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Review

The role of ADAM17 in metabolic inflammation

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ABSTRACT

The TNF-alpha Converting Enzyme (TACE), also called ADAM17 (A Disintegrin and A Metalloproteinase 17) is a type I transmembrane metalloproteinase involved in the shedding of the extracellular domain of several transmembrane proteins such as cytokines, growth factors, receptors and adhesion molecules. Some of these proteolytic events are part of cleavage cascades known as Regulated Intramembrane Proteolysis and lead to intracellular signaling. Evidence is provided that ADAM17 plays a role in atherosclerosis, in adipose tissue metabolism, insulin resistance and diabetes. The multitude of substrates cleaved by ADAM17 makes this enzyme an attractive candidate to study its role in inflammatory disorders. This review is focused on effects of ADAM17 in major metabolic tissues.

Contents

1. Introduction

The TNF-alpha Converting Enzyme (TACE), also called ADAM17 (A Disintegrin and A Metalloproteinase 17) is a type I transmembrane protein that belongs to a superfamily of Zn dependent metalloproteases. ADAM17 plays a key role in the regulation of the proteolytic release from cellular membranes of some cytokines, chemokines, growth factors and their receptors, including TNF-α, TNF receptors I and II, TGF-α, L-selectin, IL-6, and M-CSF receptor 1, affecting downstream signaling and cellular responses (Table 1) [1]. Increased ADAM17-mediated shedding has been described in a variety of diseases such as ischemia, heart failure, arthritis, atherosclerosis, diabetes, cancer, neurological and immune diseases [2]. The major pro-inflammatory cytokine processed by ADAM17 is TNF-α which is produced by a number of cell types including macrophages, monocytes, T-cells, and plays a crucial role in the pathogenesis of inflammation [3]. Recently, it has been pointed out that exclusively the extracellular domains of ADAM17 are needed for interaction with its substrates [4].

Tissue Inhibitor of MetalloProteinase 3 (TIMP3), a key endogenous inhibitor involved in regulation of the activity of Matrix Metalloproteinases (MMPs) and ADAMs, is the only known physiological inhibitor of ADAM17 (Fig. 1). ADAM17 and TIMP3 have parallel baseline expression patterns in murine organs during development [5]. Down-regulation of TIMP3 increases ADAM17

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Table 1
ADAM17 substrates. Table shows ADAM17 substrates verified by *in vivo* or *in vitro* mechanistic evidence. For other ADAM17-shed molecules with less stringent evidence, see also Ref. [1].

Cytokines	Growth factors	Receptors	Adhesion molecules	Others
TNF-α	Amphiregulin	CD30	CD44	Meprin-β
CX3CL-1	Epiregulin	CD40	L-selectin	APP
MICA	Neuregulins	c-KIT	VCAM-1	Collagen XVII
TRANCE	Betacellulin	ErbB4	ICAM-1	Notch
	TGF-α	GHR	ALCAM	Jagged
	HB-EGF	IL-1R II	JAM-A	KL-1
	Pref-1	IL-6Rα		Mucin-1
		IL-15Rα		PrP
		M-CSFR		MICA
		P75NTR		Klotho
		TNFR I		
		TNFR II		
		trkA (NGFR)		
		Notch		

activity while up-regulation of TIMP3 inhibits ADAM17 activity. Recent evidence indicates that cell surface presentation of ADAM17 is crucial for the regulation of its shedding activity [6]. ERK or p38 MAPK signaling changes the dynamic balance between ADAM17 dimers and monomers and their conformations, presumably as a result of changes in phosphorylation of its cytoplasmic domain, which is required for ADAM17 dimerization [6]. In the absence of MAPK stimulation, ADAM17 is presented as dimers at the cell surface, allowing TIMP3 to efficiently interact with and inhibit ADAM17, whereas the activation of ERK or p38 MAPK signaling, which leads to ADAM17 activation, results in increased monomer presentation and release of TIMP3 from ADAM17 [6]. Recently, iRhom2, a molecule belonging to a class of polytopic endoplasmic reticulum proteins, has been identified as an essential factor for the activity and trafficking of ADAM17, through its interaction with both endogenous full length and the mature form of ADAM17 [7,8].

