BBA - Molecular Cell Research 1864 (2017) 2059–2070

Contents lists available at ScienceDirect

BBA - Molecular Cell Research

journal homepage: www.elsevier.com/locate/bbamcr

The shedding protease ADAM17: Physiology and pathophysiology☆

Friederike Zunke, Stefan Rose-John*

Institute of Biochemistry, University of Kiel, Germany

ARTICLE INFO

Keywords:
ADAM proteases
ADAM17
IL-6R
IL-6 trans-signaling
Shedding
EGF receptor
iPS cell system

ABSTRACT

The disintegrin metalloprotease ADAM17 has been a matter of intense studies aiming to unravel structure, function and regulation of protease expression, maturation and activity. In this review, we summarize data on the physiological role of ADAM17 in health and disease. Here we provide an overview of ADAM17 substrates, mouse models of ADAM17-deficiencies and discuss recent findings of ADAM17 function in the immune system and central nervous system as well as in cancer. Whereas ADAM17 function in EGF-R-, in Interleukin-6 (IL-6)- and in TNFα-biology has been shown to play a decisive role in regulation of the immune system as well as cancer development, the role of ADAM17 in the central nervous system and neurodegeneration still remains elusive. We show ADAM17 expression in human dopaminergic neurons derived from induced pluripotent stem cells and we discuss how this state-of-the-art technology can be further exploited to study the function of this important protease in the brain and other tissues. This article is part of a Special Issue entitled: Proteolysis as a Regulatory Event in Pathophysiology edited by Stefan Rose-John.

1. Introduction

It was discovered in 1988 that the pro-inflammatory mediator tumor necrosis factor alpha (TNF*α*) was synthesized as a transmembrane protein, which needs to be proteolytically cleaved to be systemically active [1]. Since then, many researchers tried to identify the responsible proteolytic activity, which was believed to be an important therapeutic target. In 1994, it was reported that the TNF*α* cleaving enzyme was a metalloprotease, which could be inhibited by hydroxamic acid compounds. This hydroxamate not only reduced LPS-induced TNF*α* levels in vivo but also rescued mice from lethal septic shock confirming the TNF*α* cleaving enzyme being a promising therapeutic target [2]. Three years later, cDNAs coding for human and murine TNF*α* cleaving enzyme were cloned [3,4], which showed that the enzyme is a membrane bound metalloprotease, which belonged to the family of disintegrin metalloproteases called adamalysins or ADAMs [5]. Subsequently, the TNF*α* cleaving enzyme was renamed ADAM17 [5].

ADAM17 knock-out animals turned out not to be viable [6]. Moreover, they showed an open eye phenotype at birth, which was reminiscent of mice lacking transforming growth factor alpha (TGF*α*), a ligand of the epidermal growth factor receptor (EGF-R). Since all ligands of the EGF-R are transmembrane proteins, which need to be cleaved in order to act systemically [7] it was hypothesized that ligands of the EGF-R were substrates of ADAM17 [6]. This was supported by data indicating that L-selectin, IL-6R and TGF*α* were processed by the same protease [8]. Meanwhile we know that ADAM17 has more than 80 substrates ranging from cytokines, growth factors, receptors to many cell adhesion molecules (Table 1) [9]. Therefore, it is not surprising that the biology of ADAM17 is complex and the protease is involved in the regulation of many body functions and developmental processes.

2. The shedding enzyme ADAM17

At least 10% of all cell surface proteins are believed to be proteolytically cleaved leading to the release of soluble proteins [10,11]. As outlined above, ADAM17 was the first shedding protease to be molecularly characterized and it was shown to consist of an N-terminal signal sequence followed by a pro-domain, a metalloproteinase or catalytic domain, a disintegrin domain, a cysteine-rich membrane proximal domain, a single transmembrane domain and a cytoplasmic portion (Fig. 1) [3,4].

The N-terminal pro-domain of ADAM17 acts as a chaperone and is thought to inhibit the catalytic activity of the enzyme. The pro-domain is removed by sequential cleavage by the pro-protein convertase furin at two sites [12]. Interestingly, the recombinant pro-domain has been shown to be a highly specific and potent inhibitor of ADAM17 activity in vitro and in vivo [13]. The ADAM17 catalytic domain resembled snake venom metalloproteases and clearly placed ADAM17 in the adamalysin protease family [14]. The function of the disintegrin

☆ This article is part of a Special Issue entitled: Proteolysis as a Regulatory Event in Pathophysiology edited by Stefan Rose-John.

* Corresponding author.
E-mail address: rosejohn@biochem.uni-kiel.de (S. Rose-John).

http://dx.doi.org/10.1016/j.bbamcr.2017.07.001
Received 17 April 2017; Received in revised form 8 July 2017; Accepted 9 July 2017
Available online 11 July 2017

Table 1
Substrates of ADAM17.

Immune system	Development, differentiation	Cell adhesion	Others
IL-1R$_{II}$	TGFα	ALCAM	ACE-2
IL-6R	Hb-EGF	CD44	APP
IL-15R	AREG	CD62L (L-selectin)	APP-like protein2
CX3CL1 (fractalkine)	Epigen	Collagen XVII	Carbonic hydrolase 9
M-CSFR	EREG	Desmoglein 2	Prion protein
TNF-R$_{I}$	NRG1	EpCam	Ebola virus glycoprotein
TNF-R$_{II}$	FLT-3L	ICAM-1	EPCR
LDL-R	KL-1	JAM-A	GPIba
SORL1	KL-2	L1-CAM	GPV
SORT1	Jagged	NCAM	GPVI
SORCS1	DLL1	Nectin-4	Klotho
SORCS3	Notch1	SynCAM1	Muc-1
TNFα	GH-R	VACM-1	NPR
Lymphotoxin α	IGF2-R		Pre-adipocyte factor
RANKL (TRANCE)	HER4 (ErbB4)		Ptprz
CSF-1	TrkA		
TIM-1	VEGF-R2		
TIM-3	LYPD3		
TIM-4	PMEL17		
MIC-A	PTP-LAR		
MIC-B	SEMA4D		
LAG-3	Syndecan1		
CD16	Syndecan4		
CD30 (TNFRSF8)	TEMEFF2		
CD36	Vasorin		
CD40 (TNFRSF5)			
CD89			
CD91 (APOER)			
CD163			
ICOS-L			

domain is largely unknown but it was shown that recombinantly expressed disintegrin domain of ADAM17 impaired the interaction between fibroblasts and carcinoma cells [15]. The membrane proximal domain is followed by a short stalk sequence, which is highly conserved throughout the animal kingdom and which has been called CANDIS domain [16]. The membrane proximal-domain has been shown to be subject to complex regulatory control. Its structural determination enabled to prove that protein disulphide isomerase catalyzes an isomerization of disulphide bridges resulting in switching from an open to a closed conformation [17]. This consequently restricts substrate interaction and accessibility of phosphatidylserine, which acts as an activator of ADAM17 (Fig. 2) [18].

In 2012, it was shown by two groups that iRhom2, which is one of two proteolytically inactive members of the rhomboid family, was needed for trafficking of ADAM17 to the cell membrane and for activation of enzymatic activity [19,20]. Subsequently, it was revealed that also iRhom1 played a role in ADAM17 maturation, particularly in the brain [21]. Interestingly, the iRhom proteins seem to play a role in selectivity of ADAM17 for some but not all substrates [22].

Although treatment of cells with the protein kinase C (PKC) stimulator phorbol ester (PMA) leads to a strong increase in ADAM17 activity [23,24], suggesting phosphorylation of ADAM17, it was also shown that the cytoplasmic portion of ADAM17 was dispensable for short-term stimulation of ADAM17 activity [25,26]. Phosphorylation of the cytoplasmic portion of ADAM17 by MAP kinases [27] and polo like kinase 2 [28] has been detected, but the role of kinases in the regulation of ADAM17 activity is not fully understood. It is, however, clear, that shedding of many ADAM17 substrates is followed by intramembrane proteolysis by γ-secretase, a process called ripping (Fig. 2) [29,30].

G-protein coupled receptor stimulation by lysophosphatidic acid, endothelin, thrombin, bombesin and carbachol was observed to lead to the stimulation of the EGF-R by trans-activation. It was further shown that this trans-activation involved an unknown metalloprotease activity, which led to cleavage of the EGF-R ligand HB-EGF und subsequent EGF-R activation by the cleaved HB-EGF ectodomain [31]. A similar mechanism was demonstrated for the activation of the fibroblast growth factor receptor 2b (FGFR2b), which is stimulated by fibroblast growth factor (FGF7), leading to an activation of ADAM17, cleavage of HB-EGF and activation of the EGF-R (Fig. 3) [32]. This triple membrane spanning mechanism could be important for regulation of cell migration in keratinocytes and endothelial cells [32].

Although ADAM17 from human, rat and mouse is highly conserved throughout the protein it has been reported that in overexpressing transfected cells murine ADAM17 showed some species specificity towards one substrate, namely the Interleukin-6 receptor (IL-6R) [33]. In subsequent studies in mice, however, it was clarified that no such species specificity exists in vivo, since the murine IL-6R was cleaved by murine ADAM17 in mice [34]. Interestingly, in the absence of ADAM17, the levels of soluble IL-6R (sIL-6R) found in the blood of mice were unchanged as compared to wildtype (wt) mice [35], indicating that ADAM17 activity is not responsible for steady state levels of sIL-6R, which is very important for in vivo regulation of IL-6 activity (see below). A similar observation was made for the levels of soluble L-selectin, an additional substrate of ADAM17. In mice lacking ADAM17, soluble L-selectin remained unchanged [36].

Shedding of membrane proteins by ADAM proteases can not only occur at the cell surface but also from microvesicles called exosomes [37]. The full length IL-6R has been found on circulating microvesicles

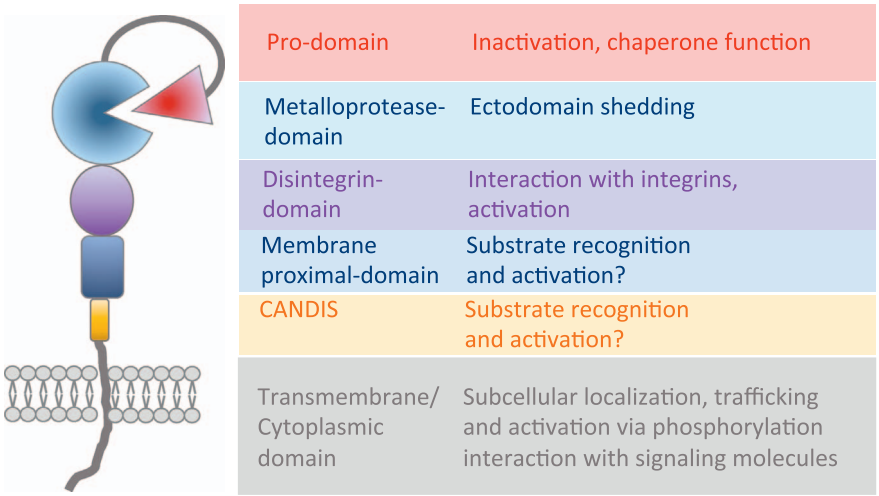

Fig. 1. Structure and function of ADAM17. The metalloprotease ADAM17 can be divided into six domains with distinct functions, here separated by different color. CANDIS: Conserved ADAM seventeen dynamic interaction sequence [16].

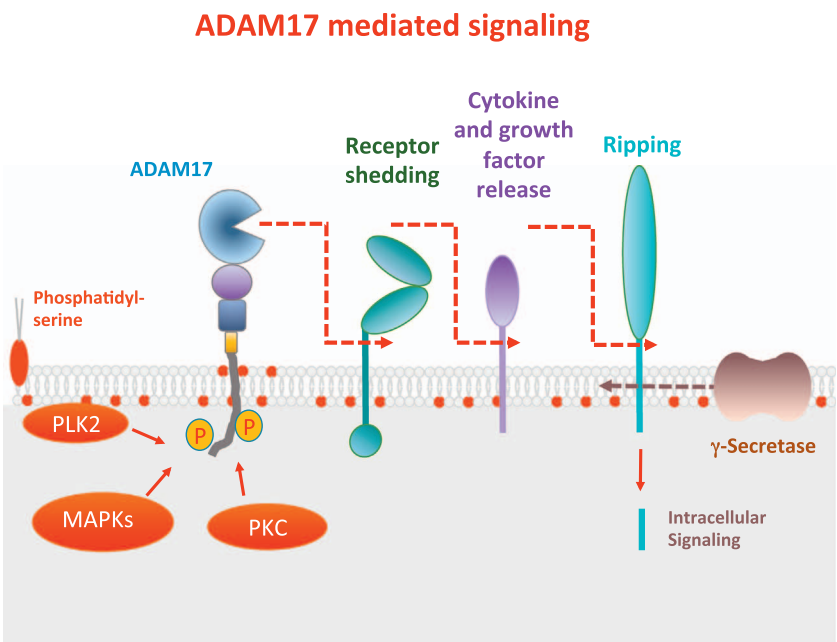

Fig. 2. Schematic overview of ADAM17-mediated shedding. ADAM17 function is regulated by phosphorylation of the cytoplasmatic tail by intracellular kinases such as PLK2, MAPK, PKC. Phosphatidylserine transferred to the outer leaflet of the membrane is needed for ADAM17 activation. ADAM17 activities include shedding of receptors, cytokines and growth factors leading to subsequent ripping of transmembrane proteins by the intramembrane protease γ-secretase, which cleaves single-pass transmembrane proteins within the transmembrane domain.

[38] from which it can be cleaved by the proteases ADAM10 and ADAM17 to release sIL-6R [39].

