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Review

Receptor fusion proteins for the inhibition of cytokines

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ABSTRACT

Cells are exposed to a large variety of cytokines that signal through corresponding cytokine receptors. In healthy tissues or tissues that respond properly to disturbed homeostasis, the cross-talk of a few conserved core signaling pathways downstream of the cytokine receptors is translated into an adequate cellular response. In chronic inflammatory diseases but also in cancer associated inflammation cytokine expression and the downstream signaling networks are dysregulated. Targeted therapies are aimed at the specific interference with dysregulated cytokine signaling. In this article some concepts of pharmacological intervention with cytokine signaling will be reviewed including biologics that target cytokines and cytokine receptors. Receptor fusion proteins consisting of the ligand-binding domains of cytokine receptors are highly specific and potent cytokine inhibitors and will be discussed in more detail.

Introduction

Cytokines are a large and heterogeneous group of glycoproteins consisting of interleukins, interferons, colony-stimulating factors and growth factors (Nathan and Sporn, 1991). As important and versatile mediators of intercellular communication, cytokines often act locally in an autocrine or paracrine fashion. Dysregulated cytokine signaling is of central importance in many diseases such as chronic inflammation and cancer. Cytokine signaling is initiated upon binding of a cytokine to its receptor. An activated cytokine receptor usually triggers several signaling cascades consisting of dynamic interactions and modifications of various signaling proteins. These signaling proteins can be enzymes such as kinases, phosphatases, proteases and ligases which catalyze the modification of target proteins and lipids. Latent transcription factors such as SMADs and STATs are early targets of modification by these enzymes leading to their rapid activation and subsequent induction of target genes. Other signaling proteins are adapter or scaffold proteins such as Shc, Gab1 or Gab2 that organize complex signaling platforms at the cytoplasmic side of the plasma membrane. Under physiological conditions all these signaling events are integrated within the cell leading to an adequate cellular response that include altered gene expression, adaption of metabolism and differentiation or proliferation of cells (Lemmon and Schlessinger, 2010). Dysregulated cytokine signaling leads to inadequate cellular responses which become manifest in the symptoms of the disease.

Targeted therapies

Targeted therapies aim to interfere with dysregulated cytokine signaling by specific inhibition of the involved proteins. In general, this can be achieved at all levels including cytokines, receptors, signaling cascades and the transcriptional machinery. Compounds that target intracellular signaling proteins must pass the plasma membrane. Intracellular localization is difficult to achieve with the most promising drug candidates such as siRNA and dominant-negatively acting proteins. Therefore, drug development concentrates on small, often hydrophobic compounds that

Abbreviations: Akt, a serine-threonine protein kinase; Bcr–Abl, fusion of the breakpoint cluster region (bcr) gene and a cellular Abelson murine leukemia viral oncogene homolog; CAPS, cryopyrin-associated periodic syndromes; CBM, cytokine binding module; CLC, cardiotrophin-like cytokine; CML, chronic myeloid leukemia; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; EGF, epidermal growth factor; Epo, erythropoietin; ErbB, protein family of EGF receptors; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; FnIII, fibronectin type III; G-CSF, granulocyte colony-stimulating factor; Gab, Grb2-associated binding protein; gp130, glycoprotein of 130 kDa; GPL, gp130-like protein; h, human; Ig, immunoglobulin; IL, interleukin; IL-1ra, IL-1 receptor antagonist; IL-1RAcP, IL-1 receptor accessory protein; JAK, Janus tyrosine kinase; LBP, LIF-binding protein; LIF, leukemia inhibitory factor; m, murine; Mabs, monoclonal antibodies; MAPK, mitogen-activated protein kinase; NMR, nuclear magnetic resonance; OSM, oncostatin M; p38, also known as stress-activated protein kinase (SAPK), a MAPK; PDGF, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; R, receptor; RFP, receptor fusion protein; Shc, an adaptor protein; s, soluble; siRNA, small interfering RNA; SMAD, transcription factors activated by transforming growth factor-β (TGF-β) receptors; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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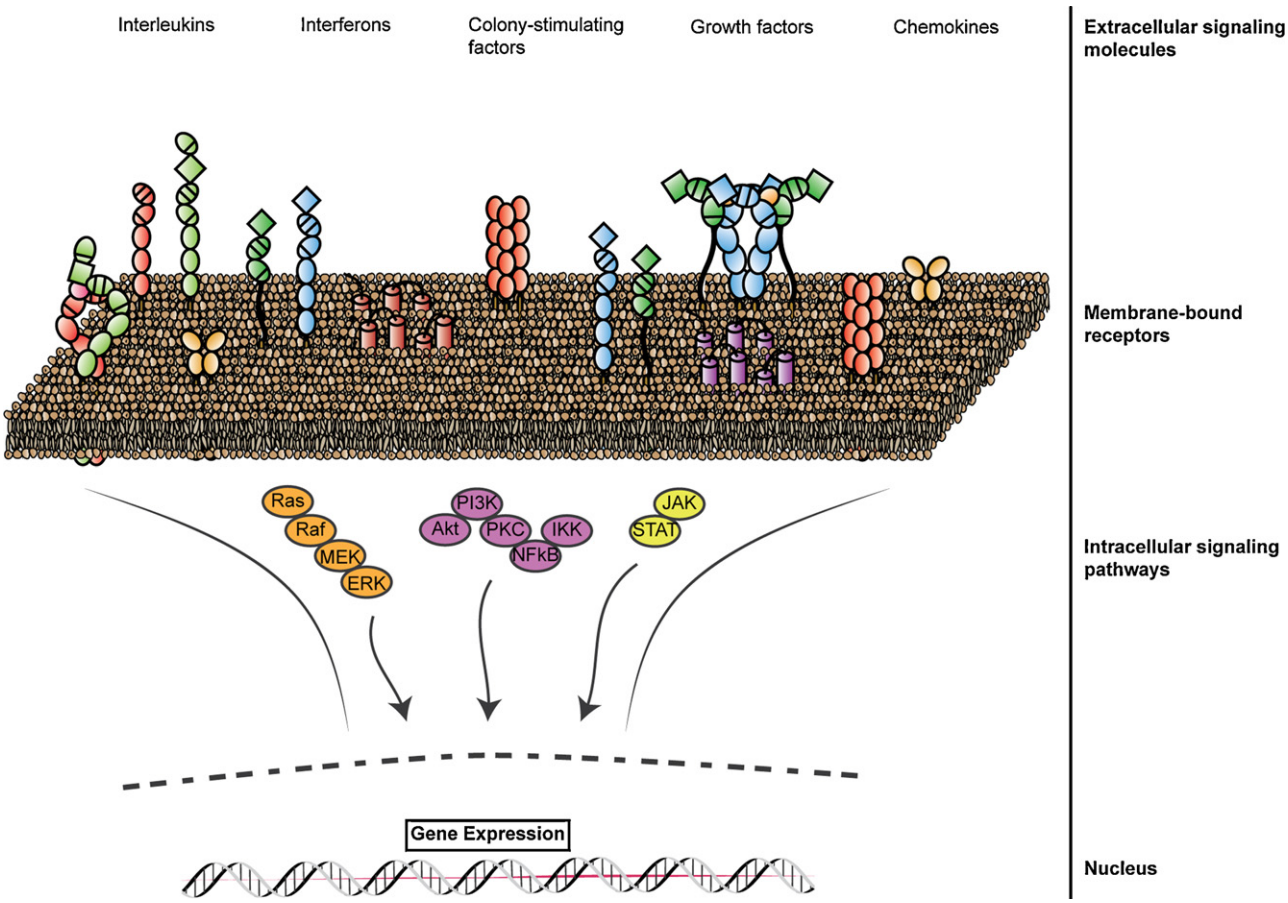

