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Review

The "A Disintegrin And Metalloproteases" ADAM10 and ADAM17: Novel drug targets with therapeutic potential?

Paul Saftig[a,*], Karina Reiss[b]

[a] Biochemical Institute, Christian-Albrechts-University Kiel, Olshausenstr. 40, D-24098 Kiel, Germany
[b] Institute of Dermatology, Christian-Albrechts-University Kiel, Olshausenstr. 40, D-24098 Kiel, Germany

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ABSTRACT

Proteolytic ectodomain release, a process known as "shedding", has been recognised as a key mechanism for regulating the function of a diversity of cell surface proteins. *A D*isintegrin *A*nd *M*etalloproteinases (ADAMs) have emerged as the major proteinase family that mediates ectodomain shedding. Dysregulation of ectodomain shedding is associated with autoimmune and cardiovascular diseases, neurodegeneration, infection, inflammation and cancer. Therefore, ADAMs are increasingly regarded as attractive targets for novel therapies. ADAM10 and its close relative ADAM17 (TNF-alpha converting enzyme (TACE)) have been studied in particular in the context of ectodomain shedding and have been demonstrated as key molecules in most of the shedding events characterised to date. Whereas the level of expression of ADAM10 may be of importance in cancer and neurodegenerative disorders, ADAM17 mainly coordinates pro- and anti-inflammatory activities during immune response. Despite the high therapeutical potential of ADAM inhibition, all clinical trials using broad-spectrum metalloprotease inhibitors have failed so far. This review will cover the emerging roles of both ADAM10 and ADAM17 in the regulation of major physiological and developmental pathways and will discuss the suitability of specifically modulating the activities of both proteases as a feasible way to inhibit inflammatory states, cancer and neurodegeneration.

Introduction

Ectodomain shedding of integral membrane proteins appears to be of general importance for type I and type II transmembrane proteins or GPI-anchored molecules. ADAM-mediated shedding is essential for a number of biological processes such as cell fate determination, cell migration, wound healing, neurite and axon guidance, heart development, immunity, cell proliferation and angiogenesis. It is estimated that up to 4% of the proteins on the cell surface undergo ectodomain shedding (Arribas and Massague, 1995) affecting functionally diverse proteins such as cadherins, L-selectin, Fas ligand, TNF-alpha, EGFR ligands, ErbB2, ErbB4, Amyloid Precursor Protein (APP), Notch receptor, Notch ligands and many others.

ADAMs (an overview is found at: http://people.virginia.edu/~jw7g/Table_of_the_ADAMs.html) as proteins of about 750 amino acid length, are characterised by a conserved domain structure (Fig. 1), consisting of an N-terminal signal sequence followed by a prodomain, a metalloproteinase domain, a disintegrin domain with a cysteine-rich region, an EGF-like domain (except ADAM10 and ADAM17), a transmembrane domain and a cytoplasmic tail (Black and White, 1998; Blobel, 1997; Blobel and White, 1992; Takeda, 2009). The hydrolytic processing of protein substrates requires a zinc-binding motif containing three histidine residues (HEXGHXXGXXHD) and a highly conserved methionine-turn in the active-site helix.

ADAM-mediated shedding is both constitutive and inducible, dependent on G-protein coupled receptors, protein kinase C, intracellular Ca^{2+} levels, membrane lipid composition and other experimental and natural stimuli. Also modulation of ADAM activity by removal of the inhibitory prodomain, by changing their intracellular distribution and by interaction of proteins, and/or posttranslational modifications of their cytoplasmic tails play a role in the regulation of ectodomain shedding. Studies in knockout mice revealed that among the ADAM family members apparently ADAM10 and ADAM17 are essential for a number of developmental and physiological processes and needed for the development of tissues and organisms (Reiss and Saftig, 2009; Tousseyn et al., 2006).

Abbreviations: ADAM, A Disintegrin And Metalloproteinase; AD, Alzheimer's disease; APP, Amyloid Precursor Protein; AR, Amphiregulin; BTC, Betacellulin; CXCL, CXC, chemokine ligand; EGF, Epidermal growth factor; EGFR, EGF receptor; EPR, Epiregulin; HB-EGF, Heparin-binding EGF; HER, Human epidermal growth factor receptor; JAM-A, Junctional adhesion molecule-A; MMP, Matrix metalloproteinase; NRG, Neuregulin; PMA, Phorbol 12-myristate 13-acetate; Pcdh, Protocadherin; PrP, Prion protein; RA, Rheumatoid arthritis; TGF, Transforming growth factor; VCAM, Vascular cell adhesion molecule.

* Corresponding author. Tel.: +49 0 431 8802216; fax: +49 0 431 8802238.
E-mail address: psaftig@biochem.uni-kiel.de (P. Saftig).

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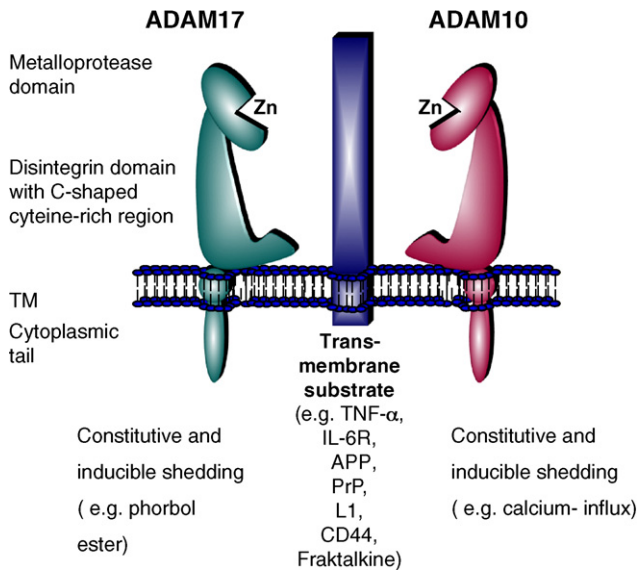

Fig. 1. ADAM10 and ADAM17 share several structural and functional homologies. Both proteins consist of a metalloproteinase domain, a disintegrin domain, and a cysteine-rich domain. Within the cytosolic domain phosphorylation sites or proline-rich regions with SH3 domains are present. The prodomain, which keeps the zymogen inactive, is removed during maturation. ADAM-mediated shedding of transmembrane (TM) proteins leads to the release of soluble extracellular domains and provides a mechanism for down-regulating cell surface proteins but also for extracellular signalling. Both proteases share common transmembrane proteins as substrates even though "preferential" substrates exist. Several stimuli have been described to increase ADAM10 and ADAM17-dependent proteolysis. Even though these stimuli are often non-physiologic and not specific they are very useful to define the characteristic properties of protease activity.