Currently, more than 80 substrates have been shown to be cleaved by ADAM17. Among these substrates are cytokines and growth factors, cytokine and growth factor receptors, scavenger receptors, cell adhesion proteins and other transmembrane proteins (Table 1) explaining the involvement of ADAM17 in many pathophysiologic processes [9].

3. In vivo studies of ADAM17

Shortly after cloning of the *Adam17* cDNA [3], inactivation of the *Adam17* gene via homologous recombination was reported, and it turned out that ADAM17 deficient mice were mostly not viable [6]. The vast majority of ADAM17 deficient mice, which were born alive, died within several hours. From 464 mice, only six mice survived but these died after 2–3 weeks [6]. Almost 10 years later, the first ADAM17 conditional knock-out was generated and deletion of ADAM17 on myeloid cells led to resistance of LPS-induced endotoxemia [40]. Many more conditional ADAM17 knock-out mice were generated in the meantime and the different observed phenotypes are summarized in Table 2.

For ADAM10 it has been demonstrated that the protease can cleave substrates not only on the same cells but also on different cells [41]. Although it has not been shown whether cleavage in trans is also possible for ADAM17, such a mechanism would question the validity of conditional knock-out models. This was one reason why hypomorphic

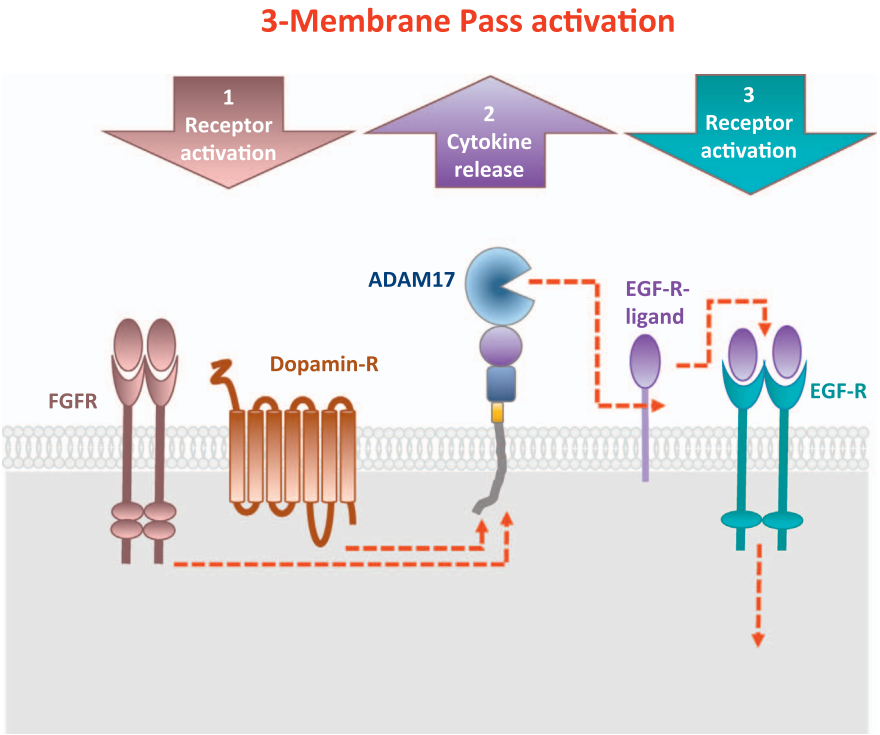

Fig. 3. ADAM17 function is mediated by a triple membrane pass mechanism. The first step of ADAM17 regulation is the intracellular activation of the transmembrane protein by fibroblasts growth factor (FGF)- or dopamine-receptors (R). Secondly, activation of ADAM17 leads to shedding of cell surface proteins and thus cytokine release, here shown for EGF-R ligands. As a third step, EGF-R binds the cleaved ligand leading to activation of intracellular signaling pathways.

Table 2
Mouse models of ADAM17 deficiencies.

Genotype	Targeted tissue	Viability	Phenotype	Reference
$ADAM17^{\Delta Zn/\Delta Zn}$	All tissues	Embryonic lethal	Epithelial abnormalities, hair defects, heart defects, skin defects, open eyes at birth	[6]
$ADAM17^{flox/flox}$ × EIIa-cre	All tissues	Embryonic lethal	Epithelial abnormalities, hair defects, heart defects, skin defects, open eyes at birth	[40]
$ADAM17^{flox/flox}$ × Mx-cre	Liver, bone marrow, spleen, and thymus	Viable	No phenotype, protected from LPS endotoxemia	[40]
$ADAM17^{flox/flox}$ × LysM-cre	Myeloid cells	Viable	No phenotype, protected from LPS endotoxemia	[40]
$ADAM17^{flox/flox}$ × Sox9-cre	Bone, cartilage, skin	Viable (5 months)	Hair defects, heart defects, skin defects, open eyes at birth, growth retardation	[167]
$ADAM17^{flox/flox}$ × vav1-cre	Leukocytes	Viable	No phenotype, protected from *E. coli* peritonitis, rapid neutrophil infiltration to inflamed tissue	[168]
$ADAM17^{flox/flox}$ × Tie2-cre	Endothelial cells	Viable	No phenotype, pathological retinal neovascularization, reduced growth of B16 melanoma cells after subcutaneous injection	[169]
$ADAM17^{flox/flox}$ × Sm-cre	Vascular smooth muscle cells, aorta, heart, small intestine	Viable	No phenotype	[169]
$ADAM17^{flox/flox}$ × Alb-cre	Hepatocytes	Viable	No phenotype, higher sensitivity to Fas-induced liver toxicity	[170]
$ADAM17^{flox/flox}$ × HB9-cre	Motor neurons	Viable	Increased Schwann cell myelination	[171]
$ADAM17^{flox/flox}$ × K14-cre	Keratinocytes	Viable	Inhibition of Notch signaling, atopic dermatitis and myeloproliferative disease,	[172]
$ADAM17^{flox/flox}$ × villin-cre	Intestinal epithelium	Viable	Blockade of EGF-R trans-activation	[173]
$ADAM17^{flox/flox}$ × Ptf1a-cre	Pancreas	Viable	Loss of EGF-R activation and protection from pancreatitis, inhibition of Kras driven tumorigenesis	[174]
$ADAM17^{flox/flox}$ × γGT-cre	Kidney proximal tubule	Viable	Protection against fibrosis after ischemia reperfusion injury	[45]
$ADAM17^{flox/flox}$ × αMHC-cre	Cardio-myocytes	Viable	Myocardial hypertrophy, fibrosis, reduced integrinβ1 cleavage	[175]
$ADAM17^{ex/ex}$	All tissues hypomorph	Viable	Epithelial abnormalities, hair defects, heart defects, skin defects, open eyes at birth, susceptibility to DSS colitis, reduced regeneration of the intestine; less susceptible to kidney fibrosis; higher susceptibility to atherosclerosis	[42,43,45]
$ADAM17^{wavedX}$	All tissues hypomorph	Viable	Hair defects, susceptibility to DSS colitis, reduced regeneration of the intestine	[51]
$ADAM17^{woe}$	All tissues hypomorph	Viable	Hair defects, open eyes at birth	[52]
Transgenic ADAM17 overexpression	All tissues	Viable	ADAM17 mRNA and protein overexpression but no increased ADAM17 activity, no phenotype	[176]

ADAM17 mice (called ADAM17$^{ex/ex}$ mice) were generated by the exon induced translational stop (EXITS) technology [42]. Using this technique, mice were produced, which in all tissues showed dramatically reduced *Adam17* mRNA and protein levels. These mice were highly susceptible to inflammatory bowel disease and upon challenge showed an impaired intestinal barrier and strongly reduced intestinal regeneration [42]. Later, it was demonstrated that ADAM17$^{ex/ex}$ mice were more susceptible to Listeria infection [34]. When atherosclerosis was studied in mice lacking LDL receptor and ADAM17, it turned out that these mice upon feeding a high fat diet developed larger atherosclerotic lesions. Interestingly, it was found that shedding of the $TNFR_{II}$ was strongly impaired resulting in constitutive $TNFR_{II}$ signaling in these mice [43]. An involvement of ADAM10 in atherosclerosis was deduced from studies with mice lacking ADAM10 in myeloid cells, although the overall plaque size was unaltered in these animals [44].

Kidney fibrosis following kidney injury is an unresolved health problem and causes significant morbidity and mortality worldwide. In a recent study into the molecular mechanism of kidney fibrosis, it was shown that ADAM17, TNF*α* and the EGF-R ligand amphiregulin were upregulated leading to sustained activation of the EGF-R and infiltration of neutrophils and macrophages, which resulted in fibrosis. Loss of ADAM17 protected against these pathophysiologic changes. These results showed that ADAM17 might represent a therapeutic target in human kidney fibrosis [45].

Interestingly, a patient with an ADAM17 loss of function mutation was identified, who showed autosomal recessive neonatal inflammatory skin and bowel lesions indicating that in humans loss of ADAM17 was compatible with life [46]. A second patient with a genetic *ADAM17* deficiency was recently identified. Apart from impaired cytokine secretion from PBMCs, NK cells of this patient exhibited abnormally high levels of the NK killer receptor CD16 [47]. Moreover, it was shown that mutations in iRhom2 were associated with tylosis, a familial esophageal cancer syndrome. Keratinocytes from these patients were characterized by sustained EGF-R signaling, which was not seen in healthy control cells [48]. A mouse mutation in the first transmembrane region of iRhom2 reduced TNF*α* shedding [49] possibly by impairing the interaction with ADAM17 [50].

A mouse mutation in the *Adam17* gene was identified in a chemical mutagenesis screen. This mutation also led to a hypomorphic ADAM17 phenotype, which was characterized by enhanced susceptibility to DSS colitis and reduced regeneration of the intestine although the phenotype was less pronounced than in ADAM17$^{ex/ex}$ mice [51]. The spontaneous recessive mouse mutation waved with open eyes (woe) was identified as a C7794T substitution in the *Adam17* gene resulted in aberrant *Adam17* splicing rendering the ADAM17 protein inactive. Since normal splicing of the *Adam17* gene still occurred besides the aberrant splicing, this mutation also resulted in a hypomorphic ADAM17 phenotype, which again was somewhat less pronounced than in ADAM17$^{ex/ex}$ mice [52] (Table 2).

4. ADAM17 in the immune system

TNF*α* is a transmembrane protein, which requires cleavage by ADAM17 in order to act systemically. Consequently, pharmacological blockade of ADAM17 [2] or genetic deletion of the *Adam17* gene [40] leads to resistance of the mice to LPS-induced endotoxemia. TNF*α* acts via two TNF*α*-receptors ($TNFR_I$ and $TNFR_{II}$), which are also subject to shedding by ADAM17 [26]. Whereas signaling via $TNFR_I$ leads to apoptosis and cell death, signaling via $TNFR_{II}$ is considered protective. Interestingly, $TNFR_I$ is mainly stimulated by soluble (cleaved) TNF*α* whereas $TNFR_{II}$ is preferentially activated by uncleaved transmembrane TNF*α* [53]. These findings have led to the hypothesis that therapeutic blockade of the $TNFR_I$ would be superior to global blockade of the cytokine TNF*α* since the protective activity of the $TNFR_{II}$ would not be inhibited [54,55].

ADAM17 also plays a decisive role in the Interleukin-6 (IL-6) pathway. IL-6 binds on the cell surface to a membrane bound IL-6 receptor (IL-6R) and the complex of IL-6 and IL-6R bind to a homodimer of the signaling receptor gp130, thereby initiating intracellular signaling. Interestingly, neither IL-6 nor the IL-6R show a measurable affinity to gp130 [56]. It is only the complex of IL-6 and IL-6R, which associates with gp130. Whereas gp130 is present on all cells of the body, IL-6R is mainly on hepatocytes and some leukocytes. The IL-6R can, however, be cleaved from the cell membrane by ADAM17, thereby generating a soluble IL-6R (sIL-6R) [57]. This sIL-6R can bind the ligand IL-6 and the complex of IL-6 and sIL-6R can bind to gp130 on cells, which do not express IL-6R [56]. Such cells in the absence of sIL-6R would not be responsive to IL-6. This pathway was called IL-6 trans-signaling [58]. Interestingly it turned out that IL-6 acting via the membrane bound IL-6R acted mainly in a protective and regenerative manner, whereas IL-6 acting via the sIL-6R was rather pro-inflammatory [59,60]. In this respect, ADAM17, by switching between classic- and trans-signaling helps to determine the nature of the resulting IL-6 signal [9].

Interestingly, in human blood high levels of sIL-6R (around 50 ng/ml) and sgp130 (around 400 ng/ml) are found. In contrast, IL-6 levels are under normal conditions extremely low (around 1–5 pg/ml) [56]. During inflammatory states, sIL-6R levels increase 2–5 fold whereas sgp130 levels remain rather constant, leading to a molar excess of sIL-6R over sgp130 [61–64]. IL-6 levels increase 100–1000 fold during inflammation and can in septic states even reach 1–2 μg/ml [65]. We have hypothesized that sIL-6R and sgp130 form a buffer for IL-6 in the blood [59,60]. Interestingly, a single nucleotide polymorphism (rs2228145) in the IL-6R gene leads to an amino acid exchange of aspartic acid 358 to alanine 358 close to the IL-6R cleavage site [57]. This amino acid exchange results in more efficient cleavage of the IL-6R and consequently to about 50% higher sIL-6R levels [66]. In several genetic studies, it was found that the minor allele of rs2228145 resulting in alanine 358 conferred protection from coronary heart disease, rheumatoid arthritis and other inflammatory diseases [67–69]. These results were explained by the higher IL-6 buffer capacity in the presence of higher sIL-6R levels [59] and underlined the importance of the IL-6 buffer in the blood [70].