Fig. 1. Level of inhibition and specificity. A wide variety of ligands and receptors signal through a limited set of core signaling pathways. Therefore, a greater specificity is often achieved with blocking of cytokine–receptor interactions than with inhibition of signaling enzymes.

have the capability to enter the cell. These drugs are usually more or less specific inhibitors of signaling enzymes such as protein kinases or histone deacetylases. However, many different cytokines and receptors use a limited set of core signaling pathways such as MAPK or PI3K/Akt signaling (Fig. 1). Depending on the cellular proteome these signaling pathways are interpreted in different cell types in different ways. Because of their central importance, inhibition of such core signaling pathways might lead to severe side effects. For example, p38 MAPK is involved in the production of pro-inflammatory cytokines and is therefore an attractive drug target. However, in clinical trials small molecule p38 inhibitors showed toxic side effects (Yong et al., 2009).

Specificity of the inhibitor and a specific pathogenetic function of the drug target in the disease is a prerequisite for the success of a targeted therapy. Prominent examples are the treatment of Bcr–Abl positive CML with the Abl-kinase inhibitor imatinib (Gleevec®) or dampening inflammation and pain with the cyclooxygenase inhibitor acetylsalicylic acid (Aspirin®). Protein–protein interactions involved in signaling networks often rely on multiple low affinity interactions that sum-up to a high affinity interaction. Such multiple-site interactions are difficult to disturb with small compounds.

If overexpression of a cytokine significantly contributes to the development or maintenance of a disease, the respective cytokine–receptor interaction will be a very promising drug target. This scenario is often observed in chronic inflammatory diseases with high levels of pro-inflammatory cytokines such as IL-1, TNF and IL-6. Here, effective anticytokine therapies have been established. With increasing recognition of the multiple connections between inflammation and cancer these approaches are also of interest for the treatment of cancer (Grivennikov et al., 2010). Cytokines are mainly expressed in the diseased tissue and often act locally. Therefore, side-effects of cytokine inhibition are comparatively low and can be tolerated. Moreover, although there is some redundancy in cytokine–receptor interactions, blockade of the cytokine–receptor interactions is usually more specific than interfering with core signaling pathways or the transcriptional machinery. The primary cytokine–receptor interaction takes place at the extracellular side of the plasma membrane and is therefore accessible for a wide variety of potential drugs including recombinant proteins.

Targeting the cytokine–receptor interaction

All cytokines signal through homooligomeric or heterooligomeric receptors meaning that cytokine receptors consist of two or more protein subunits. The simplest receptors form homodimers of two identical subunits such as the G-CSF receptor or Epo receptor. Members of the TNF family of cytokines signal through homotrimeric receptors consisting of three identical subunits. Most common are receptors that consist of a heterodimer of two different subunits such as the receptors of the IL-2 family of cytokines. Also shared receptors are known which are utilized by different cytokines such as the common γ-chain of the IL-2 family, the common β-chain of the IL-3 family and gp130 of the IL-6 family of cytokines (Wang et al., 2009). Depending on the ligand they can form homodimeric, heterodimeric and higher order receptor complexes as in the case of the shared cytokine receptor gp130 (Müller-Newen, 2003). The receptor complex is held together