Chapter 15

IL-6 Unique Functions in Inflammation, Bone Metabolism, and B-Cell Neoplasias Revealed by Studies on IL-6-Deficient Mice

Valeria Poli

Introduction

Interleukin-6 (IL-6) is a multifunctional cytokine regulating various aspects of immune response, hemopoiesis, and inflammation. It induces the maturation of B-lymphocytes into antibody-producing plasma cells and the activation of T-cells, and it stimulates proliferation and differentiation of hematopoietic stem cells and thymocytes (for review see ref. 1). IL-6 is also a central mediator of several host responses to acute inflammation, including the acute phase reaction (APR) in the liver (2). Circulating IL-6 levels are normally very low; however, they are rapidly increased by a number of stimuli such as bacterial or viral infection, tissue damage-induced inflammation, and different kinds of traumas. IL-6 disregulated production has been implicated in the pathogenesis of several diseases including autoimmune disorders, plasma-cell dyscrasias, and postmenopausal osteoporosis.

IL-6 signaling occurs through the assembly of a receptor complex composed of two subunits, the ligand binding IL-6Rα and the
signal transducing gp130. gp130 also acts as a signaling subunit for a family of cytokines structurally related to IL-6: leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), interleukin-11 (IL-11), and cardiotrophin-1 (CT-1; for review, see ref. 3). In contrast with IL-6 and IL-11, which trigger gp130 homodimerization, LIF, OSM, and CNTF assemble a heterodimeric complex between gp130 and a second signaling molecule, the LIFR. The common sharing of gp130 and the differential involvement of the LIFR are likely explanations for the overlapping and diverging functions displayed by these cytokines. Interestingly, since the IL-6Rα intracytoplasmic domain is not required for signaling, soluble IL-6Rα forms (sIL-6Rα) can act as agonists, conferring IL-6 responsiveness on cells that only harbor gp130 (4,5). Although the physiological role of sIL-6R has not yet been demonstrated, circulating forms of IL-6Rα are naturally present in both humans and mice and their levels increase in a variety of pathological conditions (6–8). Moreover, simultaneous expression of IL-6 and sIL-6R in transgenic mice triggers continuous activation of gp130 signaling (9).

The interaction of IL-6 with its receptor complex is known to trigger the activation of two different pathways: the mitogen-activated protein (MAP) kinase-dependent activation of members of the C/EBP family of transcription factors (10), and the activation through tyrosine phosphorylation of members of the Jak family of nonreceptor tyrosine kinases and of transcription factors belonging to the signal transducers and activators of transcription (STAT) family (11). Originally characterized as signaling components of the interferon (IFN)-α and -γ receptor complexes, Jak kinases and STAT proteins have been more recently shown to be important players in the signaling through many cytokines and growth factors receptors (12). All members of the IL-6 cytokine family were shown to be able to activate STAT3 and, to a lesser extent, STAT1.

The complex functional interplay between different cytokines, that influence one another’s synthesis and whose effects are different, or sometimes overlapping depending on the tissue, has made the unequivocal identification of the specific in vivo role of these molecules often evasive. The development of mutant mice lacking a specific gene product has recently provided the opportunity to unambiguously characterize which functions are “unique” to certain cytokines, and which are “redundant” and can be functionally com-