A study in ADAM17$^{ex/ex}$ mice confirmed that ADAM17 was required for retinal angiogenesis although lack of ADAM17 did not phenocopy the effect of Notch inhibition indicating an alternative signaling pathway [71]. Mechanistically, it was found that the inhibition of ADAM17 but not of ADAM10 resulted in an induction of the expression of thrombospondin 1, which is a naturally occurring inhibitor of angiogenesis [71].

The function of platelets is controlled by numerous cell surface proteins. These proteins are known to be shed by cellular proteases. This is an irreversible cellular decision since platelets are unable to synthesize new cell surface proteins. On platelets, shedding of glycoprotein VI was shown to be mediated by ADAM10 and ADAM17 but the existence of an additional protease was postulated since in vivo shedding of the glycoprotein VI was unaltered in the absence of ADAM10 and ADAM17 [72]. Interestingly, shedding of the cell surface protein CD84 was shown to be mediated by ADAM10 but not by ADAM17 [73].

5. ADAM17 in the central nervous system

The nervous system is a complex and highly dynamic system, which still lacks complete understanding of most regulatory processes in development and function. Its formation, maintenance, and repair rely on a complicated interplay of cellular mechanisms involving many progressive events like neural stem cell differentiation, axon and dendrite growth, as well as synapse formation and establishment of neural circuits. Interestingly, also regressive processes like axon pruning and synapse elimination play an important role in refining cellular connectivity and thus are crucial for the development and proper function of the central nervous system (CNS) [74]. Thereby, proteolytic

processing of membrane-anchored proteins is indispensable for neuronal development and homeostasis [74–76]. These protease-dependent modulations have major impacts on neuron and synapse growth as well as on synaptic plasticity, which is characterized by changes in shape, size and connectivity of synapses. Decreased neuronal connectivity as well as neuronal cell death are hallmarks of neurodegenerative conditions like for example amyloid lateral sclerosis (ALS), schizophrenia, Alzheimer and Parkinson disease [77,78]. This emphasizes the crucial role and necessity for a tight regulation of proteolytic events within the CNS in health and disease. Major effectors of proteolytic shedding events on cellular membranes are members of the families of metalloproteinases. Within this group, ADAM proteases have been shown to play important roles in the CNS development [75,79,80]. Accordingly, typical ADAM substrates include growth and differentiation factors, adhesion molecules, chemokines, cytokines and their receptors [80,81], which are necessary to regulate proliferation, migration, differentiation, axonal growth and myelination [75].

As one of the first ADAMs, ADAM10 function was linked to the development of the nervous system, as initially found in genetic screens of axon guidance deficiencies in *Drosophila* [82] as well as in the development [83] and formation of the murine brain [84]. The severe consequences of an ADAM10 knockout can be explained by the important neuronal and synaptic functions of ADAM10 substrates: e.g. the amyloid precursor protein (APP), Notch receptor, prion protein and N-Cadherin [80]. While new substrate identification methods unraveled novel neuronal target molecules of ADAM10 [85], the role of the closely related ADAM17 in the CNS still remains largely elusive.

ADAM17 expression has been found in the brain by Northern blot analyses in humans and rodents [3,86]. In an initial expression study from 1997, significantly higher RNA levels of *ADAM17* were found in human fetal brain tissue compared to adult brain samples [3]. This points towards a functional role of ADAM17 in neuronal development. Additional studies on neuronal substrates of ADAM17 further underline this assumption: ADAM17 was implicated in the development of the nervous system through activating neural cell adhesion and neurite outgrow by cleaving L1 [87] and neuronal cell adhesion molecule, NCAM [88]. Moreover, APP has also been described as substrate of ADAM17 [89]. Although APP has been subject of intense investigations, its functional role in health and neurogenesis is still not completely understood [90]. Studies in mice indicate a role of APP in early embryogenesis by mediating neuronal migration [91] and synaptic connectivity [92].

Besides ADAM10, ADAM17 has been shown to act as α-secretase producing a soluble and non-amyloidogenic fragment (sAPPα) [89]. This soluble sAPPα fragment is considered to be neuroprotective and amongst other things has been shown to function as a proliferation factor for adult neural progenitor cells [93]. On the other hand, shedding of APP by β-secretases [94,95] results in the formation of soluble amyloidogenic fragments (sAPPβ), which can be further processed by γ-secretases and induce amyloid plaque formation and inflammation in the brain [96,97]. Interestingly, ADAM17 has been shown to localize in areas containing amyloid plaques in Alzheimer disease patients' brains [98].

Moreover, it has been observed that FHL2, an interaction partner and regulator of ADAM17 activity, is necessary for sAPPα generation [99,100]. This additionally strengthens the link between APP processing and ADAM17 function. Due to the role of α-secretases in the non-amyloidogenic pathway of APP processing, further studies of ADAM10 and especially the -so far- less studied ADAM17 are necessary to better understand disease progression in Alzheimer disease [101,102].

Interestingly, ADAM17 function has also been implicated in learning and memory. A study in 2008 revealed the involvement of ADAM17 in glutamate receptor 1/5-induced long-term depression (LTD), which is characterized by an activity-dependent reduction in the efficacy of neuronal synapses and thus important for learning processes [103]. Furthermore, ADAM17 has been shown to process membrane proteins important for synaptic connection formation and plasticity. This includes the neuronal pentraxin (NPR) [103], which regulates the endocytosis of AMPA-type glutamate receptors, necessary for LTD in hippocampal and cerebellar synapses and the cell adhesion molecule RA175/SynCAM1, which is important for synaptic modulations and thus memory formation [104].

An increasing number of studies attempt to shed more light into the still elusive role of ADAM17 in the CNS. Recent data point towards a crucial function of the protease in neuronal development, which is mainly based on its well described role in regulating signaling through the EGF-R [79]. ADAM17 exhibits a key role in shedding of membrane-anchored growth factors such as the EGF-R ligands TGFα, amphiregulin, epiregulin and heparin-binding (HB)-EGF (Table 1) [79,80]. The EGF-R demonstrates a widespread expression profile across the CNS [105,106] with significant expression found in the neocortex, limbic cortex, cerebrovascular endothelial cells, cerebellum [107,108] and the midbrain [109]. Thus, it is not surprising that EGF-R signaling has been linked to neuronal development, synaptic plasticity and memory formation [110,111]. Lately, HB-EGF, has also been considered to play a pivotal role in the developing and adult CNS [112]. Also, HB-EGF has been shown to be widely expressed in the nervous system and to contribute to neuronal survival and glia/stem cell proliferation [113–115]. Following, a recent study elucidated the significant role of ADAM17, as the key modulator of HB-EGF, in oligodendrocyte development and the myelination of the CNS, which is crucial for proper development and function of the brain [116].

The inherited small vessel disease CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) [117] has been implicated with stroke and dementia. Since tissue inhibitor of metalloproteinase 3 (TIMP3), a natural antagonist of ADAM17, was shown to contribute to cerebrovascular dysfunction we hypothesized that ADAM17 might play a role in this pathophysiologic condition. Indeed, we could demonstrate that the role of TIMP3 in CADASIL was via the inhibition of ADAM17, which cleaved the EGF-R ligand HB-EGF and thereby contributed to the control of cerebral arterial tone and blood flow [117]. Our data highlighted a concept of a balance between ADAM17 activity and TIMP3 resulting in the regulation of cerebral blood flow [117].

Moreover, HB-EGF has recently been described to promote development and survival of dopaminergic neurons [115]. In the adult brain, dopaminergic neurons are mainly localized in the midbrain (mesencephalon) and to a very small extend in the diencephalon and the olfactory bulb [118,119]. Dopaminergic neurons originating from the substantia nigra pars compacta (SNc), a part of the midbrain, play an essential role in the control of voluntary movement, cognition and emotion [120–122]. Thus, abnormal function of the dopaminergic system results in movement disorders, like Parkinson disease [123], and can also lead to several psychiatric disorders including schizophrenia or drug addiction [124]. Interestingly, a recent study has linked the metalloproteases ADAM10 and ADAM17 to the development of murine dopaminergic neurons [125]. Hereby, the dopamine D2 receptor (D2R) induces the shedding of HB-EGF by activation of ADAM10/17. This leads to EGF-R signaling resulting in a downstream extracellular signal-regulated kinase (ERK) pathway activation (Fig. 3). Importantly, the development and differentiation of dopaminergic neurons depends on D2R-mediated ERK activation [126–128]. The D2R is member of the G protein-coupled receptor family and highly expressed in the CNS regulating diverse functions mediated by dopamine, including locomotion as well as emotional and motivational behavior [128–130].

Interestingly, administration of EGF to the cell culture could restore normal dopaminergic neuron development in the absence of D2R [125]. The work of Yoon and Baik is in accordance with the knowledge of ADAM17 being the main sheddase for HB-EGF. In addition, the HB-EGF-binding EGF-Rs (ErbB1 as well as ErbB4) are found to be expressed in the midbrain and have been shown to regulate survival and development of dopaminergic neurons [131]. Decreased levels of EGF, EGF-R

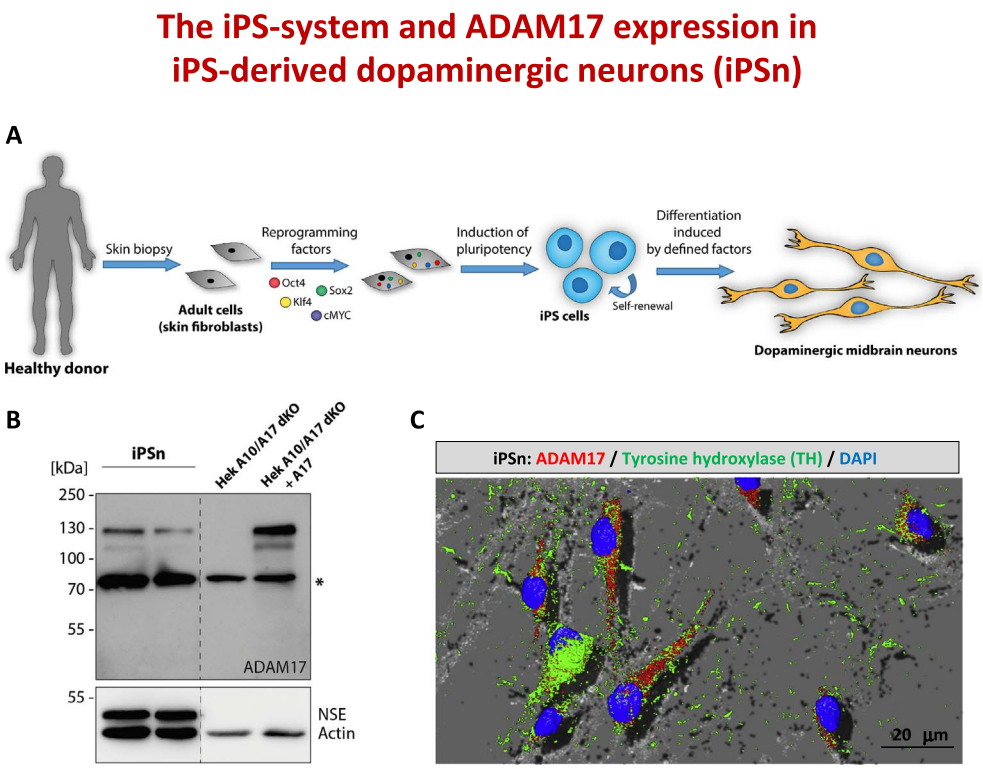

Fig. 4. Expression of ADAM17 in iPS-derived dopaminergic neurons. A) Human induced pluripotent stem (iPS) cells were derived from fibroblasts of a healthy donor. Primary human skin fibroblasts were transduced by reprogramming factors Oct4, Sox2, Klf4 and cMYC and established iPS cells lines were tested for pluripotency [139]. Directed differentiation towards dopaminergic neurons was initiated by adding a well-described mixture of growth factors including BDNF, ascorbic acid, SHH, FGF8a as well as GDNF, TGF-β3 and cyclic-AMP [140]. iPS-derived human midbrain dopaminergic neurons (iPSn) were stained for ADAM17 utilizing specific antibodies [141] in immunoblot (B) and immunocytochemical (C) analyses. B) In Western blot analyses, iPSn lysates were loaded in duplicates and β-actin as well as neuronal specific enolase (NSE) were used as loading control. To determine antibody specificity ADAM10/17-deficient (A10/17 dKO) as well as human ADAM17 overexpressing Hek cell lysates were utilised (B). Dotted line indicates lanes of the same blot were merged; * marks antibody unspecific band. C) Immunocytochemical analysis of iPS-derived dopaminergic neurons (iPSn) stained for endogenous ADAM17 (red) and tyrosine hydroxylase (TH), a marker for dopaminergic neurons (green), indicating cellular localization of ADAM17 in the cell body of neurons as well as partly in neurites (overlay of 2D image and 3D z-stack volume). iPS cells were derived from fibroblasts of a healthy donor and characterized for pluripotency [139]. Directed differentiation towards dopaminergic neurons was conducted following the *Studer* protocol [140]. Maintenance of dopaminergic neurons, cell lysis and preparation for western blotting and immunostaining was performed as described in Mazzulli et al. [177]. ADAM17-specific antibody (A300D) [141] was used in a concentration of 1:500 for Western blot analysis and the respective antibody (A300E) was applied 1:50 in immunocytochemistry. Co-staining of dopaminergic neurons was performed utilising a tyrosine hydroxylase antibody (EMD Millipore, AB5986; 1:1000). Immunofluorescence samples were analyzed by confocal laser microscopy (FluoView 1000R; Olympus). Cells were visualised at a magnification of 60× using oil objectives. The FV1000-ASW 3.0 Viewer-Software (Olympus) as well as the Chimera software (www.cgl.ucsf.edu/chimera; supported by National Institute of General Medical Sciences Grant P41-GM103311) were applied for analysis of immunofluorescent pictures. The representative image shown here is an overlay of a 2D image and 3D z-stack volume.