Previous reports have implicated the ADAM17/TIMP3 dyad as a mediator between metabolic stimuli and innate immunity. TIMP3 deficient mice have shown increased levels of TNF-α and severity of inflammation [9]. Interestingly, a genetic transmission of TIMP3 deficiency is able to impair glucose tolerance [10]; TIMP3 was found downregulated in adipose tissue of genetic models of obesity [11] and in circulating monocyte cells from human subjects with risk for diabetes and atherosclerosis [12]. Here we review the most recent findings on ADAM17 activation as a consequence of loss of TIMP3 in the context of Metabolic Syndrome (Fig. 2).

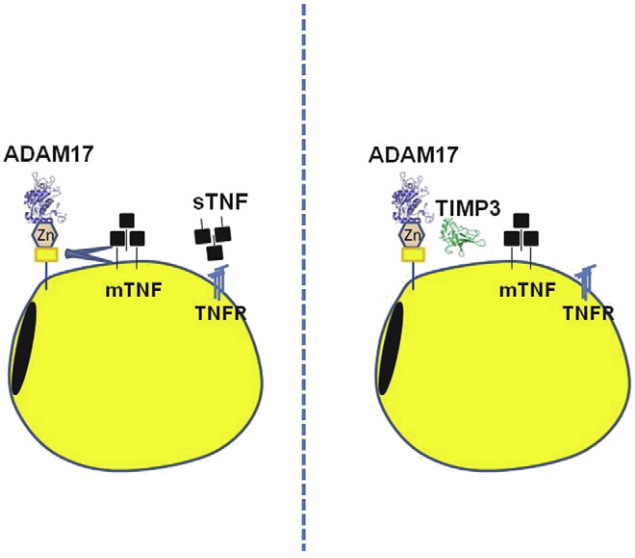

Fig. 1. ADAM17 shedding activity is regulated by TIMP3. ADAM17 sheds transmembrane TNF-α generating a soluble form that can bind to TNF receptors. Timp3 blocks ADAM17 interaction with transmembrane TNF-α restraining the inflammatory effect of the cytokine.

2. ADAM17 role in adipose tissue inflammation

The adipose tissue is a regulatory organ that, through a deregulated release of free fatty acids, adhesion molecules and inflammatory cytokines plays a key role in the obesity-associated complications such as dyslipidemia, insulin resistance and type 2 diabetes as well as the low-grade inflammation and increased risk of cardiovascular disease [13].

TNF-α was the first cytokine recognized as a link between obesity, inflammation and diabetes. TNF-α appears to be a crucial contributor to adipokine dysregulation in adipocytes and an increased expression of TNF-α is found in the adipose tissue of obese and insulin-resistant rodent models [14]. In human adipose tissue TNF-α expression correlated with BMI, percentage of body fat, and hyperinsulinemia, whereas weight loss decreased TNF-α levels [15].

The expansion of adipose tissue in obesity is associated with an increased infiltration of macrophages usually recruited to sites of tissue damage [16] and the role of immune cells, in particular monocytes and macrophages, has been found to be crucial in the inflammatory process that characterizes metabolic disorders [17]. Infiltrated macrophages have been reported to be in a pro-inflammatory state which is characterized by an increased expression of TNF-α [18]. ADAM17 activity might drive macrophage homing, via increased generation of soluble TNF-alpha, determining a mechanism for integration of metabolic and stress signals from different cell types [10]. The release of adhesion molecules caused by ADAM17 may enable macrophages to continue migration and infiltration into the inflamed adipose tissue amplifying local inflammation [19]. Moreover, the overexpression of TIMP3 in mouse macrophages *in vivo* protects from both metabolic disorders and atherosclerosis, resulting in reduced activation of oxidative stress signals related to lipid peroxidation, protein carbonylation and nitration in adipose tissue, liver and atheromas, suggesting that TIMP3 could restrain, via TACE inhibition, the inflammatory phenotype of a macrophage in a cell-autonomous manner [20,21].

In vitro, expression of ADAM17 inhibits adipocyte differentiation increasing the shedding of Pref-1 [22]. Adult homozygous ADAM17 deficient mice have a lean, profoundly hypermetabolic phenotype independent from physical activity, body temperature, or thyroid function. Developmental defects observed in ADAM17 deficient mice have been linked to impaired EGFR and/or TNF-α receptor signaling and raise the possibility that the energy homeostasis phenotype is linked to one or both of these signaling pathways [23]. ADAM17 haploinsufficiency (*Adam17*$^{+/-}$) mouse model is protected against diet induced obesity, insulin resistance and diabetes, suggesting an involvement of ADAM17 in metabolic control during high fat diet conditions (HFD) [24]. *Adam17*$^{+/-}$ mice on HFD are characterized by reduced fat pad weight and increased small adipocyte number, as well as by a decreased shedding of both TNF-α and Pref-1, suggesting that an interference with the release of ADAM17 substrates may exert a protective role during HFD, in part as a consequence of a positive effect on adipose tissue plasticity and in part via the modulation of different downstream metabolic and inflammatory signals. Temporal systemic deletion of ADAM17 protects against an HFD-induced body weight gain, insulin resistance, hepatosteatosis, and adipose tissue remodeling in association with increased energy expenditure [25]. Furthermore, *Insr*$^{+/-}$*Timp3*$^{-/-}$ mice under an HFD regimen, show an accelerated

