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Perspective

ADAM17, shedding, TACE as therapeutic targets

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ABSTRACT

ADAM17 has been molecularly cloned as the enzyme responsible for cleavage of the transmembrane protein TNFα (TNFα converting enzyme, TACE). Later it was realized that ADAM17 was also responsible for the processing of cell adhesion proteins, cytokine and growth factor receptors and many ligands of the EGF receptor. Since TNFα is a target of anti-inflammatory therapies, it was speculated that inhibition of ADAM17 might be a therapeutic strategy in the treatment of inflammation or inflammation associated cancer. Meanwhile it has been recognized that ADAM17 governs many vital functions in the body and loss of ADAM17 leads to severe defects in the skin and to high susceptibility of the intestine to inflammation. Here I summarize data on the physiologic role of ADAM17 and the feasibility of specific blockade of this enzyme.

1. Introduction

Many but by far not all membrane proteins are proteolytically released from cells with very different physiologic consequences [1]. Ligands of the epidermal growth factor receptor (EGF) are synthesized as type I transmembrane proteins and need to be cleaved and shed as soluble proteins in order to become systemically available. Many cytokines of the tumor necrosis factor alpha (TNFα) family, which are type II transmembrane proteins, are cleaved and thereby released from the producing cells and consequently can act systemically. Cytokine receptors such as the TNF receptor II (TNF-R_{II}) or the EGF receptor (EGF-R) are cleaved from the cell membrane, which thereby reduces the sensitivity of cells to the cognate ligands. Finally, the receptor for the cytokine interleukin-6 (IL-6R) is cleaved from cells and in a process called trans-signaling, the soluble IL-6R (sIL-6R) renders distinct cells, which only express the signal transducing receptor subunit gp130 responsive to the cytokine [2]. Cells, which express gp130 but no IL-6R are unresponsive to IL-6 if no sIL-6R is present [2,3] (Fig. 1).

In 1997, two groups reported the molecular cloning of the enzyme, which was responsible for the release of TNFα. Consequently, the enzyme was called TNFα converting enzyme or TACE. Mice lacking TACE were not viable and showed striking similarities with mice lacking ligands of the EGF-R, such as transforming growth factor alpha (TGFα) indicating that TACE was not only responsible for cleaving TNFα [4]. Analysis of the protein sequence of TACE revealed that it belonged to a family of proteases featuring a so-called disintegrin domain, the family of A Disintegrin and Metalloprotease (ADAM) proteins [5]. TACE was therefore renamed ADAM17 [5,6]. ADAM17 is a type I multi-domain transmembrane protein featuring a pro-domain, catalytic domain, disintegrin domain, membrane proximal domain, transmembrane domain and cytoplasmatic domain (Fig. 1).

Subsequently, it was shown that this protease was the major sheddase not only for TNFα but also for many ligands of the EGF-R [4,7], for the adhesion protein L-selectin [4] and for the IL-6R [2]. ADAM17 was also implicated in cleavage of the receptor protein notch [8], although genetic studies later identified the related ADAM protease ADAM10 to be the major notch-cleaving enzyme [9].

2. ADAM17 expression and activation

ADAM17 mRNA is expressed in virtually all cells of the body although it became clear that active ADAM17 on the cell surface is mainly found during inflammation and cancer [1,10]. Many mechanism have been reported to lead to cellular activation of ADAM17, ranging from stimulation of cells with phorbol esters [11], bacterial toxins [12], apoptotic stimuli [13] to activation of MAP and ERK kinases [14]. Multimerisation of ADAM17 might play a role in activation [14,15]. It is also unclear how the specificity of ADAM17 is achieved. So far, 76 different substrates for ADAM17 have been reported [1] and it has been shown that not only the catalytic

Abbreviations: ADAM, a disintegrin and metalloprotease; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; gp130, glycoprotein 130 kDa; IL, interleukin; MAP kinase, mitogen-activated protein kinase; PMA, 4-b-phorbol 12-myristate 13-acetate; R, receptor; RIP, regulated intramembrane proteolysis; s, soluble; TNFα, tumor necrosis factor alpha.