(ErbB1) and tyrosine hydroxylase, a marker for dopaminergic neurons, could be found in postmortem brains of Parkinson disease patients [132]. The same effects could be recapitulated in animal models with disturbed ErbB1 signaling and dopaminergic cell loss could even be impeded after administration of EGF [133,134]. Additionally, intracerebral administration of HB-EGF into an adult Parkinson disease rat model was shown to protect the dopaminergic system [135].

Taken together, these findings indicate the importance of the ADAM17-EGF-R-signaling axis in the development and maintenance of dopaminergic neurons. Thus, ADAM17 and EGF-R appear in genetic screens as Parkinson disease-modifying factors [136]. The EGF-R has found to be second strongest candidate in a 'guilt-by-association' gene map due to its interaction with six known Parkinson-related genes. Additionally, ADAM17 was implicated in Parkinson disease pathology by KEGG pathway analysis [136] and even claimed to be an indirect therapeutic target in Parkinson disease [137,138]. Although, numerous recent studies point towards a novel and crucial role of ADAM17 in the development and maintenance of dopaminergic neurons, the precise role of ADAM17 function in neuronal health and Parkinson disease pathology has to be further established.

Expression studies of ADAM17 in the brain are incomplete with no information on ADAM17 expression in human dopaminergic midbrain neurons. To generate human dopaminergic neurons, we utilized induced-pluripotent stem (iPS) cells derived from fibroblasts of a healthy proband (Fig. 4A) [139]. After differentiation of iPS cells to dopaminergic neurons (following the *Studer* protocol [140]; Fig. 4A), cells were analysed for ADAM17 expression. As shown in Fig. 4B/C, protein expression of ADAM17 could be determined by immunoblotting and immunocytochemistry utilising a human ADAM17-specific antibody [141]. Immunofluorescence studies of iPS-derived dopaminergic neurons exhibit ADAM17 expression (red) mainly in the cell bodies, as indicated by a strong staining close to the nucleus, as well as some antibody signal in neurites (Fig. 4C). The neuronal cells were co-stained with tyrosine hydroxylase (green), a marker for dopaminergic neurons. To study cellular localization of ADAM17 in neuronal cells in more detail, further co-staining studies with intracellular markers have to be performed.

The discovery of ADAM17 expression in human dopaminergic neurons underlines its potential importance in regulation of neuronal development and strengthens the attempts to further validate ADAM17 function in the CNS. Furthermore, we here demonstrate the potential of the iPS-system in unraveling -so far unknown- protease functions and expression patterns in recently not accessible human cell lines and tissue.

In the past it was observed in many cellular models that neural cells respond to IL-6 only in the presence of the soluble sIL-6R [142,143]. In order to evaluate the role of IL-6 trans-signaling in the brain, we generated mice expressing the IL-6 trans-signaling inhibiting protein sgp130Fc under the transcriptional control of the brain-specific glial fibrillary acid protein promoter [144]. Transgenic mice expressing IL-6 under the transcriptional control of the brain-specific glial fibrillary acid protein promoter are characterized by neurodegeneration and astrocytosis [145]. When we crossed the brain-specific IL-6 transgenic mice with the brain-specific sgp130Fc expressing mice, most of the detrimental effects of IL-6 overexpression were alleviated indicating that most IL-6 signaling in the brain is mediated by IL-6 trans-signaling [144,146], which again implies an important role for ADAM17 in the brain and other neuronal cells [146].

6. ADAM17 and IL-6R signaling in cancer

It was recently shown that not only the development of emphysema [64] but also Kras driven lung cancer [147] could be strongly inhibited by the sgp130Fc protein, indicating that IL-6 activity via trans-signaling was the underlying mechanism of both pathophysiologic states. These data make it likely that activation of ADAM17 and subsequent cleavage of the membrane bound IL-6R are involved in these diseases.

A role for IL-6 was demonstrated in ovarian cancer models. IL-6 trans-signaling on endothelial cells prevented chemotherapy induced apoptosis and blockade of IL-6 trans-signaling by the sgp130Fc protein in vivo resulted in reduced ascites formation and in enhanced chemotherapy sensitivity of human ovarian tumor xenografts [148]. Furthermore, in a model of ovarian hyperstimulation syndrome it was demonstrated that IL-6 via trans-signaling induced VEGF expression and increased vascular permeability of endothelial cells. Consequently, blockade of IL-6 trans-signaling prevented the ovarian hyperstimulation syndrome in treated animals [149].

Such a view was supported by the demonstration that IL-6 trans-signaling and subsequent activation of STAT3 and SOCS3 was involved in pancreatic intraepithelial neoplasia and pancreatic ductal adenocarcinoma development cancer [150,151]. Furthermore, it could be demonstrated that specific blockade of IL-6 trans-signaling by the sgp130Fc protein reduced pancreatic tumor growth in vivo [152]. Furthermore, inhibition of IL-6 trans-signaling led to a decrease in microvessel density and to a reduction of distant metastases indicating a therapeutic benefit from blockade of IL-6 trans-signaling [152].

The incidence of liver cancer is known to be higher in men than in woman and could be explained by a suppression of IL-6 synthesis by estrogen in the female organism [153,154]. We therefore asked whether the tumorigenic activity of IL-6 was mediated by IL-6 trans-signaling. We used mice, which expressed high levels of the sgp130Fc protein as a transgene [155] and treated the mice with the chemical carcinogen, diethylnitrosamine [156]. It turned out that blockade of IL-6 trans-signaling largely protected the animals from liver cancer indicating that IL-6 trans-signaling was responsible for hepatocellular carcinogenesis. Again, these data let us hypothesize that ADAM17 mediated cleavage of the IL-6R is involved in cancer development [156].

7. Blockade of ADAM17 activity

Tissue inhibitor of metalloproteinases (TIMPs), comprising of TIMP1–4, are natural metalloproteinase inhibitors, which are therefore key regulators of shedding events on the cell surface [157,158]. It has been established that TIMP-3 is an effective inhibitor of ADAM17 [157]. TIMP-3 has been found to control cytokine and growth factor bioavailability in order to regulate inflammation, cell death and survival in the liver. Moreover, TIMP3 has been found silenced in human cancers [159]. Although it has been shown that deficiencies in TIMP-3 can lead to modulations in ADAM17 function [117,160], the precise role of TIMP3-dependent ADAM17 regulation has to be further established [158].

Even before the cDNA of *Adam17* was cloned [3,161], a hydroxamate based inhibitor of ADAM17 activity was generated and it was shown that blockade of ADAM17 activity protected mice from death by a lethal dose of LPS [2]. More specific hydroxamate inhibitors were subsequently developed [162] and were used in vitro and in vivo to differentiate between ADAM17 and the closely related protease ADAM10 [30,163].

Using a two-step phage display strategy, a neutralizing antibody against human ADAM17 was developed, which proved to be a selective ADAM17 inhibitor, which blocked ADAM17, but not ADAM10 mediated shedding of the EGF receptor ligand HB-EGF [164]. More recently, it was shown that cleavage of the pro-domain required an additional proteolytic step within the pro-domain of ADAM17 [13] and it was subsequently demonstrated that the recombinantly expressed pro-domain of ADAM17 could serve as an effective and highly specific inhibitor of ADAM17 activity [12]. This pro-domain inhibitor was used to block ADAM17 activity in vivo in a murine kidney fibrosis model [45] and to inhibit ADAM17 mediated shedding of the endothelial protein C receptor [165]. The high specificity of the ADAM17 neutralizing antibody and of the ADAM17 blocking pro-domain make these proteins valuable candidates to further test the benefit of ADAM17 inhibition in animal models of inflammation and inflammation associated cancer [166].

8. Outlook

As this review points out, numerous studies on ADAM17 structure and function in health and disease have been performed. Being involved in crucial pathways of the immune system, fibrosis and cancer progression makes ADAM17 to an interesting therapeutic target. Within these disease models, inhibition of ADAM17 has been shown to be a promising treatment strategy. Nonetheless further studies have to be assigned to develop novel specific ADAM17 inhibitors and test their benefits in disease progression of cancer and inflammation.

Additionally, we here focus on the emerging role of ADAM17 in CNS development and maintenance. Until now the role of ADAM17 in the CNS is only poorly understood and needs further investigation. Interestingly, recent data point towards an important role of the protease in development and function of dopaminergic midbrain neurons. Since this cell type is particularly important for movement and thus majorly involved in Parkinson disease progression, further studies to decipher its role in this specific cell type are of great interest. Modulation of neuronal cell viability by regulation ADAM17 activity might be a future therapeutic aspect in neurodegenerative diseases, like Parkinson and Alzheimer disease. Moreover, we here highlight, how the iPS technology might provide a useful tool in unraveling protease function in various human cell types and tissues in the future.

Transparency Document

The Transparency document associated with this article can be found, in online version.

Acknowledgments

We greatly thank Dimitri Krainc and Joseph Mazzulli for kindly allowing us to use the healthy human iPS cells for our protease studies (both Northwestern University, Department of Neurology, Chicago, USA). We also thank Philipp Arnold for his help with the z-stack image processing protocol. This work was supported by the Deutsche Forschungsgemeinschaft (DFG), Bonn (SFB877, project A1) and by the Cluster of Excellence 'Inflammation at Interfaces'.

References

[1] M. Kriegler, C. Perez, K. DeFay, I. Albert, S.D. Lu, A novel form of TNF/cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF, Cell 53 (1988) 45–53.

[2] K.M. Mohler, P.R. Sleath, J.N. Fitzner, D.P. Cerretti, M. Alderson, S.S. Kerwar, D.S. Torrance, C. Otten Evans, T. Greenstreet, K. Weerawarna, S.R. Kronheim, M. Petersen, M. Gerhart, C.J. Kozlosky, C.J. March, R.A. Black, Protection against a lethal dose of endotoxin by an inhibitor of tumour necrosis factor processing, Nature 370 (1994) 218–220.

[3] R.A. Black, C.T. Rauch, C.J. Kozlosky, J.J. Peschon, J.L. Slack, M.F. Wolfson, B.J. Castner, K.L. Stocking, P. Reddy, S. Srinivasan, N. Nelson, N. Boiani, K.A. Schooley, M. Gerhart, R. Davis, J.N. Fitzner, R.S. Johnson, R.J. Paxton, C.J. March, D.P. Cerretti, A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells, Nature 385 (1997) 729–733.

[4] M.L. Moss, S.L. Jin, M.E. Milla, D.M. Bickett, W. Burkhart, H.L. Carter, W.J. Chen, W.C. Clay, J.R. Didsbury, D. Hassler, C.R. Hoffman, T.A. Kost, M.H. Lambert, M.A. Leesnitzer, P. McCauley, G. McGeehan, J. Mitchell, M. Moyer, G. Pahel, W. Rocque, L.K. Overton, F. Schoenen, T. Seaton, J.L. Su, J.D. Becherer, et al., Cloning of a disintegrin metalloproteinase that processes precursor tumour-

