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Review

Interleukin-6: An osteotropic factor influencing bone formation?

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Abstract

Interleukin (IL)-6 has long been considered as an osteoresorptive factor. However, recent data indicate that IL-6 could influence bone formation in conditions of increased bone turnover. In this paper, the effects of IL-6 and its soluble receptor on osteoblast proliferation, differentiation and apoptosis are readdressed. A brief summary of IL-6 signaling after binding to its receptor is provided and hypotheses concerning IL-6 and the central control of bone formation are also highlighted.

Keywords: Interleukin-6; Interleukin-6 soluble receptor; Osteoblasts; Bone formation

Contents

Introduction

Since its discovery 25 years ago, interleukin (IL)-6 has been recognized as a pleiotropic cytokine influencing many biological events in several organs including the bone marrow, the central nervous system (CNS) or the immune system [1]. In bone, activation of the glycoprotein(gp)-130 signaling pathway by interleukin (IL)-6 and its soluble receptor (sIL-6R) was originally regarded as a key pathway for the regulation of osteoclastogenesis [2]. However, in vitro data were not always consistent and were challenged by in vivo experiments demonstrating that IL-6 knockout ($^{-/-}$) mice were healthy and experienced no specific bone phenotype [2–5]. Moreover, the number of osteoclasts was found unexpectedly to be increased in gp-130$^{-/-}$ fetuses [6]. Thus, IL-6 did not appear to be essential for normal bone resorption and homeostasis. Nevertheless, additional studies established that IL-6$^{-/-}$ mice were protected against joint inflammation and destruction in collagen or antigen-induced arthritis [7–11]. A decrease in bone resorption was also observed after estrogen depletion (ovariectomy) in IL-6$^{-/-}$mice [12]. Therefore, inappropriate expression of IL-6 might have an impact on the increase in bone resorption observed in several diseases including post-menopausal osteoporosis, multiple myeloma or rheumatoid arthritis [7,8,13,14]. In rheumatoid arthritis and juvenile arthritis, the central role played by IL-6 in joint inflammation and destruction has lead to the development of targeted inhibition of this cytokine as a therapeutic approach [7].

More recently, by a genetic approach, N. Sims and co-workers demonstrated that IL-6 supports osteoblast generation through the gp-130-STAT1/3 pathway [15]. Once again the authors showed that IL-6 was not essential for

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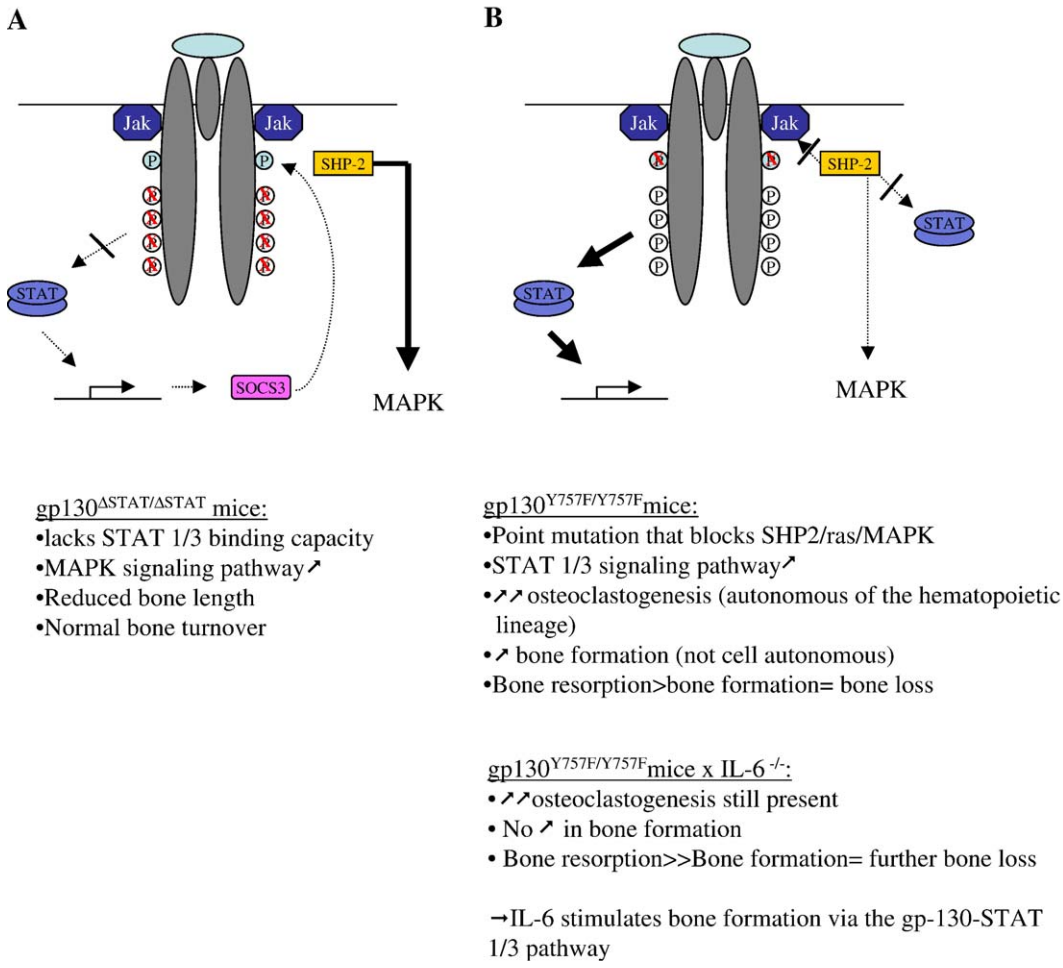

