1. INTRODUCTION

Cytokines represent a diverse group of small, soluble polypeptides that are involved in regulating a wide range of physiologic processes, including inflammation, tissue repair, and immunity. The expanding role of cytokines in these processes and the identification of over 100 putative cytokine family members have made it difficult to easily classify cytokines based on structure or function. In addition, many cytokines exhibit a variety of biologic activities and these effects may be dependent on the concentration, timing, and duration of target cell exposure to a given cytokine, as well as the influence of other cytokine and growth factors in the local microenvironment. In fact, much of the early characterization of cytokines was based on simple in vitro experiments, which have failed to accurately predict the activity of cytokines in vivo. More recent investigation using targeted knockout mice and analysis of cytokine signaling pathways is leading to new insights into the biology of many cytokines. This is perhaps best exemplified by interleukin-2 (IL-2), originally described as a T-cell growth factor and defined by its ability to induce T-cell proliferation in vitro. Such ex vivo studies predicted that IL-2 would function to promote cellular immunity through expansion of naïve T-cell populations in vivo. The availability of IL-2 and IL-2 receptor knockout mice, however, demonstrated that in the absence of IL-2 signaling T-cell proliferation was increased, significant lymphadenopathy occurred, and animals succumb to aggressive autoimmune disease. This unexpected result suggests that IL-2 may actually function in vivo, not as a T-cell stimulant, but rather as a regulatory cytokine maintaining peripheral tolerance through balancing effector and regulatory T-cell pools (1).
The cytokines were initially described as soluble factors released by immune cells with a biologic effect on the cells releasing the cytokine, also referred to as an autocrine effect. Today it is clear that whereas cytokines may have a local role at the site of their synthesis and release, the effects can mediate interactions between cells and tissues at distant sites, also referred to as a paracrine effect. The complexity of the cytokine network is inherent in the fact that different cells can produce the same cytokine, many cytokines have similar or overlapping activities, cytokine receptor expression is often tightly regulated and can bind more than one cytokine, and the effects of any individual cytokine must be considered within the context of other cytokines, growth factors, and the status of cellular differentiation at the time of exposure. Thus, cytokines differ from hormones in several key respects, most notably that cytokines rarely have a single cell of origin and exert biologic effects on a wider array of target cells. Despite this current view of cytokine biology, many cytokines were named for the cells from which they were first identified or for other functional activities that were known before the factors were recognized as a cytokine. For example, cytokines released by leukocytes were initially referred to as interleukins, those from monocytes as monokines, and so on. The ability to interfere with viral replication led to the term “interferons” for these cytokines and TNF was named for its ability to induce necrosis in transplantable murine tumors. A relatively new class of cytokines was termed “chemokines” for their ability to induce chemotaxis of immune cells, although these molecules are now known to mediate a host of other biologic effects.

Although cytokines are diverse in structure and function, the cytokine receptors appear to be more conserved and share a higher degree of sequence homology allowing them to be grouped into distinct families. The type-1 cytokine receptors generally form multimeric complexes with a single chain binding to soluble cytokine and another chain inducing cellular signaling. The extracellular component of the type-1 cytokine receptor is notable for a highly conserved 200-amino-acid sequence with four positionally conserved cysteine residues providing structural integrity to the receptor. The intracellular component of the type-1 receptor is unusual in that it lacks intrinsic tyrosine kinase activity. The type-2 cytokine receptors also form multimeric complexes with conserved extracellular domains. In contrast to the type-1 receptors, type-2 receptors contain intracellular domains with binding sites for Janus kinases and STAT proteins. Table 1 lists some of the cytokines that are specific for each receptor. By convention the $\alpha$ subunit of the cytokine receptor is the chain that binds cytokine and other designations are used for those chains that are involved in cellular signaling. Many of the cytokine receptors exist in soluble form through proteolytic cleavage of the membrane bound receptor complex. The tumor necrosis factor $\alpha$ (TNF-$\alpha$) and chemokine receptors differ from the typical cytokine receptors.

The clinical utility of cytokines as single-agent therapy in human disease has been well documented and represents one of the most successful applications of immunotherapy. Interferon-$\alpha$ (IFN-$\alpha$) is approved for the treatment of some forms of hepatitis, chronic myelogenous and hairy cell leukemia, Kaposi’s sarcoma, and as adjuvant therapy for stage III malignant melanoma. IFN-$\beta$ has shown effectiveness in multiple sclerosis. High-dose IL-2 has become the standard treatment for metastatic renal cell carcinoma and melanoma. A major obstacle to wide acceptance of single agent cytokine therapy has been the disappointing low response rates in many advanced malignancies and the often significant toxicity associated with effective treatment regimens. Our improved understanding of the signaling pathways for specific cytokines coupled with better