Substrates for ectodomain shedding by ADAM10 and ADAM17

ADAM10-mediated ectodomain shedding modulates the function of cell adhesion molecules and represents an efficient process in the regulation of paracrine, juxtacrine and autocrine signalling (Reiss et al., 2006a; Reiss and Saftig, 2009). In this context ADAM10-induced N-cadherin cleavage (Reiss et al., 2005) results in changes in the adhesive behaviour of cells and also in a dramatic redistribution of beta-catenin from the cell surface to the cytoplasmic pool, thereby influencing the expression of β-catenin target genes. Analysis of ADAM10-deficient fibroblasts, inhibitor studies, and RNA interference-mediated down-regulation of ADAM10 demonstrated that ADAM10 is also responsible for the constitutive and regulated shedding of E (epithelial)-cadherin in fibroblasts and keratinocytes (Maretzky et al., 2005a). ADAM10-mediated E-cadherin release is also regulated by proinflammatory cytokines thereby modulating keratinocyte cohesion in eczematous dermatitis (Maretzky et al., 2008). Interestingly, gamma-protocadherins (Pcdh), which are enriched at synapses and involved in synapse formation, specification, and maintenance, are also substrates for ADAM10 (Reiss et al., 2006b). It was also revealed that ADAM10 regulates the endothelial permeability and T-cell transmigration by shedding of vascular endothelial VE-cadherin (Schulz et al., 2008). Both, ADAM10 and ADAM17 play an important functional role by regulating L1-dependent neuronal cell adhesion, cell migration, and neurite outgrowth (Maretzky et al., 2005b). The emerging critical role of ADAM10 for membrane proteolysis is underlined by the fact that a number of further important transmembrane proteins which are susceptible for ADAM10-mediated ectodomain shedding and cell signalling were identified. The CXC-chemokine-ligand 16 (Abel et al., 2004), CX3CL1 (fractalkine) (Hundhausen et al., 2003), CD44 (Nagano et al., 2004), betacellulin (Sahin et al., 2004), Axl (Budagian et al., 2005), desmoglein2 (Bech-Serra et al., 2006), receptor tyrosine phosphatase (Anders et al., 2006), RAGE (Raucci et al., 2008), Klotho (Bloch et al., 2009), CD23 (Weskamp et al., 2006) and ephrin (Janes et al., 2009) are examples for the growing list of ADAM10-specific substrates. Interestingly, Bri2, as a type II-oriented transmembrane protein which is associated with familial British and Danish dementia, is first shed by ADAM10 and subsequently processed by the signal peptide peptidase like proteases SPPL2A/SPPL2B (Martin et al., 2008). Also the apoptosis-inducing Fas ligand (FasL) is a type II transmembrane protein that is involved in the downregulation of immune reactions by activation-induced cell death (AICD) as well as in T cell-mediated cytotoxicity. Using pharmacological approaches in 293T cells, *in vitro* cleavage assays as well as loss and gain of function studies in MEF cells, ADAM10 could be shown to be critically involved in the shedding of FasL (Schulte et al., 2007) which is supposed to be a prerequisite to further intramembrane cleavage by SPPL2 proteases. ADAM10 itself is also subject to regulated intramembrane proteolysis. ADAM9 and -15 were identified as the proteases responsible for releasing the ADAM10 ectodomain, and presenilin (gamma-secretase) as the protease responsible for the release of the ADAM10 intracellular domain (ICD). This domain then translocates to the nucleus and localises to nuclear speckles, thought to be involved in gene regulation. ADAM10 may perform a dual role in cells, as a metalloprotease when it is membrane-bound, and as a potential signalling protein once cleaved by ADAM9/15 and the gamma-secretase (Tousseyn et al., 2009). ADAM17, originally discovered as the protease responsible for the processing of precursor TNF-alpha, was shown to be a regulator of several cellular events due to the wide diversity of substrates, such as TNFR1 and TNFR2, APP, CD30, interleukin-6 receptor (IL-6R), L-selectin and collagen XVII (for review see Gooz (2010)). In particular, ADAM17 emerged as the major phorbol 12-myristate 13-acetate (PMA)-stimulated and constitutive sheddase of TGFα, amphiregulin, HB-EGF, and epiregulin (Le Gall et al., 2009), which is consistent with the essential role for ADAM17 in activation of the epidermal growth factor receptor (EGFR) during development as shown by EGFR-related defects of the ADAM17 knockout mouse model (Peschon et al., 1998).

Loss of function studies suggest crucial roles of ADAM10 and ADAM17

The availability of knockout mice for ADAM10 and ADAM17 allows a more comprehensive study of functions of both proteases in physiological and pathological processes. The biochemical and cell biological characterisation of ADAM10 and ADAM17 already revealed much information about candidate substrates and their putative role in cell adhesion and signalling. However, the study of constitutive and conditional knockout mice allows a more realistic insight into the role of each protease in development and disease.

ADAM10-deficient embryos were found to die around 9.5 dpc, with multiple malformations in the developing central nervous system, somites and cardiovascular system strikingly similar to that of a complete Notch deficiency. Consistent with these observations, the expression pattern of genes involved in the Notch pathway, dll-1, one of the ligands of Notch, and hes-5, a transcription factor activated by Notch signalling, was severely disrupted (Hartmann et al., 2002). The early lethality of the conventional ADAM10$^{-/-}$ mice prevented the analysis of ADAM10 function in selected tissues and later stages of development. To investigate the function of ADAM10 in brain, ADAM10 conditional knockout (cKO) mice were generated using a *nestin Cre* promoter, limiting ADAM10 inactivation to neural progenitor cells (NPC) and NPC-derived neurons and glial cells (Jorissen et al., 2010). These cKO mice die perinatally with a disrupted neocortex and a severely reduced ganglionic eminence,

due to precocious neuronal differentiation resulting in an early depletion of progenitor cells. Premature neuronal differentiation is associated with aberrant neuronal migration and a disorganised laminar architecture in the neocortex. Neurospheres derived from ADAM10-cKO mice have a disrupted sphere organisation and segregate more neurons at the expense of astrocytes. Several Notch regulated genes were severely downregulated in ADAM10-cKO brains, in accordance with the central role of ADAM10 in this signalling pathway explaining the neurogenic phenotype. Importantly, it was also found that alpha-secretase-mediated processing of APP was largely reduced in these neurons, demonstrating that ADAM10 represents the most important APP alpha-secretase in brain (Jorissen et al., 2010). The conditional knockout mice ($ADAM10^{Flox/Flox}$) will also be helpful to resolve the functions of ADAM10 in non-neuronal tissues and in adult mice and to estimate possible side-effects of a therapeutic ADAM10 inhibition.

Similar to the constitutive ADAM10 knockout mice ADAM17-deficiency leads to embryonic lethality pointing to a careful therapeutic strategy in case ADAM17 will be inhibited in early life. The phenotype of mice homozygous for an inactivating ADAM17 mutation ($ADAM17^{Zn/Zn}$) with a complete disruption of ADAM17 (our own unpublished data) is similar to that of TGF-alpha knockout mice (Luetteke et al., 1993; Mann et al., 1993). The majority of ADAM17-inactivated (deleted) mice die between 17.5 dpc and the first day after birth. T-cells derived from the $ADAM17^{Zn/Zn}$ mice showed a reduction of TNF-α release. Both knockout mice display an identical open-eye phenotype due to a failure of eyelid fusion. The additional defects in the hair, skin, lung, heart and epithelial tissues are also in part similar to the abnormalities shown in EGFR and EGF family knockout mice supporting the hypothesis that ADAM17 is important for activating several ligands of the EGFR family.

The central role of ADAM17 in adult mice using a septic shock disease model was first revealed by studies making use of conditional ADAM17 knockout mice which were challenged by administration of LPS (Horiuchi et al., 2007). These studies showed that TACE inactivation yielded in a protection from endotoxin shock lethality by preventing increased TNF-α serum levels. An additional model, more closely related to the situation when ADAM17 activity is inhibited by therapeutic drugs, are hypomorphic ADAM17 ($ADAM17^{ex/ex}$) mice (Chalaris et al., 2010). Such mice are viable but they also display eye, hair, and skin defects. The intestine of these homozygous hypomorphic ADAM17 mice showed no overt abnormalities. However, the animals displayed dramatically increased susceptibility to intestinal inflammation induced by dextran sulfate sodium. This effect seems to be a consequence of impaired EGFR-dependent regeneration caused by failure of shedding of EGFR ligands pointing to the importance of the regulation of regenerative responses. It may well be that also an impaired shedding of the IL6 receptor contributed to the inflammatory reactions seen in the ADAM17 mutant mice. It was shown that different stimuli such as PMA, bacterial toxins, bacterial metalloproteinases and apoptosis led to the cleavage of the IL6R. Induced ectodomain shedding of the IL6R is mainly mediated by ADAM17 and constitutive shedding is mediated by ADAM10. Unlike most soluble receptors, the IL6R does not act as an antagonist, but as an agonist of IL6-signalling. The pro-inflammatory activities of IL6 rely mostly on the sIL6R. Signals via the membrane bound IL6R are likely to be responsible for normal homeostasis and signals via the sIL6R could be more crucial during pathophysiological conditions.

ADAM10 and ADAM17-double deficient mice, which die at embryonic day 8.5, show even more severe defects than ADAM10 single deficient mice (our unpublished data), pointing to the importance of redundancy of both proteases *in vivo*. Even though specific ADAM inhibitors are available, this fact further complicates a prediction about how selective inhibition of one protease would be compensated in the organism.