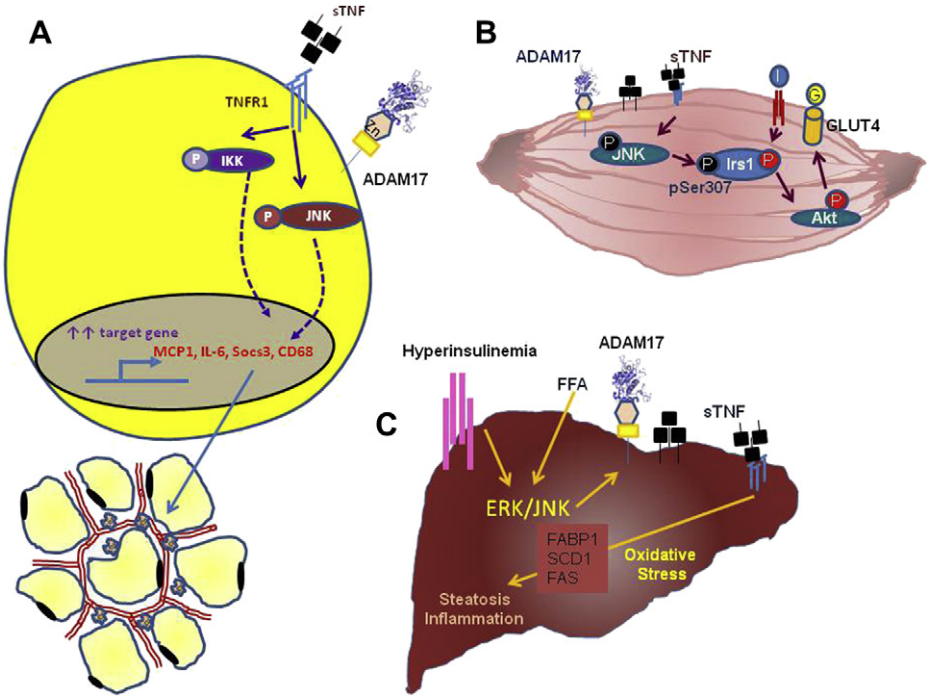

Fig. 2. ADAM17 activation by hyperinsulinemia and free fatty acids exacerbate inflammatory and stress signals in white adipose tissue, muscle and liver prompting the onset of low-grade inflammation, insulin resistance and steatosis. (A). In white adipocytes ADAM17 activation leads to the expression of inflammatory molecules such as Suppressor of Cytokine Signaling 3 (SOCS3), Interleukin 6 (IL6) and Monocyte Chemotactic Protein 1 (MCP-1). As a consequence of this low-grade inflammatory status macrophagic cells are recruited to the adipose tissue and contribute to enhance insulin resistance. (B). In skeletal muscle ADAM17-mediated release of TNF-α causes insulin resistance via JNK inhibition of glucose transport consequent to reduced ability of insulin to activate the Irs1/PI3K/Akt pathway. (C). In hepatocytes ADAM17 activity is triggered by hyperinsulinemia and Free Fatty Acids such as Palmitic Acid. In turn, TNF-α and possibly other ADAM17 substrates increase oxidative stress, FFA uptake and promote hepatic steatosis via up-regulation of key regulatory targets such as Fatty Acid Binding Protein 1 (FABP1), Stearoyl-CoA Desaturase, 1 (SCD1) and Fatty Acid Synthase (FAS).

development of obesity complications; in fact, the TIMP3 deficiency, in combination with predisposing genetic and dietary background promotes inflammation in adipose tissue, leading to macrophage accumulation and activation of inflammatory signaling pathways [26].

