Journal of Autoimmunity xxx (2017) 1–12

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Small molecules to the rescue: Inhibition of cytokine signaling in immune-mediated diseases

Massimo Gadina*, Nathalia Gazaniga, Laura Vian, Yasuko Furumoto

Translational Immunology Section, Office of Science and Technology, National Institute of Arthritis Musculoskeletal and Skin Diseases, USA

ARTICLE INFO

Article history:
Received 12 June 2017
Accepted 15 June 2017
Available online xxx

Keywords:
Cytokines
Signal transduction
Drug development
Inflammation
Autoimmunity
Therapy

ABSTRACT

Cytokines are small, secreted proteins associated with the maintenance of immune homeostasis but also implicated with the pathogenesis of several autoimmune and inflammatory diseases. Biologic agents blocking cytokines or their receptors have revolutionized the treatment of such pathologies. Nonetheless, some patients fail to respond to these drugs or do not achieve complete remission. The signal transduction originating from membrane-bound cytokine receptors is an intricate network of events that lead to gene expression and ultimately regulate cellular functionality. Our understanding of the intracellular actions that molecules such as interleukins, interferons (IFNs) and tumor necrosis factor (TNF) set into motion has greatly increased in the past few years, making it possible to interfere with cytokines' signaling cascades. The Janus kinase (JAK)/signal transducer and activator of transcription (STAT), the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), the mitogen activated protein kinase (MAPK) and the Phosphatidylinositol-3′-kinases (PI3K) pathways have all been intensively studied and key steps as well as molecules have been identified. These research efforts have led to the development of a new generation of small molecule inhibitors. Drugs capable of blocking JAK enzymatic activity or interfering with the proteasome-mediated degradation of intermediates in the NF-kB pathway have already entered the clinical arena confirming the validity of this approach. In this review, we have recapitulated the biochemical events downstream of cytokine receptors and discussed some of the drugs which have already been successfully utilized in the clinic. Moreover, we have highlighted some of the new molecules that are currently being developed for the treatment of immune-mediated pathologies and malignancies.

Contents

Abbreviations: JAK, Janus Kinase; STAT, Signal transducer and activator of transcription; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, Mitogen activated protein kinase; PI3K, Phosphatidylinositol-3′-kinases; TNF, tumor necrosis factor; IL, Interleukin; CSFs, Colony stimulating factors; IFNs, Interferons; DMARDs, disease modifying anti rheumatic drugs; TFs, Transcription factors; X-SCID, X-linked severe combined immunodeficiency; PV, polycythemia vera; HIES, hyper-IgE syndrome; RA, rheumatoid arthritis; AA, alopecia areata; AU, alopecia universalis; MTX, methotrexate; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; AD, atopic dermatitis; GVHD, graft versus host disease; SLE, systemic lupus erythematosus; CANDLE, Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature; STING, Stimulator of Interferon Genes; SAVI, STING-associated Vasculopathy with Onset in Infancy; UC, ulcerative colitis; AS, ankylosing spondylitis; TNFRs, TNF receptors; TRADD, TNFR-associated death domain protein; FADD, Fas-associated death domain protein; X-HIM, X-Linked hyper-IgM; EDA-ID, ectodermal dysplasia with immunodeficiency; TLR, Toll-like receptors; NLRP3, NLR family pyrin domain containing 3; NLRC4, NLR family CARD domain-containing protein; IPAF, ICE-protease activating factor; NAIP, NLR family apoptosis inhibitory protein; AIM2, melanoma 2; cIAP, cellular inhibitor of apoptosis; NIK, NF-kB-inducing kinase; IKKγ, inhibitor of nuclear factor kappa-B kinase; GWAS, genome-wide association studies; MS, Multiple Sclerosis; SINE, selective inhibitors of nuclear export; PIP2, phosphatidylinositol-(4,5)-phosphate; PIP3, phosphatidylinositol-(3,4,5)-phosphate; PTEN, phosphatase and tensin homolog; mTOR, mammalian target of rapamycin; ROR, retinoic-acid-orphan-receptor.

* Corresponding author. Translational Immunology Section, Office of Science and Technology, National Institute of Arthritis Musculoskeletal and Skin Diseases, National Institutes of Health, Building 10, Room 10C101-C, Bethesda, MD, 20892-1560, USA.
E-mail address: Massimo.gadina@nih.gov (M. Gadina).

http://dx.doi.org/10.1016/j.jaut.2017.06.006
0896-8411/

1. Introduction

The term cytokine defines an extensive range of soluble factors that serve as intercellular communication tools of the immune system. These molecules are critical for developmental and homeostatic immune processes including host defense, inflammation, trauma and cancer. When their expression or their intracellular pathways are dysregulated, immune homeostasis is altered leading to the development of pathologies such as chronic inflammation, autoimmune syndromes as well as malignancies [1].