Modulating ADAM activity in neurodegeneration

Due to its proven role as an alpha-secretase involved in the non-amyloidogenic processing of APP the upregulation of ADAM10-mediated proteolysis is one of the promising strategies to treat neurodegenerative Alzheimer's disease (AD). One of the hallmarks of this disease is the deposition of neurotoxic plaques of amyloid beta peptides (Aβ). The production of these peptides is avoided by an alternative APP cleavage pathway mediated mainly by ADAM10 (Fig. 2). Both, ADAM10 and APP are expressed in human cortical neurons and in brains of mice from different developmental stages (Marcinkiewicz and Seidah, 2000). Mutations in ADAM10 have been associated with a reduction of alpha-secretase in familial late-onset AD (Kim et al., 2009). In an independent study it was found that ADAM10 mRNA expression is upregulated in severe cases of AD (Gatta et al., 2002). Despite this apparent conflict the most striking evidence that an upregulation of ADAM10 may have beneficial effects in AD comes from transgenic mouse studies where ADAM10 was overexpressed. In an APP (V717I) transgenic background these mice show increased APP shedding accompanied by decreased formation of amyloid plaques (Postina et al., 2004). Interestingly, in the ADAM10/APP overexpressing mice additional beneficial effects were observed such as increased synaptogenesis, normalised long-term potentiation, learning and memory (Bell et al., 2008; Schmitt et al., 2006). In addition to the potent neurotrophic activities of soluble APP, the increased ADAM10 expression might contribute to neuroprotective effects due to the shedding of several additional substrates in the brain such as L1, N-cadherin or gamma-Pcdh (Fig. 2). The neural cell adhesion molecule L1 which is a substrate of ADAM10 and ADAM17 is known to be involved in regulating neuronal migration, neuronal survival, neurite outgrowth and myelination as well as axon guidance, fasciculation, and regeneration. The ADAM10 substrates N-cadherin and gamma-Pcdh are required for synaptic development and neuronal survival. It is very likely that shedding of these adhesion molecules does not only modulate neuronal cell contact formation and migration but also influence cell signalling pathways which might contribute to the beneficial effects observed in ADAM10 overexpressing mice (Fig. 2). In contrast, ADAM10 inhibition could lead to harmful side effects in the nervous system. This assumption is further emphasised through the recent finding, that interfering with ADAM10 function in a mouse model using cell-permeable peptides leads to an Alzheimer's disease-like neuropathology within a very short period (Epis et al., 2010).

ADAM10 and ADAM17 as targets to treat inflammatory disorders

Inflammatory diseases are mainly driven by proinflammatory cytokines including TNF-α, IL-1, IL-6 and IL-15, which stimulate gene expression of a variety of effector molecules involved in the recruitment of leukocytes. ADAM17 represents the major sheddase for these cytokines and also for the cytokine receptors TNFRI, TNFRII, IL-6R and IL15R, even though ADAM10 is also able to mediate the constitutive release of TNF-α and IL-6R (Hikita et al., 2009; Matthews et al., 2003). Moreover, both proteases modulate the function of cell adhesion molecules involved in the process of leukocyte recruitment during inflammation. While the shedding of L-selectin, Syndecan-1, Syndecan-4, VCAM-1, JAM-A and the PMA-induced release of CX3CL1 is mediated by ADAM17, ADAM10 is responsible for the constitutive and the calcium-influx-induced shedding of CX3CL1 (Hundhausen et al., 2007), for the cleavage of CXCL16 (Abel et al., 2004) and for the shedding of VE-cadherin (Schulz et al., 2008). Therefore, both proteases are in principle able to modulate inflammatory responses.

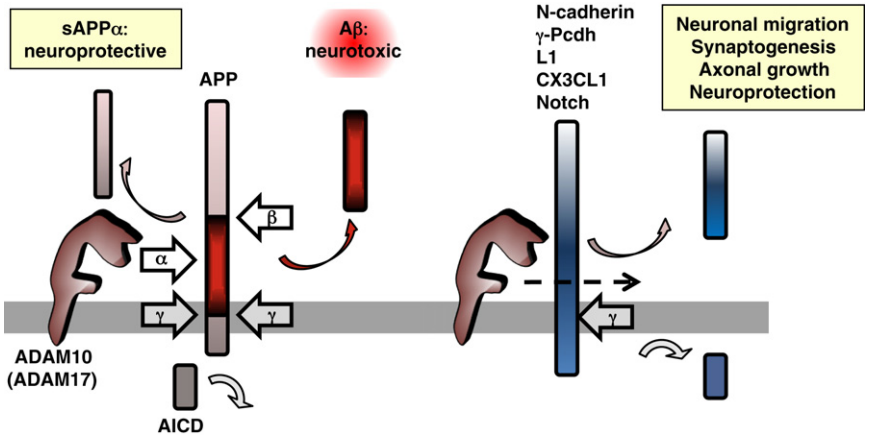

Fig. 2. ADAM function in the brain. ADAM10 has been identified as the α-secretase which releases the neuroprotective ectodomain of APP. This cleavage leads to further processing of the APP transmembrane fragment by the γ-secretase complex releasing an APP intracellular domain (AICD). α-Secretase activity prevents APP cleavage through the β-secretase/γ-secretase which would lead to the release of neurotoxic amyloid-β peptides (Aβ), the hallmark of Alzheimer's disease. Additionally, ADAM10 (and ADAM17) mediated cleavage of several adhesion molecules (e.g. N-cadherin or L1) has beneficial effects on the homeostasis of the nervous system.

TNF-α is the key player in inflammation, rheumatoid arthritis (RA), anorexia and septic shock (Bahia and Silakari, 2010; Esposito and Cuzzocrea, 2009). Since ADAM17 was the first protease identified as a TNF-α sheddase, most pharmacological approaches focused on the development of ADAM17 inhibitors to treat inflammatory diseases. In agreement with these findings the importance of ADAM17 is highlighted by increased expression of ADAM17 in various inflammatory diseases such as RA (Ohta et al., 2001), Crohn's disease (Cesaro et al., 2009), pulmonary inflammation (Ju et al., 2007), endotoxin shock (Horiuchi et al., 2007) and multiple sclerosis (Seifert et al., 2002) (Table 1). On the other hand, ADAM17 might also have beneficial regulatory functions under inflammatory conditions for example through cleavage of colony stimulating factor-1 (CSF-1) thereby downregulating macrophage activation (Rovida et al., 2001). Moreover, ADAM17-mediated release of the IL-15R might also contribute to the downregulation of collagen-induced arthritis (Ruchatz et al., 1998). In this context, it is interesting to notice that ADAM17$^{ex/ex}$ mice (Chalaris et al., 2010) showed substantially increased susceptibility to inflammation in dextran sulfate sodium colitis. These results indicate that ADAM17 might also have anti-inflammatory functions and point out that the use of ADAM inhibitors for the treatment of chronic inflammatory diseases has to be carefully considered.

Table 1
ADAM10 and ADAM17 expression and function has been described for several diseases.

Suggested associated diseases	Reference
ADAM10	
Ectopic dermatitis	Maretzky et al. (2008)
Atherosclerosis	Schulz et al. (2008)
Colon carcinoma	Gavert et al. (2005)
Gastric cancer	Yoshimura et al. (2002)
Leukaemia	Wu et al. (1997)
Prostate cancer	McCulloch et al. (2004)
Uterus	Fogel et al. (2003)
Ovarian cancer	Fogel et al. (2003)
ADAM17	
Rheumatoid arthritis	Ohta et al. (2001)
Crohn's disease	Cesaro et al. (2009)
Psoriasis	Kawaguchi et al. (2007)
Endotoxin shock	Horiuchi et al. (2007)
Pulmonary inflammation	Ju et al. (2007)
Multiple sclerosis	Seifert et al. (2002)
Breast cancer	Lendeckel et al. (2005)
Colon carcinoma	Blanchot-Jossic et al. (2005)
Hepatocellular carcinoma	Ding et al. (2004)
Lung cancer	Zhou et al. (2006)
Pancreatic carcinoma	Ringel et al. (2006)
Prostate cancer	Karan et al. (2003)
Renal cancer	Roemer et al. (2004)

ADAMs in cardiovascular diseases

Inflammation also plays a key role in coronary artery disease (CAD) and other manifestations of atherosclerosis. Atherosclerosis is a complex process, which develops in the course of specific cellular responses characterised by an initial lesion, endothelial dysfunction, infiltration of leukocytes and the formation of atherosclerotic plaques (Mallika et al., 2007). Even though it is well known that risk factors such as hypercholesterolemia, hypertension or smoking trigger the development of this disease, different theories have been proposed about the initial inflammatory responses (Bhakdi, 2003; Goldstein and Brown, 1977). One hypothesis suggests that atherosclerosis is an autoimmune disease caused by an immune reaction against autoantigens at the endothelial level (Blasi, 2008). Some models consider oxidation of entrapment low density lipoprotein (LDL) as a crucial event for the atherogenic process, while other theories describe enzymatic modification of entrapped LDL as the first step of a physiological removal process. Only when this complex machinery suffers overload detrimental effects are evoked by the unreigned activation of complement, macrophages, and other effectors of the immune system (Bhakdi et al., 2004).