3. TACE/ADAM17 in skeletal muscle insulin resistance

TNF-α has been shown to impair glucose uptake from skeletal muscle both *in vivo* and *in vitro* [27–29]. A negative effect of TNF-α on insulin signaling and glucose uptake has been demonstrated both at insulin receptor and post-receptor level including direct and indirect inhibition of insulin receptor tyrosine kinase [30], serine phosphorylation of Insulin Receptor Substrate 1 [31], inhibition of AKT substrates [32], suppression of AMPK activity [33], and activation of inhibitor of kappa B kinase β (IKK β) in a p38 MAPK-dependent manner [34]. By contrast, inhibition of TNF-α via genetic approaches improves insulin sensitivity in different models [29–35]. A skeletal muscle acute reduction of TIMP3 is able to precipitate a diabetic phenotype only when interacting with a second defect in insulin action [36,37]. Interestingly, a genome wide scan in mouse models of diabetes confirmed that a promoter variant reducing TIMP3 expression associates with diabetes [38]. Moreover, TIMP3 is downregulated during aging in association with other factors causing inflammation while caloric restriction increases TIMP3 expression [39]. Interestingly, in smooth muscle cells TIMP3 expression is regulated via promoter activation by Sirtuin-1 (SirT1), a deacetylase that is known to mimic caloric restriction [37] and transcription factor FoxO1 might negatively affect TIMP3 expression. Thus, TIMP3 is emerging as a factor favoring insulin sensitivity downstream of Sirt1 and FoxO1. In humans affected by metabolic disorders such as obesity and type 2 diabetes the concurrence of lipotoxicity and glucotoxicity was found to increase ADAM17 activity via decreased TIMP3 expression and increased ADAM17 activity correlates with insulin resistance [36].

4. TACE/ADAM17 in hepatic insulin resistance and steatosis

Recent findings showed that the ADAM17/TIMP3 dyad plays a central role in the development and progression of non-alcoholic fatty liver disease (NAFLD) [26,40]. The contribution of insulin resistance to the development of fatty liver occurs in part by deficient control of lipid storage in white adipose tissue and in part by altered control of hepatic lipogenesis and mitochondrial fatty acid oxidation [41]. TNF-α is among the cytokines involved in linking nutrient availability to inflammation and development of fatty liver disease [42], so the regulation of its release from plasma membrane by the ADAM17/TIMP3 system represents a key step in the pathogenesis of fatty liver disease. Recently, it has been shown that TIMP3 deficiency accelerates liver inflammation and steatosis when coupled to genetic-dependent ($Insr^{+/-}/Timp3^{-/-}$) and nutrient-dependent insulin resistance (HFD) [26]. In liver in particular, this synergy leads to a complex phenotype closely resembling severe NAFLD, including increased hepatic lipid content, lobular and periportal inflammation, hepatocellular ballooning and perisinusoidal fibrosis. Gene expression analysis revealed that some of the genes significantly modulated in HFD fed $Insr^{+/-}/Timp3^{-/-}$ mice are generally linked to control of fatty acid metabolism (PPARγ, CD36, SCD-1), glucose metabolism (Akt2, PGC1α, Nur77, Nurr1, NOR1, Fbp1), and inflammation (SOCS-3, CD68, CX3CR1, CXCL16, TNFα, i-NOS), further linking ADAM17/TIMP3 unbalanced interaction to main features of the metabolic syndrome [26].

In fatty liver disease associated with obesity, TIMP3 plays its role possibly through the regulation of ADAM17 [40]. It is also still unclear how metabolic toxicity initiates the inflammatory burden. The contribution of hepatic ADAM17 activation to the development of fatty liver disease has been recently analyzed coupling murine and cellular models to proteomics technologies [40]. In hepatocyte cell lines ADAM17 activity results significantly increased by stimuli linked to metabolic dysfunction. *In vivo*, prolonged uncontrolled ADAM17 activation contributes to liver degeneration following lipid overload, as demonstrated by *Timp3* deficient mice fed an HFD for 20 weeks, characterized by macrovesicular steatosis and lobular degeneration compared to wild type littermates. This phenotype can be explained at least in part by modulation of proteins playing a role in fatty acid uptake, triglyceride synthesis and methionine metabolism, a pathway known to affect steatosis in mouse models [43]. In contrast, mice double heterozygous for the insulin receptor and ADAM17 has a nearly opposite phenotype. Moreover, pharmacologic ADAM17 activity inhibition in different murine models of obesity and hepatic steatosis resulted in reversal of steatosis, coupled with improvement of surrogate markers of insulin sensitivity [44].

