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Survey

Interleukin-6: Biology, signaling and strategies of blockade

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ABSTRACT

Interleukin-6 (IL-6) is one of the most important inflammatory cytokines. IL-6 is unique in signaling *via* a membrane bound and a soluble receptor. Intriguingly, these two pathways strongly differ in their biologic consequences. While classic IL-6 signaling *via* the membrane bound receptor is mainly regenerative and protective, IL-6 trans-signaling *via* the soluble IL-6R is rather pro-inflammatory. Intracellular signaling of IL-6 in response to receptor activation is through STAT-dependent and STAT-independent signaling modules, which are regulated by a complex regulatory network. The complex biology of IL-6 has consequences for therapeutic targeting of this cytokine. We hypothesize that specific inhibition of the trans-signaling pathway may be superior to global blockade of IL-6 activity with help of antibodies directed against IL-6 or IL-6R.

Contents

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1. Introduction

Cytokines are proteins, which are engaged in the communication between cells of the immune system. Furthermore, many cytokines perform regulatory functions outside of the immune system. The majority of cytokines show a four-helical protein fold [1]. Members of other protein families such as interleukin-1 (IL-1), IL-18, tumor necrosis factor α (TNFα) and tumor growth factor α (TGFα) are often also referred to as cytokines although they belong to different protein families, which are not discussed here. Evolutionary, cytokines and cytokine receptors are first found in insects such as drosophila where they are involved in the regulation of stem cell renewal [2].

2. Interleukin-6

Interleukin-6 (IL-6) was molecularly cloned in 1986 as a B-cell stimulatory factor by the group of Kishimoto [3]. At this point it turned out that IL-6 was identical with several other factors being analyzed in several laboratories over the world. These factors included hepatocyte stimulating factor [4] and myeloid blood cell differentiation-inducing protein [5] indicating that IL-6 showed several activities outside of the immune system.

IL-6 is a 184 amino acid glycosylated protein, which can be synthesized and secreted by many cell types including monocytes, T-cells, fibroblasts and endothelial cells. IL-6 binds to a specific receptor (IL-6R), an 80 kDa type I transmembrane protein [6]. IL-6 bound to the IL-6R associates with a second transmembrane protein, gp130, which serves as a signal transducer of IL-6 [7]. Interestingly, gp130 is the common receptor subunit of all members of the IL-6 type cytokine family [8]. Dimerization of gp130 leads to initiation of several intracellular signaling pathways (see below).

While gp130 is expressed on all cells of the body [9], the expression of the IL-6R is far more restricted. IL-6R is mainly found on hepatocytes, neutrophils, monocytes and CD4 + T-cells [4,10]. Since IL-6 shows no binding affinity for gp130 in the absence of IL-6R [7], it follows that only cells, which express IL-6R can respond to the cytokine IL-6.

3. IL-6 classic- and trans-signaling

The IL-6R can be proteolytically cleaved from the cell membrane thereby generating a soluble IL-6R (sIL-6R), which can still bind its ligand IL-6 [11]. In humans, a sIL-6R can also be generated by translation of an alternatively spliced mRNA [12] although this mechanism seems to be less important than proteolytic cleavage [13]. Since the cytoplasmic portion of the IL-6R is not signaling competent, it could be removed without loss of signaling [7]. Likewise, the transmembrane domain of the IL-6R was shown not to be needed for IL-6 activity [7]. Therefore it was hypothesized that the generation of the sIL-6R is a means to stimulate cells, which only expressed gp130 but no IL-6R. Such cells are not responsive to IL-6. The paradigm of IL-6 signaling *via* the sIL-6R was called 'trans-signaling' [14]. Accordingly, IL-6 signaling *via* the membrane bound IL-6R is called 'classic signaling' [15] (Fig. 1).

In order to analyze whether IL-6 trans-signaling occurs *in vivo* two designer proteins were generated and applied in numerous *in vitro* and *in vivo* studies. Hyper-IL-6 is a fusion protein in which the sIL-6R and IL-6 are covalently connected by a flexible protein linker allowing IL-6 to engage the IL-6 binding site on the sIL-6R. This protein stimulated gp130 on cells lacking IL-6R expression and could therefore be used as a mimic of IL-6 trans-signaling [16]. It was shown *in vitro* that hematopoietic stem cell expansion depends on sIL-6R [17] and that neural cells only respond to IL-6 in the presence of sIL-6R [18]. *In vivo*, liver regeneration upon hepatectomy or chemical damage drastically accelerated upon application of the fusion protein Hyper-IL-6 [19,20].

The sgp130Fc fusion protein consists of the extracellular portion of gp130 fused to constant portion (Fc) of a human IgG1

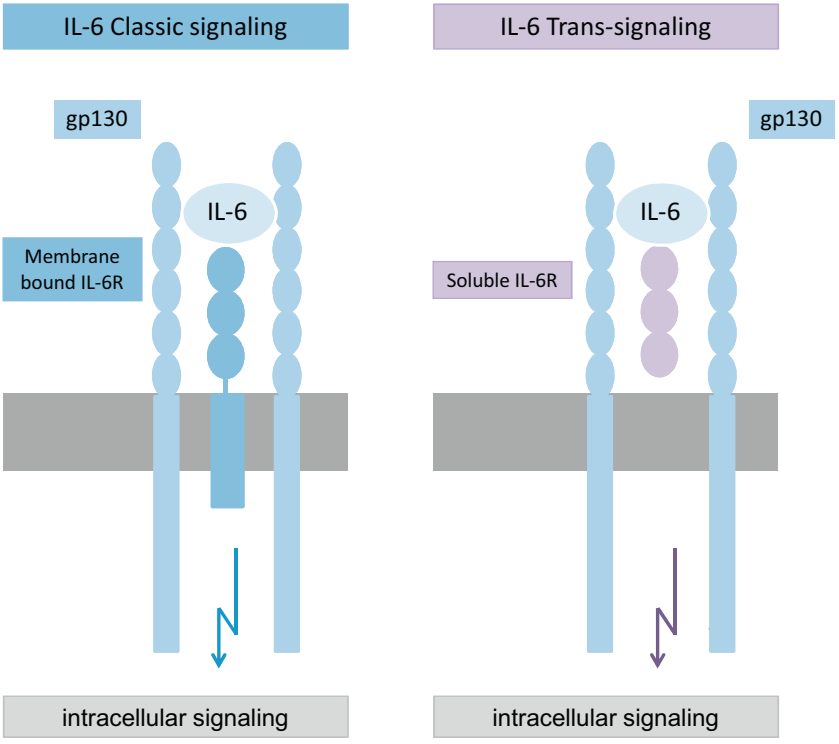

Fig. 1. *IL-6 classic and trans-signaling.* In classic signaling, IL-6 binds to the membrane bound IL-6R and subsequently associates with cellular membrane bound gp130, which initiates intracellular signaling. In IL-6 trans-signaling, IL-6 binds to the sIL-6R and the complex of IL-6 and sIL-6R binds to cellular membrane bound gp130, which thereupon initiates intracellular signaling.

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