Under these conditions increased ADAM10 and ADAM17-dependent proteolysis possibly contributes to the observed inflammatory effects. Patients with myocardial infarction also show increased expression of ADAM17 in areas of ruptured coronary plaques (Satoh et al., 2008). Increased ADAM17 immunoreactivity in atherosclerotic plaques of the aortic arch and sinus in apolipoprotein E-deficient mice and in humans has recently been described (Canault et al., 2006). Interestingly, plaque microparticles enhanced the shedding of ADAM17 substrates TNF-α, TNFR1 and TNFR2 (Canault et al., 2007). ADAM17 is also important for the VEGF receptor 2 stimulated processing of several receptors with known functions in endothelial cell biology and plays an important role in the context of pathological neovascularisation (Swendeman et al., 2008; Weskamp et al., 2010). ADAM17 inhibition could emerge as a good target for treatment of vascular diseases since conditional inactivation in endothelial cells in a mouse model demonstrated

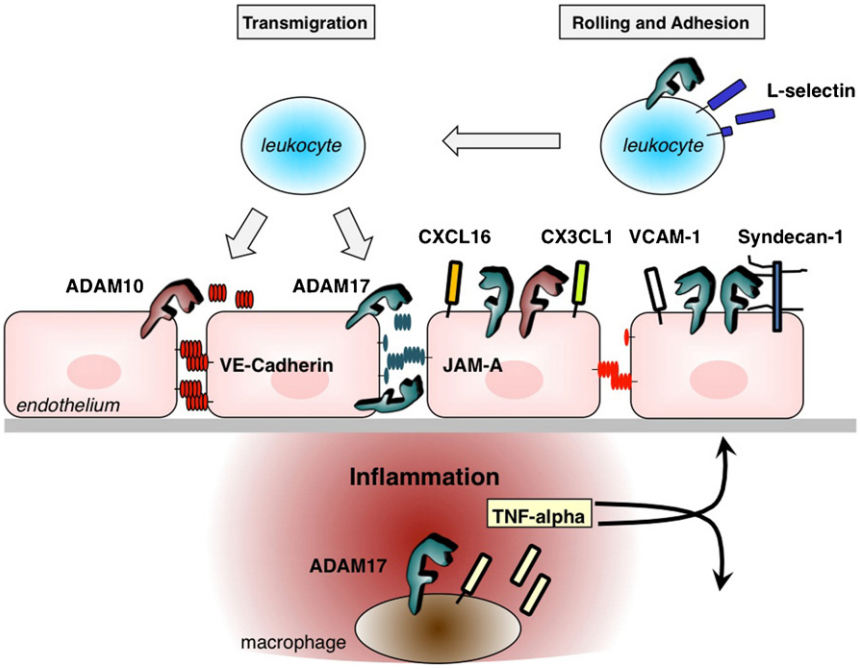

Fig. 3. ADAM10 and ADAM17 play an important role in inflammatory vascular diseases and atherosclerosis. Both proteases release proinflammatory cytokines and chemokines. Additionally, they regulate endothelial permeability through cleavage of endothelial cell adhesion molecules such as VE-cadherin or JAM-A and modulate the rolling and adhesion process of leukocytes through release of molecules such as L-selectin, VCAM-1 or Syndecan-1.

that this protease is not required for normal developmental angiogenesis or physiological vascular homeostasis (Weskamp et al., 2010). ADAM10-mediated proteolysis can also be activated in endothelial cells by different stimuli (Schulz et al., 2008). Several ADAM10 or ADAM17 substrates such as VE-cadherin or JAM-A contribute to the regulation of endothelial permeability. Increased ADAM10-mediated proteolysis correlates with decreased vascular integrity and increased production of cytokines and chemokines such as TNF-α and with increased transmigration of leukocytes (Fig. 3). Interestingly, an important role of the ADAM substrate CX3CL1 in atherosclerosis is also discussed. Shedding of this adhesive chemokine functions to control leukocyte detachment and transmigration. Moreover, scavenger rectors such as CXCL16 are also shed which should affect scavenging of oxidised lipids and adhesive functions for T cells (Galkina et al., 2007; Ludwig and Weber, 2007). Recently ADAM10 was also identified as a novel binding partner of VEGF receptor 2. It was demonstrated that ADAM10 is expressed in human atherosclerotic lesions, associated with plaque progression and neovascularisation. In addition, VEGF induced ADAM10-mediated cleavage of VE-cadherin, which could increase vascular permeability and facilitate EC migration (Donners et al., 2010). Taken together, these findings suggest that inhibiting ADAM10 as well as ADAM17 activity could be beneficial for preventing cardiovascular diseases.

The role of ADAM10 and ADAM17 in skin disorder

In knockout mouse models, ADAM10 as well as ADAM17-deficiency leads to skin defects during development and in adult mice (our unpublished observations). Both proteases are involved in the regulation of epidermal homeostasis by modulation of EGFR signalling, which is essential for keratinocyte proliferation and differentiation, hair morphogenesis, and maintenance of the skin barrier. Moreover, both proteases modulate cell adhesion and Notch receptor signalling in the epidermis. ADAM10 is essentially involved in the constitutive and induced proteolysis of E-cadherin (Maretzky et al., 2005a). This cleavage event modulates keratinocyte adhesion and cell migration *in vitro*. Additionally, ADAM10-dependent E-cadherin proteolysis has influence on β-catenin signalling and modulates the expression of typical β-catenin target genes and consequently other functions like cell proliferation. *In situ* examination of E-cadherin and ADAM10 expression in lesional skin of eczema revealed that the reduction of E-cadherin expression in areas of blister formation closely correlated with an increased level of ADAM10 expression and elevated E-cadherin shedding suggesting that ADAM10 might contribute to the impaired cohesion of keratinocytes observed in eczematous dermatitis (Maretzky et al., 2008). Since the regulation of ADAM10 and ADAM17 may be involved in epithelial barrier functions, inhibitors would in principle provide a suitable therapy to treat diseases that impair the skin barrier such as psoriasis. Psoriasis is a genetically programmed skin disease of dysregulated inflammation, which results in hyperproliferation of epidermal keratinocytes, consequential abnormal terminal differentiation, and impaired barrier function of the epidermis. Overexpression of ADAM17 mRNA in lesional psoriatic skin compared with non-lesional skin has been demonstrated by Kawaguchi et al. (2007). Using TPA-induced hyperplasia in murine skin as a model of psoriasis, Moriyama and coworkers demonstrated beneficial effects of topical metalloprotease inhibitor application. In this context, ADAM17 inhibitors might have anti-inflammatory effects through lowering the levels of TNF-α and additional beneficial effects due to reduced EGFR ligand release (Moriyama et al., 2004).

ADAM10 and ADAM17 in cancer

ADAMs also have potential implications for regulating tumor growth and metastasis as well as tumor angiogenesis through the rapid modulation of cell signalling pathways and cell adhesion (Fig. 4). An increased expression of individual ADAM family members in various types of cancer has been described even though in several cases the precise cellular expression pattern and the rele-

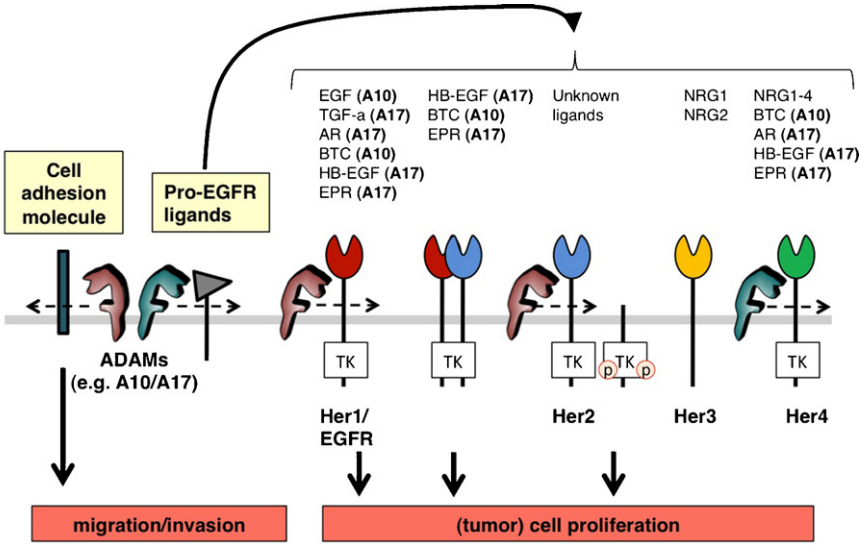

Fig. 4. Overexpression of ADAM10 and ADAM17 modulates tumour cell proliferation and metastasis. Carcinogenesis and metastasis are characterised by the detachment of cells and increased tumour cell proliferation. ADAM10 and ADAM17 activity increase tumour cell migration and invasion capacities through cell adhesion molecule cleavage. Moreover, both proteases increase tumour proliferation due to the release of pro-EGFR ligands and EGFR transactivation (TK: tyrosine kinase). ADAM10-mediated cleavage of Her2 leads to the generation of a C-terminal fragment, which strongly activates cell proliferation.