5. Future directions and therapeutical perspectives

Recent works pinpoint the role of the ADAM17-TIMP3 dyad in spatial regulation of TNF-α activity in major metabolic tissues. Many data suggest that ADAM17 is activated in metabolic disorders and contributes to progressive deterioration of metabolic homeostasis via regulation of pathways involved in adipose tissue infiltration by macrophages, reduction of glucose uptake in skeletal muscle and increased lipogenesis in liver. Altogether these actions promote the progression of insulin resistance from a subclinical defect towards a complex syndrome, favoring the onset of severe disorders such as type 2 diabetes, non-alcoholic steatohepatitis and atherosclerosis.

ADAM17 activation emerged therefore as a potential contributor for the development of metabolic inflammation, even though some pieces are still lacking for the comprehension of its role in the complex puzzle of insulin resistance and atherosclerosis.

Data from knockout models combined with *in vitro* studies have suggested a role for ADAM17 in the regulation of adipogenesis and lipogenesis in the liver, but the physiological role of the enzyme in this context is still unclear. ADAM17 overactivation in the context of the adipocyte membrane could lead to inhibition of adipogenesis through unrestrained pref-1 release but on the other hand absence of TIMP3 could promote adipogenesis through increased VEGFR2 signaling [45,46]. Transgenic mice overexpressing TIMP3 or with temporal systemic Tace deletion (TaceMx1) do not show a dominant effect on adipogenesis during a diet induced obesity protocol but the positive effect seemed associated to restrained angiogenesis or reduced inflammation [20,25]. The recent availability of several ADAM17 floxed mouse has moved forward our knowledge on ADAM17 role in angiogenesis, innate immunity and acute hepatitis [47–51]. We are currently investigating adipocyte-specific and hepatic-specific ADAM17 knockout to dissect the physiological role of this enzyme in adipogenesis and lipogenesis.

Data from human specimens and mouse models suggested a role for ADAM17 and its cognate protease ADAM10 in vascular remodeling and the progression of atherosclerosis [12,37,51–57]. Nevertheless, the exact roles of ADAM17 and TIMP3 must be still investigated through appropriate models to define their role in vascular pathology. In particular, understanding whether the inflammatory burden associated with decreased TIMP3 is dependent on ADAM17, other metalloproteases or non metalloprotease might have therapeutical implications given the preeminent role played by TIMP3 in restraining the homing of monocytes to adipose tissue and atherosclerotic plaques [20,21,56]. Furthermore, another important point is to discriminate whether the defect of TIMP3 is exclusive of patients with impaired glucose metabolism or diabetes, as this can lead to understand more on the differences between diabetic macrovascular disease and atherosclerosis in non diabetic patients [58].

Overall data from our and other laboratories suggest that inhibition of ADAM17 might be positive at least in some phases of the atherosclerotic process. However, despite several efforts made by bio-tech companies, ADAM17-specific inhibitors are still missing and a TIMP3-based approach seems more promising [59] Sirtuin-1 has been shown to regulate TIMP3 promoter particularly in monocytes [12] and unsaturated fatty acids contained in LDL particles have been shown to prime activation of ADAM17 in the endothelial layer providing a link between endothelial dysfunction and the observation of increased ADAM17 substrates in patients at risk for macrovascular events [60–63].

Therefore, it is possible to speculate about the potential therapeutic advantage of the inhibition of ADAM17 in atherosclerosis and in metabolic inflammation. Among the different anti-TNF antibodies, no one is specifically directed against ADAM17, although infliximab is known to interfere not only with soluble but also with transmembrane TNF [64]. Whether infliximab interferes with ADAM17 is unclear. More recently, a specific anti-ADAM17 antibody was shown to be effective against EGFR activation in a preclinical model of cancer, suggesting that the use of anti-ADAM17 antibodies might be proposed in humans at least in certain circumstances [65]. Alternatively, drugs used to improve Sirtuins such as Resveratrol or the proposed indirect SirT1 activators [66]might decrease ADAM17 indirectly through increased TIMP3 expression, which could also lead to other potentially beneficial TIMP3 effects such as inhibition of MMP2 and MMP9 [67]or VEGR2 [45]. More recently TIMP3 was used *in vivo* as a recombinant protein or overexpressed through adenovirus resulting in reduced inflammation in the microvascular environment at blood brain barrier level, in the kidney and in the gut suggesting that the delivery of a recombinant TIMP3 might be another approach to be tested at preclinical level in appropriate models for atherosclerosis and metabolic inflammation [68–70].

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