necrosis factor-alpha, Nature 385 (1997) 733–736.
[5] J. Mullberg, K. Althoff, T. Jostock, S. Rose-John, The importance of shedding of membrane proteins for cytokine biology, Eur. Cytokine Netw. 11 (2000) 27–38.
[6] J.J. Peschon, J.L. Slack, P. Reddy, K.L. Stocking, S.W. Sunnarborg, D.C. Lee, W.E. Russell, B.J. Castner, R.S. Johnson, J.N. Fitzner, R.W. Boyce, N. Nelson, C.J. Kozlosky, M.F. Wolfson, C.T. Rauch, D.P. Cerretti, R.J. Paxton, C.J. March, R.A. Black, An essential role for ectodomain shedding in mammalian development, Science 282 (1998) 1281–1284.
[7] J.C. Jones, S. Rustagi, P.J. Dempsey, ADAM proteases and gastrointestinal function, Annu. Rev. Physiol. 78 (2016) 243–276.
[8] J. Arribas, L. Coodly, P. Vollmer, T.K. Kishimoto, S. Rose-John, J. Massague, Diverse cell surface protein ectodomains are shed by a system sensitive to metalloprotease inhibitors, J. Biol. Chem. 271 (1996) 11376–11382.
[9] J. Scheller, A. Chalaris, C. Garbers, S. Rose-John, ADAM17: a molecular switch to control inflammation and tissue regeneration, Trends Immunol. 32 (2011) 380–387.
[10] K.P. Fong, C. Barry, A.N. Tran, E.A. Traxler, K.M. Wannemacher, H.Y. Tang, K.D. Speicher, I.A. Blair, D.W. Speicher, T. Grosser, L.F. Brass, Deciphering the human platelet sheddome, Blood, 2011 (Epub ahead of print).
[11] R. Kawahara, R.N. Lima, R.R. Domingues, B.A. Pauletti, G.V. Meirelles, M. Assis, A.C. Figueira, A.F. Paes Leme, Deciphering the role of the ADAM17-dependent secretome in cell signaling, J. Proteome Res. 13 (2014) 2080–2093.
[12] E. Wong, T. Maretzky, Y. Peleg, C.P. Blobel, I. Sagi, The functional maturation of a disintegrin and metalloproteinase (ADAM) 9, 10, and 17 requires processing at a newly identified proprotein convertase (PC) cleavage site, J. Biol. Chem. 290 (2015) 12135–12146.
[13] E. Wong, T. Cohen, E. Romi, M. Levin, Y. Peleg, U. Arad, A. Yaron, M.E. Milla, I. Sagi, Harnessing the natural inhibitory domain to control TNFalpha converting enzyme (TACE) activity in vivo, Sci Rep 6 (2016) 35598.
[14] K. Maskos, C. Fernandez-Catalan, R. Huber, G.P. Bourenkov, H. Bartunik, G.A. Ellestad, P. Reddy, M.F. Wolfson, C.T. Rauch, B.J. Castner, R. Davis, H.R. Clarke, M. Petersen, J.N. Fitzner, D.P. Cerretti, C.J. March, R.J. Paxton, R.A. Black, W. Bode, Crystal structure of the catalytic domain of human tumor necrosis factor-alpha-converting enzyme, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 3408–3412.
[15] A. Trad, M. Riese, M. Shomali, N. Hedeman, T. Effenberger, J. Grotzinger, I. Lorenzen, The disintegrin domain of ADAM17 antagonises fibroblastcarcinoma cell interactions, Int. J. Oncol. 42 (2013) 1793–1800.
[16] S. Dusterhoft, K. Hobel, M. Oldefest, J. Lokau, G.H. Waetzig, A. Chalaris, C. Garbers, J. Scheller, S. Rose-John, I. Lorenzen, J. Grotzinger, A disintegrin and metalloprotease 17 dynamic interaction sequence, the sweet tooth for the human interleukin 6 receptor, J. Biol. Chem. 289 (2014) 16336–16348.
[17] S. Dusterhoft, S. Jung, C.W. Hung, A. Tholey, F.D. Sonnichsen, J. Grotzinger, I. Lorenzen, Membrane-proximal domain of a disintegrin and metalloprotease-17 represents the putative molecular switch of its shedding activity operated by protein-disulfide isomerase, J. Am. Chem. Soc. 135 (2013) 5776–5781.
[18] A. Sommer, F. Kordowski, J. Buch, T. Maretzky, A. Evers, J. Andra, S. Dusterhoft, M. Michalek, I. Lorenzen, P. Somasundaram, A. Tholey, F.D. Sonnichsen, K. Kunzelmann, L. Heinbockel, C. Nehls, T. Gutsmann, J. Grotzinger, S. Bhakdi, K. Reiss, Phosphatidylserine exposure is required for ADAM17 sheddase function, Nat. Commun. 7 (2016) 11523.
[19] C. Adrain, M. Zettl, Y. Christova, N. Taylor, M. Freeman, Tumor necrosis factor signaling requires iRhom2 to promote trafficking and activation of TACE, Science 335 (2012) 225–228.
[20] D.R. McIlwain, P.A. Lang, T. Maretzky, K. Hamada, K. Ohishi, S.K. Maney, T. Berger, A. Murthy, G. Duncan, H.C. Xu, K.S. Lang, D. Haussinger, A. Wakeham, A. Itie-Youten, R. Khokha, P.S. Ohashi, C.P. Blobel, T.W. Mak, iRhom2 regulation of TACE controls TNF-mediated protection against *Listeria* and responses to LPS, Science 335 (2012) 229–232.
[21] X. Li, T. Maretzky, G. Weskamp, S. Monette, X. Qing, P.D. Issuree, H.C. Crawford, D.R. McIlwain, T.W. Mak, J.E. Salmon, C.P. Blobel, iRhoms 1 and 2 are essential upstream regulators of ADAM17-dependent EGFR signaling, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 6080–6085.
[22] T. Maretzky, D.R. McIlwain, P.D. Issuree, X. Li, J. Malapeira, S. Amin, P.A. Lang, T.W. Mak, C.P. Blobel, iRhom2 controls the substrate selectivity of stimulated ADAM17-dependent ectodomain shedding, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 11433–11438.
[23] J. Mullberg, H. Schooltink, T. Stoyan, M. Gunther, L. Graeve, G. Buse, A. Mackiewicz, P.C. Heinrich, S. Rose-John, The soluble interleukin-6 receptor is generated by shedding, Eur. J. Immunol. 23 (1993) 473–480.
[24] J. Mullberg, H. Schooltink, T. Stoyan, P.C. Heinrich, S. Rose-John, Protein kinase C activity is rate limiting for shedding of the interleukin-6 receptor, Biochem. Biophys. Res. Commun. 189 (1992) 794–800.
[25] P. Reddy, J.L. Slack, R. Davis, D.P. Cerretti, C.J. Kozlosky, R.A. Blanton, D. Shows, J.J. Peschon, R.A. Black, Functional analysis of the domain structure of tumor necrosis factor-alpha converting enzyme, J. Biol. Chem. 275 (2000) 14608–14614.
[26] J. Schwarz, C. Broder, A. Helmstetter, S. Schmidt, I. Yan, M. Muller, D. Schmidt-Arras, C. Becker-Pauly, F. Koch-Nolte, H.W. Mittrucker, B. Rabe, S. Rose-John, A. Chalaris, Short-term TNFalpha shedding is independent of cytoplasmic phosphorylation or furin cleavage of ADAM17, Biochim. Biophys. Acta 1833 (2013) 3355–3367.
[27] P. Xu, R. Derynck, Direct activation of TACE-mediated ectodomain shedding by p38 MAP kinase regulates EGF receptor-dependent cell proliferation, Mol. Cell 37 (2010) 551–566.
[28] J. Schwarz, S. Schmidt, O. Will, T. Koudelka, K. Kohler, M. Boss, B. Rabe, A. Tholey, J. Scheller, D. Schmidt-Arras, M. Schwake, S. Rose-John, A. Chalaris, Polo-like kinase 2, a novel ADAM17 signaling component, regulates tumor necrosis factor alpha ectodomain shedding, J. Biol. Chem. 289 (2014) 3080–3093.
[29] G. Murphy, A. Murthy, R. Khokha, Clipping, shedding and RIPping keep immunity on cue, Trends Immunol. 29 (2008) 75–82.
[30] A. Chalaris, J. Gewiese, K. Paliga, L. Fleig, A. Schneede, K. Krieger, S. Rose-John, J. Scheller, ADAM17-mediated shedding of the IL6R induces cleavage of the membrane stub by gamma-secretase, Biochim. Biophys. Acta 1803 (2010) 234–245.
[31] N. Prenzel, E. Zwick, H. Daub, M. Leserer, R. Abraham, C. Wallasch, A. Ullrich, EGF receptor transactivation by G-protein-coupled receptors requires metalloproteinase cleavage of proHB-EGF, Nature 402 (1999) 884–888.
[32] T. Maretzky, A. Evers, W. Zhou, S.L. Swendeman, P.M. Wong, S. Rafii, K. Reiss, C.P. Blobel, Migration of growth factor-stimulated epithelial and endothelial cells depends on EGFR transactivation by ADAM17, Nat. Commun. 2 (2011) 229.
[33] C. Garbers, N. Janner, A. Chalaris, M.L. Moss, D.M. Floss, D. Meyer, F. Koch-Nolte, S. Rose-John, J. Scheller, Species specificity of ADAM10 and ADAM17 proteins in interleukin-6 (IL-6) trans-signaling and novel role of ADAM10 in inducible IL-6 receptor shedding, J. Biol. Chem. 286 (2011) 14804–14811.
[34] I. Yan, J. Schwarz, K. Lucke, N. Schumacher, V. Schumacher, S. Schmidt, B. Rabe, P. Saftig, M. Donners, S. Rose-John, H.W. Mittrucker, A. Chalaris, ADAM17 controls IL-6 signaling by cleavage of the murine IL-6Ralpha from the cell surface of leukocytes during inflammatory responses, J. Leukoc. Biol. 99 (2016) 749–760.
[35] N. Schumacher, S. Schmidt, J. Schwarz, D. Dohr, J. Lokau, J. Scheller, C. Garbers, A. Chalaris, S. Rose-John, B. Rabe, Circulating soluble IL-6R but not ADAM17 activation drives mononuclear cell migration in tissue inflammation, J. Immunol. 197 (2016) 3705–3715.
[36] Y. Wang, A.C. Zhang, Z. Ni, A. Herrera, B. Walcheck, ADAM17 activity and other mechanisms of soluble L-selectin production during death receptor-induced leukocyte apoptosis, J. Immunol. 184 (2010) 4447–4454.
[37] A. Stoeck, S. Keller, S. Riedle, M.P. Sanderson, S. Runz, F. Le Naour, P. Gutwein, A. Ludwig, E. Rubinstein, P. Altevogt, A role for exosomes in the constitutive and stimulus-induced ectodomain cleavage of L1 and CD44, Biochem. J. 393 (2006) 609–618.
[38] N. Schumacher, D. Meyer, A. Mauermann, J. von der Heyde, J. Wolf, J. Schwarz, K. Knittler, G. Murphy, M. Michalek, C. Garbers, J.W. Bartsch, S. Guo, B. Schacher, P. Eickholz, A. Chalaris, S. Rose-John, B. Rabe, Shedding of endogenous interleukin-6 receptor (IL-6R) is governed by a disintegrin and metalloproteinase (ADAM) proteases while a full-length IL-6R isoform localizes to circulating microvesicles, J. Biol. Chem. 290 (2015) 26059–26071.
[39] S. Keller, M.P. Sanderson, A. Stoeck, P. Altevogt, Exosomes: from biogenesis and secretion to biological function, Immunol. Lett. 107 (2006) 102–108.
[40] K. Horiuchi, T. Kimura, T. Miyamoto, H. Takaishi, Y. Okada, Y. Toyama, C.P. Blobel, Cutting edge: TNF-{alpha}-converting enzyme (TACE/ADAM17) inactivation in mouse myeloid cells prevents lethality from endotoxin shock, J. Immunol. 179 (2007) 2686–2689.
[41] P.W. Janes, N. Saha, W.A. Barton, M.V. Kolev, S.H. Wimmer-Kleikamp, E. Nievergall, C.P. Blobel, J.P. Himanen, M. Lackmann, D.B. Nikolov, Adam meets Eph: an ADAM substrate recognition module acts as a molecular switch for ephrin cleavage in trans, Cell 123 (2005) 291–304.
[42] A. Chalaris, N. Adam, C. Sina, P. Rosenstiel, J. Lehmann-Koch, P. Schirmacher, D. Hartmann, J. Cichy, O. Gavrilova, S. Schreiber, T. Jostock, V. Matthews, R. Häsler, C. Becker, M.F. Neurath, K. Reiss, P. Saftig, J. Scheller, S. Rose-John, Critical role of the disintegrin metalloprotease ADAM17 for intestinal inflammation and regeneration in mice, J. Exp. Med. 207 (2010) 1617–1624.
[43] A. Nicolaou, Z. Zhao, B.H. Northoff, K. Sass, A. Herbst, A. Kohlmaier, A. Chalaris, C. Wolfrum, C. Weber, S. Steffens, S. Rose-John, D. Teupser, L.M. Holdt, Adam17 deficiency promotes atherosclerosis by enhanced TNFR2 signaling in mice, Arterioscler. Thromb. Vasc. Biol. 37 (2017) 247–257.
[44] E.P. van der Vorst, M. Jeurissen, I.M. Wolfs, A. Keijbeck, K. Theodorou, E. Wijnands, L. Schurgers, S. Weber, M.J. Gijbels, A.A. Hamers, D. Dreymueller, S. Rose-John, M.P. de Winther, A. Ludwig, P. Saftig, E.A. Biessen, M.M. Donners, Myeloid A disintegrin and metalloproteinase domain 10 deficiency modulates atherosclerotic plaque composition by shifting the balance from inflammation toward fibrosis, Am. J. Pathol. 185 (2015) 1145–1155.
[45] E. Kefaloyianni, M.L. Muthu, J. Kaeppler, X. Sun, V. Sabbisetti, A. Chalaris, S. Rose-John, E. Wong, I. Sagi, S.S. Waikar, H. Rennke, B.D. Humphreys, J.V. Bonventre, A. Herrlich, ADAM17 substrate release in proximal tubule drives kidney fibrosis, JCI Insight 1 (2016).
[46] D.C. Blaydon, P. Biancheri, W.L. Di, V. Plagnol, R.M. Cabral, M.A. Brooke, D.A. van Heel, F. Ruschendorf, M. Toynbee, A. Walne, E.A. O'Toole, J.E. Martin, K. Lindley, T. Vulliamy, D.J. Abrams, T.T. MacDonald, J.I. Harper, D.P. Kelsell, Inflammatory skin and bowel disease linked to ADAM17 deletion, N. Engl. J. Med. 365 (2011) 1502–1508.
[47] P. Tsukerman, E.M. Eisenstein, M. Chavkin, D. Schmiedel, E. Wong, M. Werner, B. Yaacov, D. Averbuch, V. Molho-Pessach, P. Stepensky, N. Kaynan, Y. Bar-On, E. Seidel, R. Yamin, I. Sagi, O. Elpeleg, O. Mandelboim, Cytokine secretion and NK cell activity in human ADAM17 deficiency, Oncotarget 6 (2015) 44151–44160.
[48] D.C. Blaydon, S.L. Etheridge, J.M. Risk, H.C. Hennies, L.J. Gay, R. Carroll, V. Plagnol, F.E. McRonald, H.P. Stevens, N.K. Spurr, D.T. Bishop, A. Ellis, J. Jankowski, J.K. Field, I.M. Leigh, A.P. South, D.P. Kelsell, RHBDF2 mutations are associated with tylosis, a familial esophageal cancer syndrome, Am. J. Hum. Genet. 90 (2012) 340–346.
[49] O.M. Siggs, N. Xiao, Y. Wang, H. Shi, W. Tomisato, X. Li, Y. Xia, B. Beutler, iRhom2 is required for the secretion of mouse TNFalpha, Blood 119 (2012) 5769–5771.
[50] X. Li, T. Maretzky, J.M. Perez-Aguilar, S. Monette, G. Weskamp, S. Le Gall, B. Beutler, H. Weinstein, C.P. Blobel, Structural modeling defines transmembrane

