It could be possible that the interaction of TSPAN15 with ADAM10 masks the triple arginine ER retention motif in the C-terminus of ADAM10, thus allowing its exit from ER regions and subsequent activation of ADAM10 by furin.

Therapeutic visions

Studies of the role of the metalloprotease ADAM10 in the CNS have not only revealed the importance of ADAM10 for the development of the brain, but also its relevance to modulation of the function of the adult CNS. ADAM10 contributes to the processing of APP. Its role as a non-amyloidogenic protease triggered development of clinical approaches aimed at activating the protease and thereby preventing the production of neurotoxic Aβ peptides. Due to the multiple functions of ADAM10, it remains an open question whether such therapeutic approaches are tolerated without any side effects. Particularly the roles of ADAM10 in the Notch signaling pathway and synaptogenesis have to be considered in this context. Studies addressing the complex mechanisms of ADAM10 regulation and potential substrate specificities in more detail will presumably uncover additional therapeutic targets.

A complete list of references can be requested from the authors.

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Since 2001, Paul Saftig has been Professor of Biochemistry and director of the Biochemical Institute at the University of Kiel, Germany. He studied biology and earned his PhD from the University of Göttingen in 1994, where he worked in Prof. Kurt von Figura's lab to characterize the in vivo functions of lysosomal hydrolases. Until his habilitation in biochemistry in 2000, Paul Saftig's research was focused on analysis of the functions of lysosomal membrane proteins and lysosomal proteases, as well as those of proteases (secretases) involved in cleavage of the amyloid precursor protein. His current research interests are elucidation of the biological functions of proteins of the lysosomal compartment and the study of the APP secretases, with a focus on understanding their role in the central nervous system. In 2010 he was awarded the famous "Hans & Ilse Breuer" price for research into Alzheimer's disease.

Johannes Prox has been employed as a postdoc in Prof. Christoph Becker-Pauly's lab in the Biochemical Institute of the University of Kiel since 2013. He studied biochemistry at the University of Bielefeld and received his PhD in 2012 for work in Prof. Paul Saftig's lab. During his PhD thesis he worked on the metalloprotease ADAM10, its role in CNS development and its functions in the adult CNS. He also worked on the molecular regulation of this protease via tetraspanins. Today his research focusses on other metalloproteases (meprins) and their functions in pathological conditions of the organism such as fibrosis and inflammatory diseases.

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Compliance with ethical guidelines

Conflict of interest. J. Prox and P. Saftig state that there are no conflicts of interest. The accompanying manuscript does not include studies on humans or animals.

References

1. Altmeppen HC, Prox J, Puig B et al (2011) Lack of a-disintegrin-and-metalloproteinase ADAM10 leads to intracellular accumulation and loss of shedding of the cellular prion protein in vivo. Mol Neurodegener 6:36
2. Jorissen E, Prox J, Bernreuther C et al (2010) The disintegrin/metalloproteinase ADAM10 is essential for the establishment of the brain cortex. J Neurosci 30:4833–4844
3. Kuhn PH, Wang H, Dislich B et al (2010) ADAM10 is the physiologically relevant, constitutive alpha-secretase of the amyloid precursor protein in primary neurons. EMBO J 29:3020–3032
4. Postina R, Schroeder A, Dewachter I et al (2004) A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model. J Clin Invest 113:1456–1464
5. Prox J, Bernreuther C, Altmeppen H et al (2013) Postnatal disruption of the disintegrin/metalloproteinase ADAM10 in brain causes epileptic seizures, learning deficits, altered spine morphology, and defective synaptic functions. J Neurosci 33:12915–12928
6. Prox, J, Rittger, A, Saftig (2012) Physiological functions of the amyloid precursor protein secretases ADAM10, BACE1, and presenilin.Exp. Brain Res 217:331–341
7. Prox J, Willenbrock M, Weber S et al (2012) Tetraspanin15 regulates cellular trafficking and activity of the ectodomain sheddase ADAM10. Cell Mol Life Sci 69:2919–2932
8. Reiss K, Saftig P (2009) The "a disintegrin and metalloprotease" (ADAM) family of sheddases: physiological and cellular functions. Semin Cell Dev Biol 20:126–137
9. Suh J, Choi SH, Romano DM et al (2013) ADAM10 missense mutations potentiate β-amyloid accumulation by impairing prodomain chaperone function. Neuron 80:385–401
10. Suzuki K, Hayashi Y, Nakahara S et al (2012) Activity-dependent proteolytic cleavage of neuroligin-1. Neuron 76:410–422
11. Weber S, Saftig P (2013) Ectodomain shedding and ADAMs in development. Development 139:3693–3709