vance for tumor progression is not clear (Murphy, 2008). Increased mRNA or protein expression of ADAM17 was shown in several different tumour tissues such as breast (Lendeckel et al., 2005), brain (Zheng et al., 2007), colon (Blanchot-Jossic et al., 2005), kidney (Roemer et al., 2004), liver (Ding et al., 2004), lung (Zhou et al., 2006), ovary (Tanaka et al., 2005), pancreas (Ringel et al., 2006), prostate (Karan et al., 2003) and renal cancer (Roemer et al., 2004). In breast cancer, ADAM17 expression correlated with the invasive state of the tumour. The proliferation of breast cancer cell lines could be inhibited using anti-ADAM17 antibodies (Lendeckel et al., 2005). High ADAM17 expression correlated with a shorter survival rate of the patients indicating a prometastatic role of this protease (McGowan et al., 2008).

Overexpression of ADAM10 has been reported for colon (Gavert et al., 2005), gastric (Yoshimura et al., 2002), leukaemia (Wu et al., 1997), prostate (McCulloch et al., 2004) and ovary (Fogel et al., 2003) cancer. In prostate cancer cell lines, the mRNA expression level of ADAM10 was upregulated in response to androgens and growth factors such as insulin-like growth factor I and EGF (McCulloch et al., 2004). Even though the upregulation of ADAM10 in prostate cancer did not correlate with increased tumour stage the cellular localisation changed from cell surface immunoreactivity to a nuclear staining pattern, suggesting a direct role of ADAM10 for cell signalling during tumour progression.

It is very likely, that both ADAM10 and ADAM17 modulate tumour progression through their influence on several distinct cellular pathways. The release of cell adhesion molecules including L1, L-selectin, CD44, E-cadherin and N-cadherin affects cell–cell interaction, cell migration as well as cell signalling. Additionally, both proteases regulate the activation of the EGFR tyrosine kinase family. ADAM10 and ADAM17 are differentially involved in the shedding of EGFR ligands. ADAM17 is the phorbol ester-stimulated major sheddase for most of these receptor ligands such as transforming growth factor (TGF)-α, amphiregulin, epiregulin, epigen and heparin-binding epidermal growth factor (HB-EGF). Therefore, ADAM17 inhibitors could be particularly useful in tumours that are dependent on EGFR/Her-2 signalling. ADAM10 releases not only the signal-competent extracellular domains of betacellulin and EGF, but also Her2/ErbB2 from the cell membrane, an event that is necessary for Her2 positive tumour cells to proliferate. The extracellular domain of Her2 in blood samples of cancer patients is an indicator of poor prognosis (Christianson et al., 1998). Therefore, specific inhibitors for ADAM10 could have beneficial effects against EGFR/ErbB1 and/or Her4/ErbB4 receptor positive tumour cells that are betacellulin-dependent and against Her2 overexpressing tumours.

Metalloprotease inhibitors

Not only ADAM10 and ADAM17, but also other metalloproteases like MMPs show a high similarity of their catalytic site structure and they all bind zinc with the same geometry. A variety of metalloprotease inhibitors have been developed for the treatment of pathological processes such as chronic inflammation, cancer metastasis, arthritis or heart diseases. Most of these compounds have common structural features; they contain a 'headgroup', such as hydroxamate, which binds the catalytic zinc, a peptide or pseudopeptide backbone that lies in the side of the active-site cleft, and side chains binding to the different subpockets. These first generation peptide-like inhibitors suffered from bioavailability, pharmacokinetic problems and non-selectivity. Clinical phase studies of such inhibitors e.g. Batimastat, Ilomastat (GM6001) or Marimastat were discontinued after phase I or phase II because of side effects such as musculoskeletal toxicity. Not only the second generation of non-peptidic inhibitors like prinomastat was designed on the basis of the conformation of the active proteinase site but also none of these inhibitors reached the market. So far all clinical trials have failed to prove a beneficial effect. Because of their immense therapeutic potential, the next generation of long-acting, low-molecular mass, highly selective, orally bioavailable non-peptidic inhibitors is now being developed by different companies, which still have to prove their effectiveness (Murumkar et al., 2010).

Conclusions

Since ectodomain shedding may be dysregulated in autoimmune and cardiovascular diseases, infection, inflammation and cancer ADAM proteases are regarded as important therapeutic targets in drug discovery research. A number of ADAM-inhibitors

have been or are currently been developed. Unfortunately, the efforts so far have failed largely due to unfavourable toxicology. One major problem is still the inhibitor selectivity and the other problem is the fact that ADAMs like ADAM10 or ADAM17 are involved in the shedding of various physiologically important membrane-bound proteins, including not only several adhesion molecules but also several cytokines and growth factors, increasing the possibility of unwanted side effects. Provided that compounds with increased selectivity for one proteinase will be developed, ADAMs still remain promising targets for effective and safe drugs. Instead of using such drugs for long-term treatment of chronic diseases it seems they are more useful for specific disease states, under a certain dose and short time periods.

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References

Abel, S., Hundhausen, C., Mentlein, R., Schulte, A., Berkhout, T.A., Broadway, N., Hartmann, D., Sedlacek, R., Dietrich, S., Muetze, B., Schuster, B., Kallen, K.J., Saftig, P., Rose-John, S., Ludwig, A., 2004. The transmembrane CXC-chemokine ligand 16 is induced by IFN-gamma and TNF-alpha and shed by the activity of the disintegrin-like metalloproteinase ADAM10. J. Immunol. 172, 6362–6372.

Anders, L., Mertins, P., Lammich, S., Murgia, M., Hartmann, D., Saftig, P., Haass, C., Ullrich, A., 2006. Furin- ADAM 10-, and gamma-secretase-mediated cleavage of a receptor tyrosine phosphatase and regulation of beta-catenin's transcriptional activity. Mol. Cell Biol. 26, 3917–3934.

Arribas, J., Massague, J., 1995. Transforming growth factor-alpha and beta-amyloid precursor protein share a secretory mechanism. J. Cell Biol. 128, 433–441.

Bahia, M.S., Silakari, O., 2010. Tumor necrosis factor alpha converting enzyme: an encouraging target for various inflammatory disorders. Chem. Biol. Drug Des. 75, 415–443.

Bech-Serra, J.J., Santiago-Josefat, B., Esselens, C., Saftig, P., Baselga, J., Arribas, J., Canals, F., 2006. Proteomic identification of desmoglein 2 and activated leukocyte cell adhesion molecule as substrates of ADAM17 and ADAM10 by difference gel electrophoresis. Mol. Cell Biol. 26, 5086–5095.

Bell, K.F., Zheng, L., Fahrenholz, F., Cuello, A.C., 2008. ADAM-10 over-expression increases cortical synaptogenesis. Neurobiol. Aging 29, 554–565.

Bhakdi, S., 2003. An hypothesis for the immunopathogenesis of atherosclerosis. Clin. Nephrol. 60 (Suppl. 1), S49–S52.

Bhakdi, S., Lackner, K.J., Han, S.R., Torzewski, M., Husmann, M., 2004. Beyond cholesterol: the enigma of atherosclerosis revisited. Thromb. Haemost. 91, 639–645.

Black, R.A., White, J.M., 1998. ADAMs: focus on the protease domain. Curr. Opin. Cell Biol. 10, 654–659.

Blanchot-Jossic, F., Jarry, A., Masson, D., Bach-Ngohou, K., Paineau, J., Denis, M.G., Laboisse, C.L., Mosnier, J.F., 2005. Up-regulated expression of ADAM17 in human colon carcinoma: co-expression with EGFR in neoplastic and endothelial cells. J. Pathol. 207, 156–163.

