ADAM17: a potential therapeutic target for rheumatoid arthritis?

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KEYWORDS: cytokine blockage ■ EGF-receptor ■ gp130 ■ IL-6 trans-signaling ■ sIL-6R ■ soluble cytokine receptor ■ TNF-α

In recent years we have seen a breakthrough in the use of biologics for the treatment of chronic inflammatory diseases. For over 10 years, patients with rheumatoid arthritis have been treated with inhibitors of the cytokine TNF-α, such as monoclonal antibodies or a soluble TNF-α receptor protein [1]. More recently, blockade of the IL-6 pathway using a monoclonal antibody against the human IL-6 receptor (IL-6R) has been approved in Japan, Europe and the USA [2]. Many more IL-6-targeting antibodies are in clinical trials or in preclinical development, underlining the growing interest in blockade of the cytokine IL-6 [3]. Although the therapeutic success of the TNF-α and IL-6 pathway blockades is impressive, it should be kept in mind that not all patients respond to therapy with a given biologic and that cytokine blockade may lead to an impairment of the immune system [1–3]. Therefore, novel approaches and therapeutic strategies are urgently warranted.

It has been recognized that the signaling pathways of TNF-α and IL-6 are both regulated by the membrane-bound metalloproteinase ADAM17. TNF-α is a type II transmembrane protein, which only becomes systemically available after cleavage by ADAM17 [4,5]. Conditional gene targeting of *ADAM17* in murine myeloid cells resulted in a loss of shedding of TNF-α from the cell surface and, moreover, resistance to lipopolysaccharide-mediated septic shock [6]. This indicated that the proinflammatory activity of TNF-α requires cleavage by ADAM17. This interpretation was strongly supported by the finding that mice expressing an uncleavable version of TNF-α are protected against intracellular bacterial infections, chronic inflammation and autoimmunity [7]. It appears, therefore, that the membrane version of TNF-α acts via an anti-inflammatory method, whereas the soluble version of this cytokine, which is generated by ADAM17 cleavage, has proinflammatory activities.

In the case of IL-6, it has been shown that only cells that express the membrane-bound IL-6R on the cell surface are responsive to the cytokine [8]. Interestingly, only a few cells in the body express the IL-6R. We have shown that on cells that do express the IL-6R, the enzyme ADAM17 can cleave the IL-6R generating a soluble receptor (sIL-6R), which can still bind its ligand IL-6 [9]. Remarkably, on cells that are not responsive to IL-6 (because they do not express the IL-6R) the complex of IL-6 and sIL-6R can bind to the ubiquitously expressed gp130 protein, induce its dimerization and induce signaling. This process has been called trans-signaling [8]. Cells that do not respond to IL-6 alone include endothelial cells, smooth muscle cells and many neural cells. It has become clear that the proinflammatory activities of IL-6 are mediated by IL-6 trans-signaling, whereas regenerative responses and the induction of the hepatic acute phase response are induced via the membrane-bound IL-6R [10].

Therefore, the activation of ADAM17 to generate soluble TNF-α and sIL-6R results in an increased inflammatory activity. In this regard, it is interesting that apoptosis of neutrophils, which are the first cells to be attracted to a site of injury, results in the activation of ADAM17 and concomitant shedding of the IL-6R [11]. The sIL-6R leads to IL-6 trans-signaling of endothelial cells, inducing the secretion of the CC-chemokine MCP-1 and resulting in the recruitment of mononuclear cells [12]. In this case, the dying neutrophils serve as a gauge to measure the extent of damage, which is reflected in the amount of sIL-6R generated [13].

Is ADAM17 a therapeutic target for the treatment of inflammatory states? It has indeed been speculated that targeting ADAM17 might be

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beneficial to patients with rheumatoid arthritis [14]. We have recently generated hypomorphic ADAM17 mice, which express only 5% of normal levels of ADAM17 in all tissues [15]. These mice are an excellent model for the consequences of a pharmacological inhibition of ADAM17. It turned out that these mice, among other abnormalities, were highly susceptible to the induction of inflammatory bowel disease. This could be explained by a comprised activation of the EGF receptor (EGF-R), the ligands of which are cleaved by ADAM17 [15]. EGF-R activity in the epithelium of the intestine is necessary for regeneration of these cells upon irritation or wounding [16,17]. Recently, a single patient was identified, who was deficient in ADAM17. This patient had a very similar phenotype to our ADAM17 hypomorphic mice [15] and developed neonatal-onset inflammatory skin and bowel disease [18]. We hypothesized that ADAM17 is not only involved in the regulation of inflammation, but also governs regenerative responses [19]. How the activity of ADAM17 is regulated and how a single enzyme can orchestrate inflammatory and regenerative activities in the body is subject to intensive research.

> "*It has ... been speculated that targeting ADAM17 might be beneficial to patients with rheumatoid arthritis.*"

Chronic inflammatory diseases are not cured by therapy with biologics and, therefore, the patients need life-long treatment. In view of the consequences of ADAM17 deficiency in mice and humans, we argue that it might not be a good idea to treat rheumatoid arthritis patients with an inhibitor of ADAM17. On the other hand, we have shown that in the absence of ADAM17 the EGF-R pathway is completely inhibited [15]. The EGF-R pathway is crucial in the development of several types of cancer [20]. Targeted therapies using monoclonal antibodies or small molecule inhibitors have been shown to be effective only transiently due to the emergence of resistant tumor cells [20]. Therefore, it should be speculated whether inhibition of ADAM17 would be an alternative method to block the activity of the EGF-R in patients with tumors.

As mentioned above, the membrane-bound IL-6R is processed by ADAM17. We could show that the proinflammatory activities of IL-6 could be specifically inhibited by the soluble gp130Fc fusion protein without affecting the function of the membrane bound IL-6R, which mediates the regenerative and anti-inflammatory activities of IL-6 [10]. This protein has been extensively characterized in many preclinical models of inflammatory diseases and cancer, and initiate clinical trials are planned in the near future [3]. This selective IL-6 trans-signaling inhibitor will be a most welcome addition to the existing armamentarium of biologics that are used to curb chronic inflammatory conditions.

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