Produced by a plethora of cell types and having diverse functions which are not limited to just the immune response, cytokines are better classified based on the type of receptors they bind. This classification also allows us to highlight similarities in their signal transduction cascades. It is possible to identify 5 distinct classes of receptors: the so-called type I and type II cytokine receptors, the tumor necrosis factor (TNF) receptor family, the interleukin (IL)-1 receptor and the IL-17 family of receptors. The final subgroup of cytokines is the transforming growth factor receptor superfamily which will not be covered by this review.

Type I cytokines include molecules such as IL-2 through 7, colony stimulating factors (CSFs), hematopoietic factors and many others. Notably, they have critical functions in lymphocyte development and can act as positive as well as negative regulators of the immune responses.

Interferons (IFNs) and cytokines of the IL-10 family are all members of the group designated as type II cytokines. There are over 20 IFNs subdivided into three major groups, and their primary activity is to inhibit viral infections and stimulate the immune system to fight pathogens. The IL-10 family includes IL-10, IL-19 through 24, and IL-26. IL-10 is the most extensively studied and plays an essential role in both anti-inflammatory and immunosuppressive functions.

The TNF family contains a large number of molecules which are also potent modulators of either immune cell development or pro-inflammatory responses. Overall, these molecules comprise a structurally related group of ligands, receptors, and inhibitory decoy receptors, with tissue-specific expression, ligand-receptor binding and biological functions [2,3].

Similarly to TNF, the IL-1 family also includes inhibitory decoy receptors and ligands of this IL-1 family have been shown to have pro- as well as anti-inflammatory effects. Indeed, IL-1, IL-18, and IL-36 are potent inducers of other pro-inflammatory cytokines whereas IL-37 and IL-38 act as negative regulators.

The IL-17 family includes IL-17A through IL-17E, which is also known as IL-25. Members of this family induce the production of other cytokines including TNF and IL-1, chemokines (e.g IL-8), prostaglandins and antimicrobial peptides. Moreover, they are critical for host defense against gram-negative extracellular bacteria like *Klebsiella pneumoniae* and fungi like *Candida albicans* [4].

Several studies have shown that these molecules or their receptors can be targeted therapeutically to treat chronic inflammatory conditions and immune related disorders. Therefore, it is not surprising that blocking cytokines and their receptors with biologic disease modifying antirheumatic drugs (DMARDs) has revolutionized the treatment of the above-mentioned pathologies. Nonetheless, blocking the action of a single cytokine is sometimes not sufficient and only a percentage of patients benefit from this therapeutic approach. Moreover, parenteral or endovenous administration are often required; thus, the development of novel therapeutic strategies is needed. In the past few years, our understanding of the cytokine signaling cascades has greatly expanded and inhibition of the enzymatic activity of intracellular molecules, such as receptor-associated kinases and of transcription factors (TFs) is not only very attractive but more importantly, feasible. The aim of this review is to briefly describe the signaling cascades downstream of cytokine receptors and present the molecules which have been pharmacologically targeted or being considered as possible targets for the development of novel *ad hoc* therapies for inflammatory, immune-related disorders as well as malignancies.

2. Type I and type II cytokines and the JAK/STAT pathway

Type I and type II cytokine receptors do not possess intrinsic enzymatic activities but instead rely on specific cytosolic kinases, known as the JAKs, to transmit the signal inside the cell. The family is constituted of four members: JAK1, JAK2, JAK3, and TYK2. They were all discovered in the early 1990's [5] and are named after the Roman god Janus Bifrons. Similar to the two-faced god, JAK C-terminus architecture is constituted by a kinase domain preceded by a pseudokinase domain that are structurally very similar to each other. Although initially thought to be deprived of a clear enzymatic activity, the pseudokinase domain is instead catalytically active and can phosphorylate and activate the kinase domain therefore serving an important regulatory role. Moreover, Janus was the god of beginnings and entryways; likewise, JAKs oversee the start of the signaling cascade which originates outside the cell and continues in the cytoplasm.

The binding of a cytokine to its cognate receptor results in alteration of the conformational structure of the receptor chains, bringing the associated JAKs in close proximity to each other, and ultimately, in activation of their phosphotransferase activity. Thus, JAKs, which work in pairs, phosphorylate themselves and, in turn, the intracellular portion of the receptors. The phosphorylated receptors become substrate for the binding of several intracellular molecules including the SH2 domain-containing latent cytoplasmic transcription factors known as STATs. This family of DNA-binding proteins is composed of seven family members, namely, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Binding to the receptors results in their phosphorylation by the JAKs upon which they detach from the receptor chains, dimerize and translocate to the nucleus to regulate transcription of specific target genes [6].

Please cite this article in press as: M. Gadina, et al., Small molecules to the rescue: Inhibition of cytokine signaling in immune-mediated diseases, Journal of Autoimmunity (2017), http://dx.doi.org/10.1016/j.jaut.2017.06.006