residues in ADAM17 that are crucial for Rhbdf2/ADAM17-dependent proteolysis, J. Cell Sci. (2017).
[51] K. Brandl, L. Sun, C. Neppl, O.M. Siggs, S.M. Le Gall, W. Tomisato, X. Li, X. Du, D.N. Maennel, C.P. Blobel, B. Beutler, MyD88 signaling in nonhematopoietic cells protects mice against induced colitis by regulating specific EGF receptor ligands, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 19967–19972.
[52] E.L. Hassemer, S.M. Le Gall, R. Liegel, M. McNally, B. Chang, C.J. Zeiss, R.D. Dubielzig, K. Horiuchi, T. Kimura, Y. Okada, C.P. Blobel, D.J. Sidjanin, The waved with open eyelids (woe) locus is a hypomorphic mouse mutation in Adam17, Genetics 185 (2010) 245–255.
[53] M. Grell, E. Douni, H. Wajant, M. Lohden, M. Clauss, B. Maxeiner, S. Georgopoulos, W. Lesslauer, G. Kollias, K. Pfizenmaier, P. Scheurich, The transmembrane form of tumor necrosis factor is the prime activating ligand of the 80 kDa tumor necrosis factor receptor, Cell 83 (1995) 793–802.
[54] F. Van Hauwermeiren, L. Puimege, S. Vandevyver, T. Van Bogaert, I. Vanlaere, L. Huys, L. Dejager, C. Libert, Strategies to inhibit the toxicity of systemic TNF treatment, Adv. Exp. Med. Biol. 691 (2011) 481–484.
[55] F. Van Hauwermeiren, R.E. Vandenbroucke, C. Libert, Treatment of TNF mediated diseases by selective inhibition of soluble TNF or TNFR1, Cytokine Growth Factor Rev. 22 (2011) 311–319.
[56] S. Rose-John, IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6, Int. J. Biol. Sci. 8 (2012) 1237–1247.
[57] S. Riethmueller, P. Somasundaram, J.C. Ehlers, C.W. Hung, C.M. Flynn, J. Lokau, M. Agthe, S. Dusterhoft, Y. Zhu, J. Grotzinger, I. Lorenzen, T. Koudelka, K. Yamamoto, U. Pickhinke, R. Wichert, C. Becker-Pauly, M. Radisch, A. Albrecht, M. Hessefort, D. Stahnke, C. Unverzagt, S. Rose-John, A. Tholey, C. Garbers, Proteolytic origin of the soluble human IL-6R in vivo and a decisive role of N-glycosylation, PLoS Biol. 15 (2017) e2000080.
[58] S. Rose-John, P.C. Heinrich, Soluble receptors for cytokines and growth factors: generation and biological function, Biochem. J. 300 (Pt 2) (1994) 281–290.
[59] J. Scheller, S. Rose-John, The interleukin 6 pathway and atherosclerosis, Lancet 380 (2012) 338.
[60] F. Schaper, S. Rose-John, Interleukin-6: biology, signaling and strategies of blockade, Cytokine Growth Factor Rev. 26 (2015) 475–487.
[61] G.S. Braun, Y. Nagayama, Y. Maruta, F. Heymann, C.R. van Roeyen, B.M. Klinkhammer, P. Boor, L. Villa, D.J. Salant, U. Raffetseder, S. Rose-John, T. Ostendorf, J. Floege, IL-6 trans-signaling drives murine crescentic GN, J. Am. Soc. Nephrol. 27 (2016) 132–142.
[62] M. Luig, M.A. Kluger, B. Goerke, M. Meyer, A. Nosko, I. Yan, J. Scheller, H.W. Mittrucker, S. Rose-John, R.A. Stahl, U. Panzer, O.M. Steinmetz, Inflammation-induced IL-6 functions as a natural brake on macrophages and limits GN, J. Am. Soc. Nephrol. 26 (2015) 1597–1607.
[63] M.A. Nowell, P.J. Richards, S. Horiuchi, N. Yamamoto, S. Rose-John, N. Topley, A.S. Williams, S.A. Jones, Soluble IL-6 receptor governs IL-6 activity in experimental arthritis: blockade of arthritis severity by soluble glycoprotein 130, J. Immunol. 171 (2003) 3202–3209.
[64] S.M. Ruwanpura, L. McLeod, L.F. Dousha, H.J. Seow, S. Alhayyani, M.D. Tate, V. Deswaerte, G.D. Brooks, S. Bozinovski, M. MacDonald, C. Garbers, P.T. King, P.G. Bardin, R. Vlahos, S. Rose-John, G.P. Anderson, B.J. Jenkins, Therapeutic targeting of the IL-6 trans-signaling/mechanistic target of rapamycin complex 1 axis in pulmonary emphysema, Am. J. Respir. Crit. Care Med. 194 (2016) 1494–1505.
[65] A. Waage, P. Brandtzaeg, A. Halstensen, P. Kierulf, T. Espevik, The complex pattern of cytokines in serum from patients with meningococcal septic shock. Association between interleukin 6, interleukin 1, and fatal outcome, J. Exp. Med. 169 (1989) 333–338.
[66] C. Garbers, N. Monhasery, S. Aparicio-Siegmund, J. Lokau, P. Baran, M.A. Nowell, S.A. Jones, S. Rose-John, J. Scheller, The interleukin-6 receptor Asp358Ala single nucleotide polymorphism rs2228145 confers increased proteolytic conversion rates by ADAM proteases, Biochim. Biophys. Acta 1842 (2014) 1485–1494.
[67] I.R.G.C.E.R.F. Collaboration, N. Sarwar, A.S. Butterworth, D.F. Freitag, J. Gregson, P. Willeit, D.N. Gorman, P. Gao, D. Saleheen, A. Rendon, C.P. Nelson, P.S. Braund, A.S. Hall, D.I. Chasman, A. Tybjaerg-Hansen, J.C. Chambers, E.J. Benjamin, P.W. Franks, R. Clarke, A.A. Wilde, M.D. Trip, M. Steri, J.C. Witteman, L. Qi, C.E. van der Schoot, U. de Faire, J. Erdmann, H.M. Stringham, W. Koenig, D.J. Rader, D. Melzer, D. Reich, B.M. Psaty, M.E. Kleber, D.B. Panagiotakos, J. Willeit, P. Wennberg, M. Woodward, S. Adamovic, E.B. Rimm, T.W. Meade, R.F. Gillum, J.A. Shaffer, A. Hofman, A. Onat, J. Sundstrom, S. Wassertheil-Smoller, D. Mellstrom, J. Gallacher, M. Cushman, R.P. Tracy, J. Kauhanen, M. Karlsson, J.T. Salonen, L. Wilhelmsen, P. Amouyel, B. Cantin, L.G. Best, Y. Ben-Shlomo, J.E. Manson, G. Davey-Smith, P.I. de Bakker, C.J. O'Donnell, J.F. Wilson, A.G. Wilson, T.L. Assimes, J.O. Jansson, C. Ohlsson, A. Tivesten, O. Ljunggren, M.P. Reilly, A. Hamsten, E. Ingelsson, F. Cambien, J. Hung, G.N. Thomas, M. Boehnke, H. Schunkert, F.W. Asselbergs, J.J. Kastelein, V. Gudnason, V. Salomaa, T.B. Harris, J.S. Kooner, K.H. Allin, B.G. Nordestgaard, J.C. Hopewell, A.H. Goodall, P.M. Ridker, H. Holm, H. Watkins, W.H. Ouwehand, N.J. Samani, S. Kaptoge, E. Di Angelantonio, O. Harari, J. Danesh, Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies, Lancet 379 (2012) 1205–1213.
[68] C. Interleukin-6 Receptor Mendelian Randomisation Analysis, D.I. Swerdlow, M.V. Holmes, K.B. Kuchenbaecker, J.E. Engmann, T. Shah, R. Sofat, Y. Guo, C. Chung, A. Peasey, R. Pfister, S.P. Mooijaart, H.A. Ireland, M. Leusink, C. Langenberg, K.W. Li, J. Palmen, P. Howard, J.A. Cooper, F. Drenos, J. Hardy, M.A. Nalls, Y.R. Li, G. Lowe, M. Stewart, S.J. Bielinski, J. Peto, N.J. Timpson, J. Gallacher, M. Dunlop, R. Houlston, I. Tomlinson, I. Tzoulaki, J. Luan, J.M. Boer, N.G. Forouhi, N.C. Onland-Moret, Y.T. van der Schouw, R.B. Schnabel, J.A. Hubacek, R. Kubinova, M. Baceviciene, A. Tamosiunas, A. Pajak, R. Topor-Madry, S. Malyutina, D. Baldassarre, B. Sennblad, E. Tremoli, U. de Faire, L. Ferrucci, S. Bandenelli, T. Tanaka, J.F. Meschia, A. Singleton, G. Navis, I. Mateo Leach, S.J. Bakker, R.T. Gansevoort, I. Ford, S.E. Epstein, M.S. Burnett, J.M. Devaney, J.W. Jukema, R.G. Westendorp, G. Jan de Borst, Y. van der Graaf, P.A. de Jong, A.H. Mailand-van der Zee, O.H. Klungel, A. de Boer, P.A. Doevendans, J.W. Stephens, C.B. Eaton, J.G. Robinson, J.E. Manson, F.G. Fowkes, T.M. Frayling, J.F. Price, P.H. Whincup, R.W. Morris, D.A. Lawlor, G.D. Smith, Y. Ben-Shlomo, S. Redline, L.A. Lange, M. Kumari, N.J. Wareham, W.M. Verschuren, E.J. Benjamin, J.C. Whittaker, A. Hamsten, F. Dudbridge, J.A. Delaney, A. Wong, D. Kuh, R. Hardy, B.A. Castillo, J.J. Connolly, P. van der Harst, E.J. Brunner, M.G. Marmot, C.L. Wassel, S.E. Humphries, P.J. Talmud, M. Kivimaki, F.W. Asselbergs, M. Voevoda, M. Bobak, H. Pikhart, J.G. Wilson, H. Hakonarson, A.P. Reiner, B.J. Keating, N. Sattar, A.D. Hingorani, J.P. Casas, The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomisation analysis, Lancet 379 (2012) 1214–1224.
[69] R.C. Ferreira, D.F. Freitag, A.J. Cutler, J.M. Howson, D.B. Rainbow, D.J. Smyth, S. Kaptoge, P. Clarke, C. Boreham, R.M. Coulson, M.L. Pekalski, W.M. Chen, S. Onengut-Gumuscu, S.S. Rich, A.S. Butterworth, A. Malarstig, J. Danesh, J.A. Todd, Functional IL6R 358Ala allele impairs classical IL-6 receptor signaling and influences risk of diverse inflammatory diseases, PLoS Genet. 9 (2013) e1003444.
[70] L.H. Calabrese, S. Rose-John, IL-6 biology: implications for clinical targeting in rheumatic disease, Nat. Rev. Rheumatol. 10 (2014) 720–727.
[71] V. Caolo, G. Swennen, A. Chalaris, A. Wagenaar, S. Verbruggen, S. Rose-John, D.G. Molin, M. Vooijs, M.J. Post, ADAM10 and ADAM17 have opposite roles during sprouting angiogenesis, Angiogenesis 18 (2015) 13–22.
[72] M. Bender, S. Hofmann, D. Stegner, A. Chalaris, M. Bösl, A. Braun, J. Scheller, S. Rose-John, B. Nieswandt, Differentially regulated GPVI ectodomain shedding by multiple platelet-expressed proteinases, Blood 116 (2010) 3347–3355.
[73] S. Hofmann, T. Vogtle, M. Bender, S. Rose-John, B. Nieswandt, The SLAM family member CD84 is regulated by ADAM10 and calpain in platelets, J. Thromb. Haemost. 10 (2012) 2581–2592.
[74] G. Bai, S.L. Pfaff, Protease regulation: the Yin and Yang of neural development and disease, Neuron 72 (2011) 9–21.
[75] P. Yang, K.A. Baker, T. Hagg, The ADAMs family: coordinators of nervous system development, plasticity and repair, Prog. Neurobiol. 79 (2006) 73–94.
[76] P. Saftig, P. Bovolenta, Proteases at work: cues for understanding neural development and degeneration, Front. Mol. Neurosci. 8 (2015) 13.
[77] D.E. Bredesen, R.V. Rao, P. Mehlen, Cell death in the nervous system, Nature 443 (2006) 796–802.
[78] K.J. Friston, C.D. Frith, Schizophrenia: a disconnection syndrome? Clin. Neurosci. 3 (1995) 89–97.
[79] C.P. Blobel, ADAMs: key components in EGFR signaling and development, Nat. Rev. Mol. Cell Biol. 6 (2005) 32–43.
[80] S. Weber, P. Saftig, Ectodomain shedding and ADAMs in development, Development 139 (2012) 3693–3709.
[81] K. Reiss, P. Saftig, The "a disintegrin and metalloprotease" (ADAM) family of sheddases: physiological and cellular functions, Semin. Cell Dev. Biol. 20 (2009) 126–137.
[82] D. Fambrough, D. Pan, G.M. Rubin, C.S. Goodman, The cell surface metalloprotease/disintegrin Kuzbanian is required for axonal extension in *Drosophila*, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 13233–13238.
[83] E. Jorissen, J. Prox, C. Bernreuther, S. Weber, R. Schwanbeck, L. Serneels, A. Snellinx, K. Craessaerts, A. Thathiah, I. Tesseur, U. Bartsch, G. Weskamp, C.P. Blobel, M. Glatzel, B. De Strooper, P. Saftig, The disintegrin/metalloproteinase ADAM10 is essential for the establishment of the brain cortex, J. Neurosci. 30 (2010) 4833–4844.
[84] J. Prox, C. Bernreuther, H. Altmeppen, J. Grendel, M. Glatzel, R. D'Hooge, S. Stroobants, T. Ahmed, D. Balschun, M. Willem, S. Lammich, D. Isbrandt, M. Schweizer, K. Horre, B. De Strooper, P. Saftig, Postnatal disruption of the disintegrin/metalloproteinase ADAM10 in brain causes epileptic seizures, learning deficits, altered spine morphology, and defective synaptic functions, J. Neurosci. 33 (2013) 12915–12928 (12928a).
[85] P.H. Kuhn, A.V. Colombo, B. Schusser, D. Dreymueller, S. Wetzel, U. Schepers, J. Herber, A. Ludwig, E. Kremmer, D. Montag, U. Muller, M. Schweizer, P. Saftig, S. Brase, S.F. Lichtenthaler, Systematic substrate identification indicates a central role for the metalloprotease ADAM10 in axon targeting and synapse function, elife 5 (2016).
[86] I. Karkkainen, E. Rybnikova, M. Pelto-Huikko, A.P. Huovila, Metalloprotease-disintegrin (ADAM) genes are widely and differentially expressed in the adult CNS, Mol. Cell. Neurosci. 15 (2000) 547–560.
[87] T. Maretzky, M. Schulte, A. Ludwig, S. Rose-John, C. Blobel, D. Hartmann, P. Altevogt, P. Saftig, K. Reiss, 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 (2005) 9040–9053.
[88] I. Kalus, U. Bormann, M. Mzoughi, M. Schachner, R. Kleene, Proteolytic cleavage of the neural cell adhesion molecule by ADAM17/TACE is involved in neurite outgrowth, J. Neurochem. 98 (2006) 78–88.
[89] T.M. Allinson, E.T. Parkin, A.J. Turner, N.M. Hooper, ADAMs family members as amyloid precursor protein alpha-secretases, J. Neurosci. Res. 74 (2003) 342–352.
[90] R. van der Kant, L.S. Goldstein, Cellular functions of the amyloid precursor protein from development to dementia, Dev. Cell 32 (2015) 502–515.
[91] T.L. Young-Pearse, J. Bai, R. Chang, J.B. Zheng, J.J. LoTurco, D.J. Selkoe, A critical function for beta-amyloid precursor protein in neuronal migration revealed

