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Review

Interleukin-6 subfamily cytokines and rheumatoid arthritis: Role of antagonists

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ABSTRACT

Many cytokines have been implicated in the inflammatory pathways that characterize rheumatoid arthritis (RA) and related inflammatory diseases of the joints. These include members of the interleukin-6 (IL-6) family of cytokines, several of which have been detected in excess in the synovial fluid from RA patients. What makes the IL-6 group of cytokines a family is their common use of the glycoprotein 130 (gp130) receptor subunit, to which they bind with different affinities. Several strategies have been developed to block the pro-inflammatory activities of IL-6 subfamily cytokines. These include the application of monoclonal antibodies, the creation of mutant form(s) of the cytokine with enhanced binding affinity to gp130 receptor and the generation of antagonists by selective mutagenesis of the specific cytokine/gp130 receptor-binding site(s). The rationale for the use of anti-cytokine therapy in inflammatory joint diseases is based on evidence from studies *in vitro* and *in vivo*, which implicate major cytokines such as interleukin-1 (IL-1), tumour necrosis factor (TNF)-α and IL-6 in RA pathogenesis. In particular, IL-6 subfamily antagonists have a wide range of potential therapeutic and research applications. This review focuses on the role of some of the IL-6 subfamily cytokines in the pathogenesis of the inflammatory diseases of the joints (IJDs), such as RA. In addition, an overview of the recently developed antagonists will be discussed.

Contents

Abbreviations: LIF, leukemia inhibitory factor; OSM, oncostatin M; MMP, matrix metalloproteinases; TIMP, tissue inhibitor matrix metalloproteinases; gp130, glycoprotein 130; IL-6, interleukin-6; qRT-PCR, quantitative reverse transcriptase-polymerase chain reaction; TNF-α, tumour necrosis factor-alpha; RA, rheumatoid arthritis; IJD, inflammatory joint disease; OA, osteoarthritis; DMARD, disease-modifying anti-rheumatic drug; CIA, collagen induced arthritis; AOSD, adult-onset Still's disease.

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1. Introduction

The interleukin-6 (IL-6) subfamily is a group of hematopoietic cytokines with a broad range of physiological functions in diverse fields including inflammation, immune responses, and cell survival. Members of this family include IL-6 (26 kDa), leukemia inhibitory factor (LIF, 23 kDa), oncostatin M (OSM, 28 kDa) ciliary neurotrophic factor (CNTF, 24 kDa), IL-11, (23 kDa), cardiotrophin like cytokine (CLC, 22.5 kDa) and cardiotrophin-1 (CT-1, 21.5 kDa) [1]. Other rather more distant members recently included in this family include IL-27 (28 kDa) and IL-31 (24 kDa) [2,3]. All of the members of this family of cytokines signal through the common membrane receptor subunit called glycoprotein 130 (gp130) (Fig. 1). However, binding of cytokine(s) to gp130 receptor takes place at different sites (Table 1). It is possible to use components of these receptors, either alone or in combination for the purpose of research or as therapeutics. A few such antagonists, in particular those targeting the IL-6/gp130 complex, have reached clinical trials [4,5]. The humanized monoclonal IL-6R antibody called Tocilizumab (Actemra or RoActemra) is now approved for treatment of RA in clinical practice in Europe and approved pending further animal, but not clinical studies in the United States.

Over the past 10 to 15 years, biological therapies, such as the TNF blockers, which include anti-TNF monoclonal antibodies such as Infliximab (REMICADE) and Adalimumab (HUMIRA) and TNFR-Fc fusion proteins such as Etanercept (ENBREL), have been very successfully used to treat RA patients who have failed to respond adequately to one or more conventional or non-biologic disease-modifying antirheumatic drugs (DMARDs). However, a proportion of RA patients do not respond adequately to DMARDs and at least 20% do not tolerate or respond well to these agents or eventually fail to continue to respond. For these patients, alternative therapies are required. For most members of the IL-6 cytokine subfamily, effective receptor antagonists have been developed. Some have reached clinical trials, however, their full potential, as disease suppressive agents is still to be determined. An overview of the developments in this field follows.