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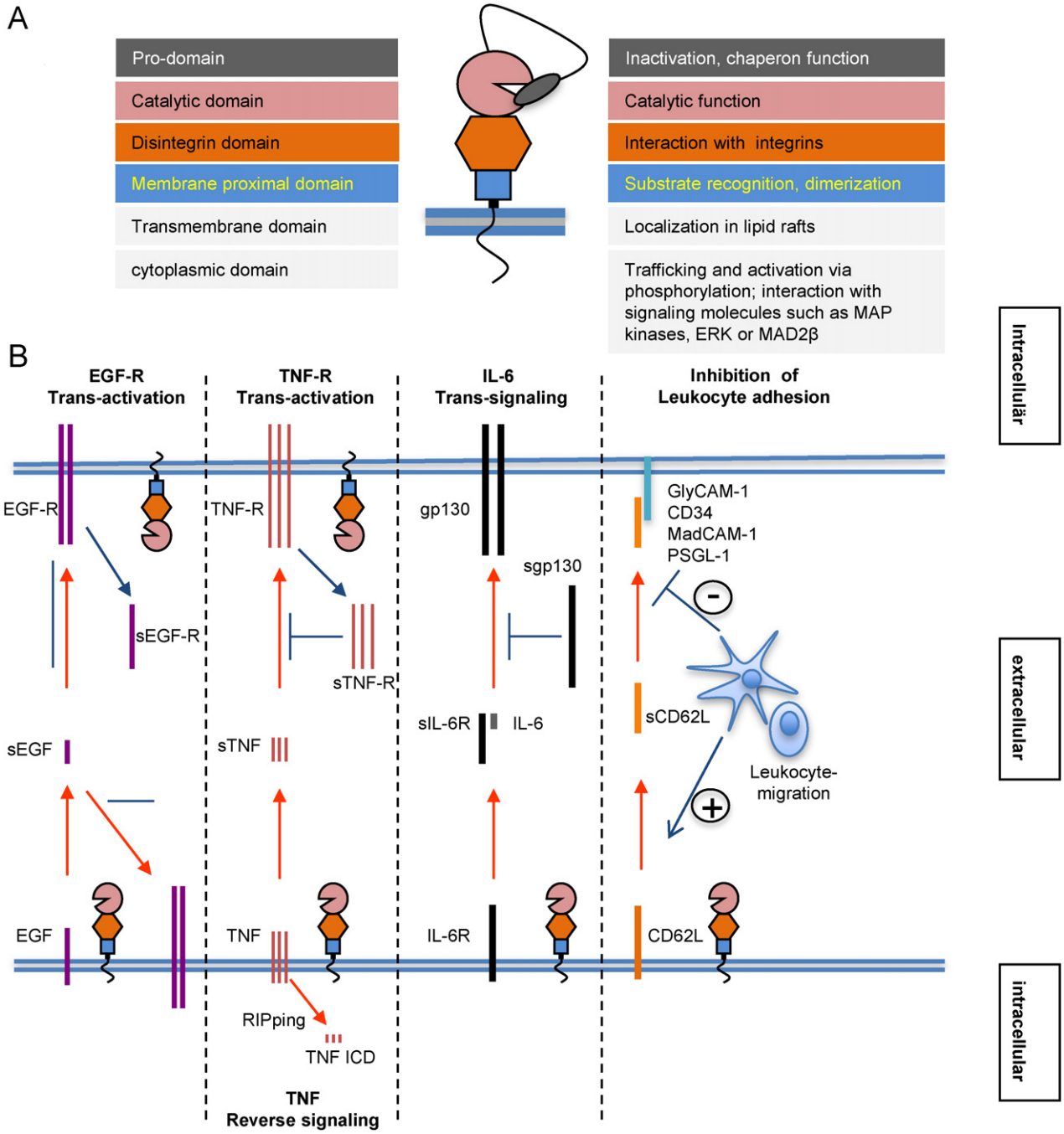

Fig. 1. Structure and function of ADAM17. (A) Domain structure of the metalloprotease ADAM17. (B) ADAM17 cleaves transmembrane proteins such as EGF receptor (EGF-R) ligands, TNFα, IL-6R and L-selectin and thereby induces EGF-R transactivation via shedding of EGF-R ligands, TNF-R transactivation via soluble TNFα, TNFα inhibition via generation of an antagonistic soluble TNF-R and IL-6 transsignaling via agonistic soluble IL-6R. Cleavage of L-selectin (CD62L) generates a soluble ectodomain having an anti-inflammatory effect by inhibiting adhesion of leukocytes to the endothelium.

domain but also the membrane proximal domain of ADAM17 is needed for interaction with the substrate [16]. Recently it was suggested that thiol isomerases play an important role in the activation of ADAM17 [17].

Since virtually all cells in the body express ADAM17 but the enzyme is barely detectable on the surface of most cells [10,18,19], trafficking of ADAM17 seems to be regulated. Indeed, it has been shown that ERK-mediated phosphorylation of ADAM17 leads to translocation of the protein to the cell surface [20]. Recently, it was discovered that the inactive member of the rhomboid family of proteases iRhom2 was needed for the trafficking of ADAM17 to the cell surface [21,22].

3. Physiologic functions of ADAM17

Since ADAM17$^{-/-}$ mice were not viable, conditional knock-out mice were generated and ADAM17 was shown to be important for TNFα release [23], for bone formation [24] and for protection of hepatocytes from apoptosis [25]. Hypomorphic ADAM17$^{ex/ex}$ mice, which only express 5% of wt levels of ADAM17 in all tissues showed drastically enhanced susceptibility to inflammatory bowel disease models [26]. These data were confirmed in ADAM17 mutated mice [27]. Furthermore, it could be shown in ADAM17$^{ex/ex}$ mice that in the absence of ADAM17 no milk ducts in the breast of female mice were generated [26]. Since milk duct formation is dependent on the