by in utero RNA interference, J. Neurosci. 27 (2007) 14459–14469.
[92] J. Loffler, G. Huber, Beta-amyloid precursor protein isoforms in various rat brain regions and during brain development, J. Neurochem. 59 (1992) 1316–1324.
[93] M.P. Demars, A. Bartholomew, Z. Strakova, O. Lazarov, Soluble amyloid precursor protein: a novel proliferation factor of adult progenitor cells of ectodermal and mesodermal origin, Stem Cell Res Ther 2 (2011) 36.
[94] R. Vassar, B.D. Bennett, S. Babu-Khan, S. Kahn, E.A. Mendiaz, P. Denis, D.B. Teplow, S. Ross, P. Amarante, R. Loeloff, Y. Luo, S. Fisher, J. Fuller, S. Edenson, J. Lile, M.A. Jarosinski, A.L. Biere, E. Curran, T. Burgess, J.C. Louis, F. Collins, J. Treanor, G. Rogers, M. Citron, Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE, Science 286 (1999) 735–741.
[95] C. Becker-Pauly, C.U. Pietrzik, The metalloprotease Meprin beta is an alternative beta-secretase of APP, Front. Mol. Neurosci. 9 (2016) 159.
[96] R.J. O'Brien, P.C. Wong, Amyloid precursor protein processing and Alzheimer's disease, Annu. Rev. Neurosci. 34 (2011) 185–204.
[97] M. Sastre, J. Walter, S.M. Gentleman, Interactions between APP secretases and inflammatory mediators, J. Neuroinflammation 5 (2008) 25.
[98] D.M. Skovronsky, S. Fath, V.M. Lee, M.E. Milla, Neuronal localization of the TNFalpha converting enzyme (TACE) in brain tissue and its correlation to amyloid plaques, J. Neurobiol. 49 (2001) 40–46.
[99] M. Canault, E. Tellier, B. Bonardo, E. Mas, M. Aumailley, I. Juhan-Vague, G. Nalbone, F. Peiretti, FHL2 interacts with both ADAM-17 and the cytoskeleton and regulates ADAM-17 localization and activity, J. Cell. Physiol. 208 (2006) 363–372.
[100] H. Tanahashi, K. Yoshioka, RNA interference silencing of DRAL affects processing of amyloid precursor protein, Neurosci. Lett. 439 (2008) 293–297.
[101] P. Saftig, K. Reiss, The “a disintegrin and metalloproteases” ADAM10 and ADAM17: novel drug targets with therapeutic potential? Eur. J. Cell Biol. 90 (2011) 527–535.
[102] R. Postina, Activation of alpha-secretase cleavage, J. Neurochem. 120 (Suppl. 1) (2012) 46–54.
[103] R.W. Cho, J.M. Park, S.B. Wolff, D. Xu, C. Hopf, J.A. Kim, R.C. Reddy, R.S. Petralia, M.S. Perin, D.J. Linden, P.F. Worley, mGluR1/5-dependent long-term depression requires the regulated ectodomain cleavage of neuronal pentraxin NPR by TACE, Neuron 57 (2008) 858–871.
[104] Y. Tanabe, T. Kasahara, T. Momoi, E. Fujita, Neuronal RA175/SynCAM1 isoforms are processed by tumor necrosis factor-alpha-converting enzyme (TACE)/ADAM17-like proteases, Neurosci. Lett. 444 (2008) 16–21.
[105] S. Siddiqui, M. Fang, B. Ni, D. Lu, B. Martin, S. Maudsley, Central role of the EGF receptor in neurometabolic aging, Int. J. Endocrinol. 2012 (2012) 739428.
[106] M. Yamada, T. Ikeuchi, H. Hatanaka, The neurotrophic action and signaling of epidermal growth factor, Prog. Neurobiol. 51 (1997) 19–37.
[107] J.H. Fallon, K.B. Seroogy, S.E. Loughlin, R.S. Morrison, R.A. Bradshaw, D.J. Knaver, D.D. Cunningham, Epidermal growth factor immunoreactive material in the central nervous system: location and development, Science 224 (1984) 1107–1109.
[108] M.H. Werner, L.B. Nanney, C.M. Stoscheck, L.E. King, Localization of immunoreactive epidermal growth factor receptors in human nervous system, J. Histochem. Cytochem. 36 (1988) 81–86.
[109] H. Namba, Y. Zheng, Y. Abe, H. Nawa, Epidermal growth factor administered in the periphery influences excitatory synaptic inputs onto midbrain dopaminergic neurons in postnatal mice, Neuroscience 158 (2009) 1731–1741.
[110] A. Oyagi, S. Moriguchi, A. Nitta, K. Murata, Y. Oida, K. Tsuruma, M. Shimazawa, K. Fukunaga, H. Hara, Heparin-binding EGF-like growth factor is required for synaptic plasticity and memory formation, Brain Res. 1419 (2011) 97–104.
[111] A. Aguirre, M.E. Rubio, V. Gallo, Notch and EGFR pathway interaction regulates neural stem cell number and self-renewal, Nature 467 (2010) 323–327.
[112] A. Oyagi, H. Hara, Essential roles of heparin-binding epidermal growth factor-like growth factor in the brain, CNS Neurosci. Ther. 18 (2012) 803–810.
[113] T. Nakagawa, M. Sasahara, Y. Hayase, M. Haneda, H. Yasuda, R. Kikkawa, S. Higashiyama, F. Hazama, Neuronal and glial expression of heparin-binding EGF-like growth factor in central nervous system of prenatal and early-postnatal rat, Brain Res. Dev. Brain Res. 108 (1998) 263–272.
[114] H.I. Kornblum, S.D. Zurcher, Z. Werb, R. Derynck, K.B. Seroogy, Multiple trophic actions of heparin-binding epidermal growth factor (HB-EGF) in the central nervous system, Eur. J. Neurosci. 11 (1999) 3236–3246.
[115] L.M. Farkas, K. Krieglstein, Heparin-binding epidermal growth factor-like growth factor (HB-EGF) regulates survival of midbrain dopaminergic neurons, J. Neural Transm. 109 (2002) 267–277.
[116] J. Palazuelos, H.C. Crawford, M. Klingener, B. Sun, J. Karelis, E.W. Raines, A. Aguirre, TACE/ADAM17 is essential for oligodendrocyte development and CNS myelination, J. Neurosci. 34 (2014) 11884–11896.
[117] C. Capone, F. Dabertrand, C. Baron-Menguy, A. Chalaris, L. Ghezali, V. Domenga-Denier, S. Schmidt, C. Huneau, S. Rose-John, M.T. Nelson, A. Joutel, Mechanistic insights into a TIMP3-sensitive pathway constitutively engaged in the regulation of cerebral hemodynamics, elife 5 (2016).
[118] O. Arias-Carrion, M. Stamelou, E. Murillo-Rodriguez, M. Menendez-Gonzalez, E. Poppel, Dopaminergic reward system: a short integrative review, Int. Arch. Med. 3 (2010) 24.
[119] A. Bjorklund, S.B. Dunnett, Dopamine neuron systems in the brain: an update, Trends Neurosci. 30 (2007) 194–202.
[120] R.M. Villalba, H. Lee, Y. Smith, Dopaminergic denervation and spine loss in the striatum of MPTP-treated monkeys, Exp. Neurol. 215 (2009) 220–227.
[121] A. Barbeau, High-level levodopa therapy in Parkinson's disease: five years later, Trans. Am. Neurol. Assoc. 99 (1974) 160–163.
[122] A.G. Phillips, G. Vacca, S. Ahn, A top-down perspective on dopamine, motivation and memory, Pharmacol. Biochem. Behav. 90 (2008) 236–249.
[123] H. Braak, K. Del Tredici, U. Rub, R.A. de Vos, E.N. Jansen Steur, E. Braak, Staging of brain pathology related to sporadic Parkinson's disease, Neurobiol. Aging 24 (2003) 197–211.
[124] A.A. Grace, Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression, Nat. Rev. Neurosci. 17 (2016) 524–532.
[125] S. Yoon, J.H. Baik, Dopamine D2 receptor-mediated epidermal growth factor receptor transactivation through a disintegrin and metalloprotease regulates dopaminergic neuron development via extracellular signal-related kinase activation, J. Biol. Chem. 288 (2013) 28435–28446.
[126] S.Y. Kim, H.J. Lee, Y.N. Kim, S. Yoon, J.E. Lee, W. Sun, E.J. Choi, J.H. Baik, Striatal-enriched protein tyrosine phosphatase regulates dopaminergic neuronal development via extracellular signal-regulated kinase signaling, Exp. Neurol. 214 (2008) 69–77.
[127] S. Yoon, M.H. Choi, M.S. Chang, J.H. Baik, Wnt5a-dopamine D2 receptor interactions regulate dopamine neuron development via extracellular signal-regulated kinase (ERK) activation, J. Biol. Chem. 286 (2011) 15641–15651.
[128] S.Y. Kim, K.C. Choi, M.S. Chang, M.H. Kim, S.Y. Kim, Y.S. Na, J.E. Lee, B.K. Jin, B.H. Lee, J.H. Baik, The dopamine D2 receptor regulates the development of dopaminergic neurons via extracellular signal-regulated kinase and Nurr1 activation, J. Neurosci. 26 (2006) 4567–4576.
[129] J.H. Baik, R. Picetti, A. Saiardi, G. Thiriet, A. Dierich, A. Depaulis, M. Le Meur, E. Borrelli, Parkinsonian-like locomotor impairment in mice lacking dopamine D2 receptors, Nature 377 (1995) 424–428.
[130] H.R. Sim, T.Y. Choi, H.J. Lee, E.Y. Kang, S. Yoon, P.L. Han, S.Y. Choi, J.H. Baik, Role of dopamine D2 receptors in plasticity of stress-induced addictive behaviours, Nat. Commun. 4 (2013) 1579.
[131] Y. Iwakura, H. Nawa, ErbB1-4-dependent EGF/neuregulin signals and their cross talk in the central nervous system: pathological implications in schizophrenia and Parkinson's disease, Front. Cell. Neurosci. 7 (2013) 4.
[132] Y. Iwakura, Y.S. Piao, M. Mizuno, N. Takei, A. Kakita, H. Takahashi, H. Nawa, Influences of dopaminergic lesion on epidermal growth factor-ErbB signals in Parkinson's disease and its model: neurotrophic implication in nigrostriatal neurons, J. Neurochem. 93 (2005) 974–983.
[133] G. Pezzoli, A. Zecchinelli, S. Ricciardi, R.E. Burke, S. Fahn, G. Scarlato, A. Carenzi, Intraventricular infusion of epidermal growth factor restores dopaminergic pathway in hemiparkinsonian rats, Mov. Disord. 6 (1991) 281–287.
[134] L.L. Ventrella, Effect of intracerebroventricular infusion of epidermal growth factor in rats hemitransected in the nigro-striatal pathway, J. Neurosurg. Sci. 37 (1993) 1–8.
[135] M. Hanke, L.M. Farkas, M. Jakob, R. Ries, J. Pohl, A.M. Sullivan, Heparin-binding epidermal growth factor-like growth factor: a component in chromaffin granules which promotes the survival of nigrostriatal dopaminergic neurones in vitro and in vivo, Neuroscience 124 (2004) 757–766.
[136] S. Chandrasekaran, D. Bonchev, A network view on Parkinson's disease, Comput. Struct. Biotechnol. J. 7 (2013) e201304004.
[137] Y.F. Cui, G. Hargus, J.C. Xu, J.S. Schmid, Y.Q. Shen, M. Glatzel, M. Schachner, C. Bernreuther, Embryonic stem cell-derived L1 overexpressing neural aggregates enhance recovery in Parkinsonian mice, Brain 133 (2010) 189–204.
[138] M.M. Pabon, A.D. Bachstetter, C.E. Hudson, C. Gemma, P.C. Bickford, CX3CL1 reduces neurotoxicity and microglial activation in a rat model of Parkinson's disease, J. Neuroinflammation 8 (2011) 9.
[139] P. Seibler, J. Graziotto, H. Jeong, F. Simunovic, C. Klein, D. Krainc, Mitochondrial Parkin recruitment is impaired in neurons derived from mutant PINK1 induced pluripotent stem cells, J. Neurosci. 31 (2011) 5970–5976.
[140] S. Kriks, J.W. Shim, J. Piao, Y.M. Ganat, D.R. Wakeman, Z. Xie, L. Carrillo-Reid, G. Auyeung, C. Antonacci, A. Buch, L. Yang, M.F. Beal, D.J. Surmeier, J.H. Kordower, V. Tabar, L. Studer, Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease, Nature 480 (2011) 547–551.
[141] K. Yamamoto, A. Trad, A. Baumgart, L. Huske, I. Lorenzen, A. Chalaris, J. Grotzinger, T. Dechow, J. Scheller, S. Rose-John, A novel bispecific single-chain antibody for ADAM17 and CD3 induces T-cell-mediated lysis of prostate cancer cells, Biochem. J. 445 (2012) 135–144.
[142] P. Marz, J.G. Cheng, R.A. Gadient, P.H. Patterson, T. Stoyan, U. Otten, S. Rose-John, Sympathetic neurons can produce and respond to interleukin 6, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 3251–3256.
[143] P. Marz, U. Otten, S. Rose-John, Neural activities of IL-6-type cytokines often depend on soluble cytokine receptors, Eur. J. Neurosci. 11 (1999) 2995–3004.
[144] I.L. Campbell, M. Erta, S.L. Lim, R. Frausto, U. May, S. Rose-John, J. Scheller, J. Hidalgo, Trans-signaling is a dominant mechanism for the pathogenic actions of interleukin-6 in the brain, J. Neurosci. 34 (2014) 2503–2513.
[145] I.L. Campbell, C.R. Abraham, E. Masliah, P. Kemper, J.D. Inglis, M.B. Oldstone, L. Mucke, Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 10061–10065.
[146] M. Rothaug, C. Becker-Pauly, S. Rose-John, The role of interleukin-6 signaling in nervous tissue, Biochim. Biophys. Acta 1863 (2016) 1218–1227.
[147] G.D. Brooks, L. McLeod, S. Alhayyani, A. Miller, P.A. Russell, W. Ferlin, S. Rose-John, S. Ruwanpura, B.J. Jenkins, IL6 trans-signaling promotes KRAS-driven lung carcinogenesis, Cancer Res. 76 (2016) 866–876.
[148] C.W. Lo, M.W. Chen, M. Hsiao, S. Wang, C.A. Chen, S.M. Hsiao, J.S. Chang, T.C. Lai, S. Rose-John, M.L. Kuo, L.H. Wei, IL-6 trans-signaling in formation and progression of malignant ascites in ovarian cancer, Cancer Res. 71 (2011) 424–434.
[149] L.H. Wei, C.H. Chou, M.W. Chen, S. Rose-John, M.L. Kuo, S.U. Chen, Y.S. Yang,