Blasi, C., 2008. The autoimmune origin of atherosclerosis. Atherosclerosis 201, 17–32.

Blobel, C.P., 1997. Metalloprotease-disintegrins: links to cell adhesion and cleavage of TNF alpha and notch. Cell 90, 589–592.

Blobel, C.P., White, J.M., 1992. Structure, function and evolutionary relationship of proteins containing a disintegrin domain. Curr. Opin. Cell Biol. 4, 760–765.

Bloch, L., Sineshchekova, O., Reichenbach, D., Reiss, K., Saftig, P., Kuro-o, M., Kaether, C., 2009. Klotho is a substrate for alpha-, beta- and gamma-secretase. FEBS Lett. 583, 3221–3224.

Budagian, V., Bulanova, E., Orinska, Z., Duitman, E., Brandt, K., Ludwig, A., Hartmann, D., Lemke, G., Saftig, P., Bulfone-Paus, S., 2005. Soluble Axl is generated by ADAM10-dependent cleavage and associates with Gas6 in mouse serum. Mol. Cell Biol. 25, 9324–9339.

Canault, M., Leroyer, A.S., Peiretti, F., Leseche, G., Tedgui, A., Bonardo, B., Alessi, M.C., Boulanger, C.M., Nalbone, G., 2007. Microparticles of human atherosclerotic plaques enhance the shedding of the tumor necrosis factor-alpha converting enzyme/ADAM17 substrates, tumor necrosis factor and tumor necrosis factor receptor-1. Am. J. Pathol. 171, 1713–1723.

Canault, M., Peiretti, F., Kopp, F., Bonardo, B., Bonzi, M.F., Coudeyre, J.C., Alessi, M.C., Juhan-Vague, I., Nalbone, G., 2006. The TNF alpha converting enzyme (TACE/ADAM17) is expressed in the atherosclerotic lesions of apolipoprotein E-deficient mice: possible contribution to elevated plasma levels of soluble TNF alpha receptors. Atherosclerosis 187, 82–91.

Cesaro, A., Abakar-Mahamat, A., Brest, P., Lassalle, S., Selva, E., Filippi, J., Hebuterne, X., Hugot, J.P., Doglio, A., Galland, F., Naquet, P., Vouret-Craviari, V., Mograbi, B., Hofman, P.M., 2009. Differential expression and regulation of ADAM17 and TIMP3 in acute inflamed intestinal epithelia. Am. J. Physiol. Gastrointest. Liver Physiol. 296, G1332–G1343.

Chalaris, A., Adam, N., Sina, C., Rosenstiel, P., Lehmann-Koch, J., Schirmacher, P., Hartmann, D., Cichy, J., Gavrilova, O., Schreiber, S., Jostock, T., Matthews, V., Hasler, R., Becker, C., Neurath, M.F., Reiss, K., Saftig, P., Scheller, J., Rose-John, S., 2010. Critical role of the disintegrin metalloprotease ADAM17 for intestinal inflammation and regeneration in mice. J. Exp. Med. 207, 1617–1624.

Christianson, T.A., Doherty, J.K., Lin, Y.J., Ramsey, E.E., Holmes, R., Keenan, E.J., Clinton, G.M., 1998. NH_2-terminally truncated Her-2/neu protein: relationship with shedding of the extracellular domain and with prognostic factors in breast cancer. Cancer Res. 58, 5123–5129.

Ding, X., Yang, L.Y., Huang, G.W., Wang, W., Lu, W.Q., 2004. ADAM17 mRNA expression and pathological features of hepatocellular carcinoma. World J. Gastroenterol. 10, 2735–2739.

Donners, M.M., Wolfs, I.M., Olieslagers, S., Mohammadi-Motahhari, Z., Tchaikovski, V., Heeneman, S., van Buul, J.D., Caolo, V., Molin, D.G., Post, M.J., Waltenberger, J., 2010. A Disintegrin And Metalloprotease 10 is a novel mediator of vascular endothelial growth factor-induced endothelial cell function in angiogenesis and is associated with atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 30, 2188–2195.

Epis, R., Marcello, E., Gardoni, F., Vastagh, C., Malinverno, M., Balducci, C., Colombo, A., Borroni, B., Vara, H., Dell'agli, M., Cattabeni, F., Giustetto, M., Borsello, T., Forloni, G., Padovani, A., Di Luca, M., 2010. Blocking ADAM10 synaptic trafficking generates a model of sporadic Alzheimer's disease. Brain 133, 3323–3335.

Esposito, E., Cuzzocrea, S., 2009. TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury and trauma. Curr. Med. Chem. 16, 3152–3167.

Fogel, M., Gutwein, P., Mechtersheimer, S., Riedle, S., Stoeck, A., Smirnov, A., Edler, L., Ben-Arie, A., Huszar, M., Altevogt, P., 2003. L1 expression as a predictor of progression and survival in patients with uterine and ovarian carcinomas. Lancet 362, 869–875.

Galkina, E., Harry, B.L., Ludwig, A., Liehn, E.A., Sanders, J.M., Bruce, A., Weber, C., Ley, K., 2007. CXCR6 promotes atherosclerosis by supporting T-cell homing, interferon-gamma production, and macrophage accumulation in the aortic wall. Circulation 116, 1801–1811.

Gatta, L.B., Albertini, A., Ravid, R., Finazzi, D., 2002. Levels of beta-secretase BACE and alpha-secretase ADAM10 mRNAs in Alzheimer hippocampus. Neuroreport 13, 2031–2033.

Gavert, N., Conacci-Sorrell, M., Gast, D., Schneider, A., Altevogt, P., Brabletz, T., Ben-Ze'ev, A., 2005. L1, a novel target of beta-catenin signaling, transforms cells and is expressed at the invasive front of colon cancers. J. Cell Biol. 168, 633–642.

Goldstein, J.L., Brown, M.S., 1977. Atherosclerosis: the low-density lipoprotein receptor hypothesis. Metabolism 26, 1257–1275.

Gooz, M., 2010. ADAM-17: the enzyme that does it all. Crit. Rev. Biochem. Mol. Biol. 45, 146–169.

Hartmann, D., de Strooper, B., Serneels, L., Craessaerts, K., Herreman, A., Annaert, W., Umans, L., Lubke, T., Lena Illert, A., von Figura, K., Saftig, P., 2002. The disintegrin/metalloprotease ADAM 10 is essential for Notch signalling but not for alpha-secretase activity in fibroblasts. Hum. Mol. Genet. 11, 2615–2624.

Hikita, A., Tanaka, N., Yamane, S., Ikeda, Y., Furukawa, H., Tohma, S., Suzuki, R., Tanaka, S., Mitomi, H., Fukui, N., 2009. Involvement of A Disintegrin And Metalloproteinase 10 and 17 in shedding of tumor necrosis factor-alpha. Biochem. Cell Biol. 87, 581–593.

Horiuchi, K., Kimura, T., Miyamoto, T., Takaishi, H., Okada, Y., Toyama, Y., Blobel, C.P., 2007. Cutting edge: TNF-alpha-converting enzyme (TACE/ADAM17) inactivation in mouse myeloid cells prevents lethality from endotoxin shock. J. Immunol. 179, 2686–2689.

Hundhausen, C., Misztela, D., Berkhout, T.A., Broadway, N., Saftig, P., Reiss, K., Hartmann, D., Fahrenholz, F., Postina, R., Matthews, V., Kallen, K.J., Rose-John, S., Ludwig, A., 2003. The disintegrin-like metalloproteinase ADAM10 is involved in constitutive cleavage of CX3CL1 (fractalkine) and regulates CX3CL1-mediated cell–cell adhesion. Blood 102, 1186–1195.

Hundhausen, C., Schulte, A., Schulz, B., Andrzejewski, M.G., Schwarz, N., von Hundelshausen, P., Winter, U., Paliga, K., Reiss, K., Saftig, P., Weber, C., Ludwig, A., 2007. Regulated shedding of transmembrane chemokines by the disintegrin and metalloproteinase 10 facilitates detachment of adherent leukocytes. J. Immunol. 178, 8064–8072.

Janes, P.W., Wimmer-Kleikamp, S.H., Frangakis, A.S., Treble, K., Griesshaber, B., Sabet, O., Grabenbauer, M., Ting, A.Y., Saftig, P., Bastiaens, P.I., Lackmann, M., 2009. Cytoplasmic relaxation of active Eph controls ephrin shedding by ADAM10. PLoS Biol. 7, e1000215.