Recombinant cytokine receptor antagonists can be cheaply and easily made in bacteria, and are very useful for identifying drug targets *in vitro* or in *vitro* and in animal models may be more suitable than neutralizing antibodies. For example recombinant LIF-R antagonists have been used to define the receptor usage of CT-1 when CT-1 was first characterized. LIF-R antagonists have been shown to block all LIF-R-dependent cytokines such as OSM, CNTF, CT-1, and LIF, *in vitro* [6–8]. In addition the LIF-R antagonist has been shown to block the induction of *c-fos* by CT-1 in murine cardiac myotubes, showing that CT-1 responses in the heart are in fact dependent on LIF-R for signal transduction. Other advantages of receptor antagonists include generation of different specificities as compared to antibodies. Although antibodies can easily be produced in large scale and can neutralize cytokines they are not equivalent to the receptor antagonists.

The *in vivo* applications of receptor antagonists pose several challenges such as rapid clearance from the body. Such disadvantages have been dealt with by addition of either PEG or Fc to the molecules in order to increase their serum half lives. Another challenge is the possibility that antagonists may elicit neutralizing immune responses as a result of repeated applications over a long period of time, with the potential for tachyphylaxis and maybe toxicity.

2. Role of IL-6 in RA

IL-6 is considered to play a central role in chronic inflammation and is expressed in excess at sites of inflammation. Like IL-1 and TNF, IL-6 stimulates acute phase protein production [9,10]. It also elicits the development of specific cellular and humoral immune responses such as B-cell differentiation and T cell activation [11]. There is substantial evidence that IL-6 plays an important role in rheumatoid inflammation [12]. For example, IL-6 levels are considerably elevated in the serum of RA patients, and this elevation has been directly correlated with clinical indices of disease activity [13]. In addition, high levels of soluble IL-6 receptor (sIL-6R) have been shown to correlate with the degree of joint destruction, in particular in advanced stages of RA

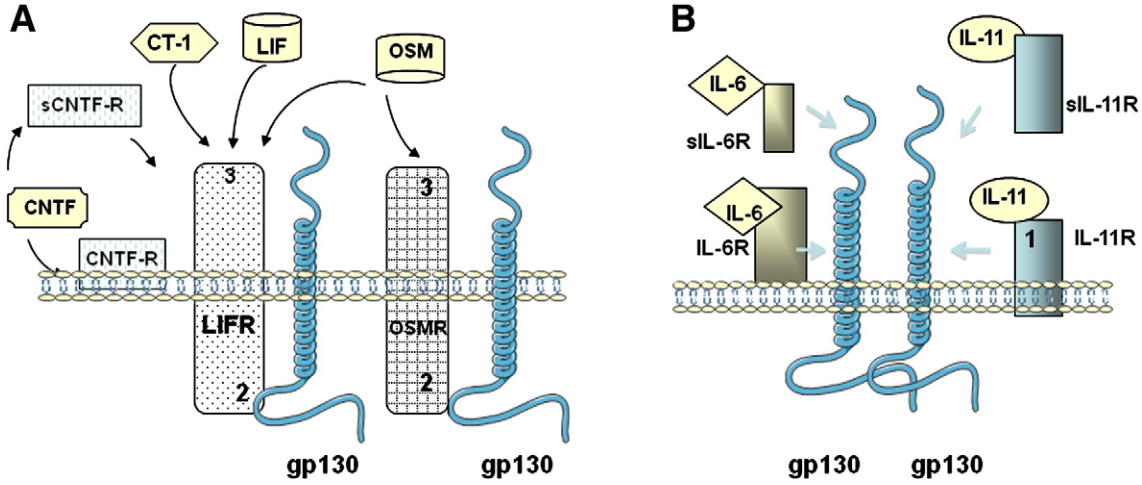

Fig. 1. IL-6 subfamily cytokines sharing gp130 Receptor complex (A) LIF, OSM, CT-1, and CNTF can all bind to LIF-R and induce gp130/LIF-R hetero-dimerisation. OSM and CNTF have additional options of binding to their own receptors; OSM-R and sCNTFR, leading to the formation of gp130/OSM-R and gp130/LIFR respectively. LIF initially binds to the LIF-R alpha chain with low affinity, the LIF: LIF-R complex is then able to bind to gp130 to form a LIF: LIF-R: gp130 signalling complex. OSM, on the other hand, binds to LIF-R and signals through either a gp130: LIF-R or gp130 and OSM receptor (OSM-R) hetero-dimer. (B) IL-6 and IL-11 have both membrane bound and soluble forms of their receptors. Binding of IL-6 or IL-11 to either leads to homodimerisation of gp130. The IL-6 receptor has two subunits (i) an α-subunit (IL-6Rα) that binds IL-6 with low affinity and (ii) a β-subunit (gp130) that binds IL-6/IL-6Rα complex with high affinity and triggers intracellular signalling.