The role of IL-6 trans-signaling in vascular leakage: implications for ovarian hyperstimulation syndrome in a murine model, J. Clin. Endocrinol. Metab. 98 (2013) E472–E484.
[150] M. Lesina, M.U. Kurkowski, K. Ludes, S. Rose-John, M. Treiber, G. Kloppel, A. Yoshimura, W. Reindl, B. Sipos, S. Akira, R.M. Schmid, H. Algul, Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer, Cancer Cell 19 (2011) 456–469.
[151] S.M. Wormann, L. Song, J. Ai, K.N. Diakopoulos, M.U. Kurkowski, K. Gorgulu, D. Ruess, A. Campbell, C. Doglioni, D. Jodrell, A. Neesse, I.E. Demir, A.P. Karpathaki, M. Barenboim, T. Hagemann, S. Rose-John, O. Sansom, R.M. Schmid, M.P. Protti, M. Lesina, H. Algul, Loss of P53 function activates JAK2-STAT3 signaling to promote pancreatic tumor growth, stroma modification, and gemcitabine resistance in mice and is associated with patient survival, Gastroenterology 151 (2016) 180–193 (e112).
[152] F.A. Goumas, R. Holmer, J.H. Egberts, A. Gontarewicz, C. Heneweer, U. Geisen, C. Hauser, M.M. Mende, K. Legler, C. Rocken, T. Becker, G.H. Waetzig, S. Rose-John, H. Kalthoff, Inhibition of IL-6 signaling significantly reduces primary tumor growth and recurrencies in orthotopic xenograft models of pancreatic cancer, Int. J. Cancer 137 (2015) 1035–1046.
[153] W.E. Naugler, T. Sakurai, S. Kim, S. Maeda, K. Kim, A.M. Elsharkawy, M. Karin, Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production, Science 317 (2007) 121–124.
[154] G. He, D. Dhar, H. Nakagawa, J. Font-Burgada, H. Ogata, Y. Jiang, S. Shalapour, E. Seki, S.E. Yost, K. Jepsen, K.A. Frazer, O. Harismendy, M. Hatziapostolou, D. Iliopoulos, A. Suetsugu, R.M. Hoffman, R. Tateishi, K. Koike, M. Karin, Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling, Cell 155 (2013) 384–396.
[155] B. Rabe, A. Chalaris, U. May, G.H. Waetzig, D. Seegert, A.S. Williams, S.A. Jones, S. Rose-John, J. Scheller, Transgenic blockade of interleukin 6 transsignaling abrogates inflammation, Blood 111 (2008) 1021–1028.
[156] J. Bergmann, M. Muller, N. Baumann, M. Reichert, C. Heneweer, J. Bolik, K. Lucke, S. Gruber, A. Carambia, S. Boretius, I. Leuschner, T. Becker, B. Rabe, J. Herkel, F.T. Wunderlich, H.W. Mittrucker, S. Rose-John, D. Schmidt-Arras, IL-6 trans-signaling is essential for the development of hepatocellular carcinoma in mice, Hepatology 65 (2017) 89–103.
[157] K. Brew, H. Nagase, The tissue inhibitors of metalloproteinases (TIMPs): an ancient family with structural and functional diversity, Biochim. Biophys. Acta 1803 (2010) 55–71.
[158] H.W. Jackson, V. Defamie, P. Waterhouse, R. Khokha, TIMPs: versatile extracellular regulators in cancer, Nat. Rev. Cancer 17 (2017) 38–53.
[159] V. Defamie, O. Sanchez, A. Murthy, R. Khokha, TIMP3 controls cell fate to confer hepatocellular carcinoma resistance, Oncogene 34 (2015) 4098–4108.
[160] Y. Yang, F.Y. Jalal, J.F. Thompson, E.J. Walker, E. Candelario-Jalil, L. Li, R.R. Reichard, C. Ben, Q.X. Sang, L.A. Cunningham, G.A. Rosenberg, Tissue inhibitor of metalloproteinases-3 mediates the death of immature oligodendrocytes via TNF-alpha/TACE in focal cerebral ischemia in mice, J. Neuroinflammation 8 (2011) 108.
[161] M.L. Moss, L. Sklair-Tavron, R. Nudelman, Drug insight: tumor necrosis factor-converting enzyme as a pharmaceutical target for rheumatoid arthritis, Nat. Clin. Pract. Rheumatol. 4 (2008) 300–309.
[162] C. Hundhausen, D. Misztela, T.A. Berkhout, N. Broadway, P. Saftig, K. Reiss, D. Hartmann, F. Fahrenholz, R. Postina, V. Matthews, K.J. Kallen, S. Rose-John, A. Ludwig, The disintegrin-like metalloproteinase ADAM10 is involved in constitutive cleavage of CX3CL1 (fractalkine) and regulates CX3CL1-mediated cell-cell adhesion, Blood 102 (2003) 1186–1195.
[163] D. Dreymueller, S. Uhlig, A. Ludwig, ADAM-family metalloproteinases in lung inflammation: potential therapeutic targets, Am. J. Physiol. Lung Cell. Mol. Physiol. 308 (2015) L325–L343.
[164] C.J. Tape, S.H. Willems, S.L. Dombernowsky, P.L. Stanley, M. Fogarasi, W. Ouwehand, J. McCafferty, G. Murphy, Cross-domain inhibition of TACE ectodomain, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 5578–5583.
[165] S. Gur-Cohen, T. Itkin, S. Chakrabarty, C. Graf, O. Kollet, A. Ludin, K. Golan, A. Kalinkovich, G. Ledergor, E. Wong, E. Niemeyer, Z. Porat, A. Erez, I. Sagi, C.T. Esmon, W. Ruf, T. Lapidot, PAR1 signaling regulates the retention and recruitment of EPCR-expressing bone marrow hematopoietic stem cells, Nat. Med. 21 (2015) 1307–1317.
[166] S. Rose-John, ADAM17, shedding, TACE as therapeutic targets, Pharmacol. Res. 71 (2013) 19–22.
[167] K. Horiuchi, T. Kimura, T. Miyamoto, K. Miyamoto, H. Akiyama, H. Takaishi, H. Morioka, T. Nakamura, Y. Okada, C.P. Blobel, Y. Toyama, Conditional inactivation of TACE by a Sox9 promoter leads to osteoporosis and increased granulopoiesis via dysregulation of IL-17 and G-CSF, J. Immunol. 182 (2009) 2093–2101.
[168] C. Long, Y. Wang, A.H. Herrera, K. Horiuchi, B. Walcheck, In vivo role of leukocyte ADAM17 in the inflammatory and host responses during *E. coli*-mediated peritonitis, J. Leukoc. Biol. 87 (2010) 1097–1101.
[169] G. Weskamp, K. Mendelson, S. Swendeman, S. Le Gall, Y. Ma, S. Lyman, A. Hinoki, S. Eguchi, V. Guaiquil, K. Horiuchi, C.P. Blobel, Pathological neovascularization is reduced by inactivation of ADAM17 in endothelial cells but not in pericytes, Circ. Res. 106 (2010) 932–940.
[170] A. Murthy, V. Defamie, D.S. Smookler, M.A. Di Grappa, K. Horiuchi, M. Federici, M. Sibilia, C.P. Blobel, R. Khokha, Ectodomain shedding of EGFR ligands and TNFR1 dictates hepatocyte apoptosis during fulminant hepatitis in mice, J. Clin. Invest. 120 (2010) 2731–2744.
[171] R. La Marca, F. Cerri, K. Horiuchi, A. Bachi, M.L. Feltri, L. Wrabetz, C.P. Blobel, A. Quattrini, J.L. Salzer, C. Taveggia, TACE (ADAM17) inhibits Schwann cell myelination, Nat. Neurosci. 14 (2011) 857–865.
[172] A. Murthy, Y.W. Shao, S.R. Narala, S.D. Molyneux, J.C. Zuniga-Pflucker, R. Khokha, Notch activation by the metalloproteinase ADAM17 regulates myeloproliferation and atopic barrier immunity by suppressing epithelial cytokine synthesis, Immunity 36 (2012) 105–119.
[173] F. Yan, L. Liu, P.J. Dempsey, Y.H. Tsai, E.W. Raines, C.L. Wilson, H. Cao, Z. Cao, L. Liu, D.B. Polk, A *Lactobacillus rhamnosus* GG-derived soluble protein, p40, stimulates ligand release from intestinal epithelial cells to transactivate epidermal growth factor receptor, J. Biol. Chem. 288 (2013) 30742–30751.
[174] C.M. Ardito, B.M. Gruner, K.K. Takeuchi, C. Lubeseder-Martellato, N. Teichmann, P.K. Mazur, K.E. Delgiorno, E.S. Carpenter, C.J. Halbrook, J.C. Hall, D. Pal, T. Briel, A. Herner, M. Trajkovic-Arsic, B. Sipos, G.Y. Liou, P. Storz, N.R. Murray, D.W. Threadgill, M. Sibilia, M.K. Washington, C.L. Wilson, R.M. Schmid, E.W. Raines, H.C. Crawford, J.T. Siveke, EGF receptor is required for KRAS-induced pancreatic tumorigenesis, Cancer Cell 22 (2012) 304–317.
[175] D. Fan, A. Takawale, M. Shen, V. Samokhvalov, R. Basu, V. Patel, X. Wang, C. Fernandez-Patron, J.M. Seubert, G.Y. Oudit, Z. Kassiri, A disintegrin and metalloprotease-17 regulates pressure overload-induced myocardial hypertrophy and dysfunction through proteolytic processing of integrin beta1, Hypertension 68 (2016) 937–948.
[176] M. Yoda, T. Kimura, T. Tohmonda, H. Morioka, M. Matsumoto, Y. Okada, Y. Toyama, K. Horiuchi, Systemic overexpression of TNFalpha-converting enzyme does not lead to enhanced shedding activity in vivo, PLoS One 8 (2013) e54412.
[177] J.R. Mazzulli, F. Zunke, O. Isacson, L. Studer, D. Krainc, alpha-Synuclein-induced lysosomal dysfunction occurs through disruptions in protein trafficking in human midbrain synucleinopathy models, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 1931–1936.