Jorissen, E., Prox, J., Bernreuther, C., Weber, S., Schwanbeck, R., Serneels, L., Snellinx, A., Craessaerts, K., Thathiah, A., Tesseur, I., Bartsch, U., Weskamp, G., Blobel, C.P., Glatzel, M., De Strooper, B., Saftig, P., 2010. The disintegrin/metalloproteinase ADAM10 is essential for the establishment of the brain cortex. J. Neurosci. 30, 4833–4844.

Ju, C.R., Xia, X.Z., Chen, R.C., 2007. Expressions of tumor necrosis factor-converting enzyme and ErbB3 in rats with chronic obstructive pulmonary disease. Chin. Med. J. (Engl.) 120, 1505–1510.

Karan, D., Lin, F.C., Bryan, M., Ringel, J., Moniaux, N., Lin, M.F., Batra, S.K., 2003. Expression of ADAMs (A Disintegrin And Metalloproteases) and TIMP-3 (tissue inhibitor of metalloproteinase-3) in human prostatic adenocarcinomas. Int. J. Oncol. 23, 1365–1371.

Kawaguchi, N., Horiuchi, K., Becherer, J.D., Toyama, Y., Besmer, P., Blobel, C.P., 2007. Different ADAMs have distinct influences on Kit ligand processing: phorbolester-stimulated ectodomain shedding of Kitl1 by ADAM17 is reduced by ADAM19. J. Cell. Sci. 120, 943–952.

Kim, M., Suh, J., Romano, D., Truong, M.H., Mullin, K., Hooli, B., Norton, D., Tesco, G., Elliott, K., Wagner, S.L., Moir, R.D., Becker, K.D., Tanzi, R.E., 2009. Potential late-onset Alzheimer's disease-associated mutations in the ADAM10 gene attenuate {alpha}-secretase activity. Hum. Mol. Genet. 18, 3987–3996.

Le Gall, S.M., Bobe, P., Reiss, K., Horiuchi, K., Niu, X.D., Lundell, D., Gibb, D.R., Conrad, D., Saftig, P., Blobel, C.P., 2009. ADAMs 10 and 17 represent differentially regulated components of a general shedding machinery for membrane proteins such as transforming growth factor alpha, L-selectin, and tumor necrosis factor alpha. Mol. Biol. Cell 20, 1785–1794.

Lendeckel, U., Kohl, J., Arndt, M., Carl-McGrath, S., Donat, H., Rocken, C., 2005. Increased expression of ADAM family members in human breast cancer and breast cancer cell lines. J. Cancer Res. Clin. Oncol. 131, 41–48.

Ludwig, A., Weber, C., 2007. Transmembrane chemokines: versatile 'special agents' in vascular inflammation. Thromb. Haemost. 97, 694–703.

Luetteke, N.C., Qiu, T.H., Peiffer, R.L., Oliver, P., Smithies, O., Lee, D.C., 1993. TGF alpha deficiency results in hair follicle and eye abnormalities in targeted and waved-1 mice. Cell 73, 263–278.

Mallika, V., Goswami, B., Rajappa, M., 2007. Atherosclerosis pathophysiology and the role of novel risk factors: a clinicobiochemical perspective. Angiology 58, 513–522.

Mann, G.B., Fowler, K.J., Gabriel, A., Nice, E.C., Williams, R.L., Dunn, A.R., 1993. Mice with a null mutation of the TGF alpha gene have abnormal skin architecture, wavy hair, and curly whiskers and often develop corneal inflammation. Cell 73, 249–261.

Marcinkiewicz, M., Seidah, N.G., 2000. Coordinated expression of beta-amyloid precursor protein and the putative beta-secretase BACE and alpha-secretase ADAM10 in mouse and human brain. J. Neurochem. 75, 2133–2143.

Maretzky, T., Reiss, K., Ludwig, A., Buchholz, J., Scholz, F., Proksch, E., de Strooper, B., Hartmann, D., Saftig, P., 2005a. ADAM10 mediates E-cadherin shedding and regulates epithelial cell–cell adhesion, migration, and beta-catenin translocation. Proc. Natl. Acad. Sci. U.S.A. 102, 9182–9187.

Maretzky, T., Scholz, F., Koten, B., Proksch, E., Saftig, P., Reiss, K., 2008. ADAM10-mediated E-cadherin release is regulated by proinflammatory cytokines and modulates keratinocyte cohesion in eczematous dermatitis. J. Invest. Dermatol. 128, 1737–1746.

Maretzky, T., Schulte, M., Ludwig, A., Rose-John, S., Blobel, C., Hartmann, D., Altevogt, P., Saftig, P., Reiss, K., 2005b. L1 is sequentially processed by two differently activated metalloproteases and presenilin/gamma-secretase and regulates neural cell adhesion, cell migration, and neurite outgrowth. Mol. Cell Biol. 25, 9040–9053.

Martin, L., Fluhrer, R., Reiss, K., Kremmer, E., Saftig, P., Haass, C., 2008. Regulated intramembrane proteolysis of Bri2 (Itm2b) by ADAM10 and SPPL2a/SPPL2b. J. Biol. Chem. 283, 1644–1652.

Matthews, V., Schuster, B., Schutze, S., Bussmeyer, I., Ludwig, A., Hundhausen, C., Sadowski, T., Saftig, P., Hartmann, D., Kallen, K.J., Rose-John, S., 2003. Cellular cholesterol depletion triggers shedding of the human interleukin-6 receptor by ADAM10 and ADAM17 (TACE). J. Biol. Chem. 278, 38829–38839.

McCulloch, D.R., Akl, P., Samaratunga, H., Herington, A.C., Odorico, D.M., 2004. Expression of the disintegrin metalloprotease, ADAM-10, in prostate cancer and its regulation by dihydrotestosterone, insulin-like growth factor I, and epidermal growth factor in the prostate cancer cell model LNCaP. Clin. Cancer Res. 10, 314–323.

McGowan, P.M., McKiernan, E., Bolster, F., Ryan, B.M., Hill, A.D., McDermott, E.W., Evoy, D., O'Higgins, N., Crown, J., Duffy, M.J., 2008. ADAM-17 predicts adverse outcome in patients with breast cancer. Ann. Oncol. 19, 1075–1081.

Moriyama, H., Tsukida, T., Inoue, Y., Yokota, K., Yoshino, K., Kondo, H., Miura, N., Nishimura, S., 2004. Azasugar-based MMP/ADAM inhibitors as antipsoriatic agents. J. Med. Chem. 47, 1930–1938.

Murphy, G., 2008. The ADAMs: signalling scissors in the tumour microenvironment. Nat. Rev. Cancer 8, 929–941.

Murumkar, P.R., DasGupta, S., Chandani, S.R., Giridhar, R., Yadav, M.R., 2010. Novel TACE inhibitors in drug discovery: a review of patented compounds. Expert Opin. Ther. Pat. 20, 31–57.

Nagano, O., Murakami, D., Hartmann, D., De Strooper, B., Saftig, P., Iwatsubo, T., Nakajima, M., Shinohara, M., Saya, H., 2004. Cell–matrix interaction via CD44 is independently regulated by different metalloproteinases activated in response to extracellular Ca(2+) influx and PKC activation. J. Cell Biol. 165, 893–902.

Ohta, S., Harigai, M., Tanaka, M., Kawaguchi, Y., Sugiura, T., Takagi, K., Fukasawa, C., Hara, M., Kamatani, N., 2001. Tumor necrosis factor-alpha (TNF-alpha) converting enzyme contributes to production of TNF-alpha in synovial tissues from patients with rheumatoid arthritis. J. Rheumatol. 28, 1756–1763.

Peschon, J.J., Slack, J.L., Reddy, P., Stocking, K.L., Sunnarborg, S.W., Lee, D.C., Russell, W.E., Castner, B.J., Johnson, R.S., Fitzner, J.N., Boyce, R.W., Nelson, N., Kozlosky, C.J., Wolfson, M.F., Rauch, C.T., Cerretti, D.P., Paxton, R.J., March, C.J., Black, R.A., 1998. An essential role for ectodomain shedding in mammalian development. Science 282, 1281–1284.

Postina, R., Schroeder, A., Dewachter, I., Bohl, J., Schmitt, U., Kojro, E., Prinzen, C., Endres, K., Hiemke, C., Blessing, M., Flamez, P., Dequenne, A., Godaux, E., van Leuven, F., Fahrenholz, F., 2004. A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model. J. Clin. Invest. 113, 1456–1464.

