ADAM17: a potential therapeutic target for rheumatoid arthritis?

“We hypothesized that ADAM17 is not only involved in the regulation of inflammation, but also governs regenerative responses.”

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
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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