Raucci, A., Cugusi, S., Antonelli, A., Barabino, S.M., Monti, L., Bierhaus, A., Reiss, K., Saftig, P., Bianchi, M.E., 2008. A soluble form of the receptor for advanced glycation endproducts (RAGE) is produced by proteolytic cleavage of the membrane-bound form by the sheddase A Disintegrin And Metalloprotease 10 (ADAM10). FASEB J. 22, 3716–3727.

Reiss, K., Ludwig, A., Saftig, P., 2006a. Breaking up the tie: disintegrin-like metalloproteinases as regulators of cell migration in inflammation and invasion. Pharmacol. Ther. 111, 985–1006.

Reiss, K., Maretzky, T., Haas, I.G., Schulte, M., Ludwig, A., Frank, M., Saftig, P., 2006b. Regulated ADAM10-dependent ectodomain shedding of gamma-protocadherin C3 modulates cell–cell adhesion. J. Biol. Chem. 281, 21735–21744.

Reiss, K., Maretzky, T., Ludwig, A., Tousseyn, T., de Strooper, B., Hartmann, D., Saftig, P., 2005. ADAM10 cleavage of N-cadherin and regulation of cell–cell adhesion and beta-catenin nuclear signalling. EMBO J. 24, 742–752.

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.

Ringel, J., Jesnowski, R., Moniaux, N., Luttges, J., Choudhury, A., Batra, S.K., Kloppel, G., Lohr, M., 2006. Aberrant expression of A Disintegrin And Metalloproteinase 17/tumor necrosis factor-alpha converting enzyme increases the malignant potential in human pancreatic ductal adenocarcinoma. Cancer Res. 66, 9045–9053.

Roemer, A., Schwettmann, L., Jung, M., Roigas, J., Kristiansen, G., Schnorr, D., Loening, S.A., Jung, K., Lichtinghagen, R., 2004. Increased mRNA expression of ADAMs in renal cell carcinoma and their association with clinical outcome. Oncol. Rep. 11, 529–536.

Rovida, E., Paccagnini, A., Del Rosso, M., Peschon, J., Dello Sbarba, P., 2001. TNF-alpha-converting enzyme cleaves the macrophage colony-stimulating factor receptor in macrophages undergoing activation. J. Immunol. 166, 1583–1589.

Ruchatz, H., Leung, B.P., Wei, X.Q., McInnes, I.B., Liew, F.Y., 1998. Soluble IL-15 receptor alpha-chain administration prevents murine collagen-induced arthritis: a role for IL-15 in development of antigen-induced immunopathology. J. Immunol. 160, 5654–5660.

Sahin, U., Weskamp, G., Kelly, K., Zhou, H.M., Higashiyama, S., Peschon, J., Hartmann, D., Saftig, P., Blobel, C.P., 2004. Distinct roles for ADAM10 and ADAM17 in ectodomain shedding of six EGFR ligands. J. Cell Biol. 164, 769–779.

Satoh, M., Ishikawa, Y., Itoh, T., Minami, Y., Takahashi, Y., Nakamura, M., 2008. The expression of TNF-alpha converting enzyme at the site of ruptured plaques in patients with acute myocardial infarction. Eur. J. Clin. Invest. 38, 97–105.

Schmitt, U., Hiemke, C., Fahrenholz, F., Schroeder, A., 2006. Over-expression of two different forms of the alpha-secretase ADAM10 affects learning and memory in mice. Behav. Brain Res. 175, 278–284.

Schulte, M., Reiss, K., Lettau, M., Maretzky, T., Ludwig, A., Hartmann, D., de Strooper, B., Janssen, O., Saftig, P., 2007. ADAM10 regulates FasL cell surface expression and modulates FasL-induced cytotoxicity and activation-induced cell death. Cell Death Differ. 14, 1040–1049.

Schulz, B., Pruessmeyer, J., Maretzky, T., Ludwig, A., Blobel, C.P., Saftig, P., Reiss, K., 2008. ADAM10 regulates endothelial permeability and T-Cell transmigration by proteolysis of vascular endothelial cadherin. Circ. Res. 102, 1192–1201.

Seifert, T., Kieseier, B.C., Ropele, S., Strasser-Fuchs, S., Quehenberger, F., Fazekas, F., Hartung, H.P., 2002. TACE mRNA expression in peripheral mononudear cells precedes new lesions on MRI in multiple sclerosis. Mult. Scler. 8, 447–451.

Swendeman, S., Mendelson, K., Weskamp, G., Horiuchi, K., Deutsch, U., Scherle, P., Hooper, A., Rafii, S., Blobel, C.P., 2008. VEGF-A stimulates ADAM17-dependent shedding of VEGFR2 and crosstalk between VEGFR2 and ERK signaling. Circ. Res. 103, 916–918.

Takeda, S., 2009. Three-dimensional domain architecture of the ADAM family proteinases. Semin. Cell Dev. Biol. 20, 146–152.

Tanaka, Y., Miyamoto, S., Suzuki, S.O., Oki, E., Yagi, H., Sonoda, K., Yamazaki, A., Mizushima, H., Maehara, Y., Mekada, E., Nakano, H., 2005. Clinical significance of heparin-binding epidermal growth factor-like growth factor and A Disintegrin And Metalloprotease 17 expression in human ovarian cancer. Clin. Cancer Res. 11, 4783–4792.

Tousseyn, T., Jorissen, E., Reiss, K., Hartmann, D., 2006. (Make) stick and cut loose—disintegrin metalloproteases in development and disease. Birth Defects Res. C: Embryo Today 78, 24–46.

Tousseyn, T., Thathiah, A., Jorissen, E., Raemaekers, T., Konietzko, U., Reiss, K., Maes, E., Snellinx, A., Serneels, L., Nyabi, O., Annaert, W., Saftig, P., Hartmann, D., De Strooper, B., 2009. ADAM10, the rate-limiting protease of regulated intramembrane proteolysis of Notch and other proteins, is processed by ADAMS-9, ADAMS-15, and the gamma-secretase. J. Biol. Chem. 284, 11738–11747.

Weskamp, G., Ford, J.W., Sturgill, J., Martin, S., Docherty, A.J., Swendeman, S., Broadway, N., Hartmann, D., Saftig, P., Umland, S., Sehara-Fujisawa, A., Black, R.A., Ludwig, A., Becherer, J.D., Conrad, D.H., Blobel, C.P., 2006. ADAM10 is a principal 'sheddase' of the low-affinity immunoglobulin E receptor CD23. Nat. Immunol. 7, 1293–1298.

Weskamp, G., Mendelson, K., Swendeman, S., Le Gall, S., Ma, Y., Lyman, S., Hinoki, A., Eguchi, S., Guaiquil, V., Horiuchi, K., Blobel, C.P., 2010. Pathological neovascularization is reduced by inactivation of ADAM17 in endothelial cells but not in pericytes. Circ. Res. 106, 932–940.

Wu, E., Croucher, P.I., McKie, N., 1997. Expression of members of the novel membrane linked metalloproteinase family ADAM in cells derived from a range of haematological malignancies. Biochem. Biophys. Res. Commun. 235, 437–442.

Yoshimura, T., Tomita, T., Dixon, M.F., Axon, A.T., Robinson, P.A., Crabtree, J.E., 2002. ADAMs (A Disintegrin And Metalloproteinase) messenger RNA expression in

Helicobacter pylori-infected, normal, and neoplastic gastric mucosa. J. Infect. Dis. 185, 332–340.

Zheng, X., Jiang, F., Katakowski, M., Kalkanis, S.N., Hong, X., Zhang, X., Zhang, Z.G., Yang, H., Chopp, M., 2007. Inhibition of ADAM17 reduces hypoxia-induced brain tumor cell invasiveness. Cancer Sci. 98, 674–684.

Zhou, B.B., Peyton, M., He, B., Liu, C., Girard, L., Caudler, E., Lo, Y., Baribaud, F., Mikami, I., Reguart, N., Yang, G., Li, Y., Yao, W., Vaddi, K., Gazdar, A.F., Friedman, S.M., Jablons, D.M., Newton, R.C., Fridman, J.S., Minna, J.D., Scherle, P.A., 2006. Targeting ADAM-mediated ligand cleavage to inhibit HER3 and EGFR pathways in non-small cell lung cancer. Cancer Cell 10, 39–50.