Fig. 1. Negative feed-back between the STAT 1/3 and the MAPK pathways and results from the knock-in mutations of gp-130. A. Docking of STAT 1 and 3 to the membrane-distal phospho-tyrosine residues of gp-130 results in nuclear translocation of STAT and activation of target genes including the two suppressor of cytokine signaling (SOCS) proteins. SOCS3 is recruited to the phosphorylated Y757 SHP-2 binding site of gp-130 and attenuates the MAPK signaling cascade. In gp-130$^{\Delta STAT/\Delta STAT}$ mice, the induction of SOCS3 by STAT3 is impaired which results in a better accessibility of SHP-2 docking site and a subsequent increase in the MAPK activity. The bone phenotype of the gp-130$^{\Delta STAT/\Delta STAT}$ mice is described in the lower panel [15]. B. Phosphorylation of the single Y757 (Y759 in human) of gp-130 results in the recruitment of the protein tyrosine phosphatase SHP-2 and the activation of the Ras/ERK-MAPK pathway. As a tyrosine phosphatase, SHP-2 might dephosphorylate its associated signal molecules including Jak or STAT (negative retrocontrol). Therefore, gp130$^{Y757F/Y757F}$ mice display an increase in STAT signaling activity. The bone phenotype of the gp130$^{Y757F/Y757F}$ mice and the mice obtained from the crossing of gp130$^{Y757F/Y757F}$ mice and IL-6$^{-/-}$ mice are described in the lower panel.

physiological bone remodeling but was required for the enhanced osteoblast response observed in mice (gp-130$^{Y757F/Y757F}$) carrying a point mutation that selectively blocks the SHP2/Ras/MAPK pathway (and favors the Jak/STAT pathway) [15]. Indeed, gp-130$^{Y757F/Y757F}$ mice displayed a high bone turnover and a decrease in trabecular bone volume. When crossed to IL-6$^{-/-}$ mice, the level of bone formation was reduced to the levels of wild-type mice while no change in osteoclast number or activity was observed, leading to further bone loss (Fig. 1, [15]).

In the light of N. Sims and co-workers 's study readdressing IL-6 function in bone formation in conditions of increased bone remodeling, we discuss in this review the effects of IL-6 and sIL-6R on osteoblast proliferation, differentiation and apoptosis. We describe briefly the agonist role of sIL-6R for IL-6 as well as IL-6 major signaling pathways. We also explain the analogies between leptin and IL-6 and the potential role of IL-6 in the central control of bone formation.

Signaling through the IL-6 receptor

IL-6 binds to a specific receptor α-subunit (IL-6Rα), an 80 kDa glycoprotein that lacks intrinsic signaling properties. The IL-6/IL-6Rα complex then interacts with two gp-130 molecules to form a hexameric complex [1,16]. Importantly, membrane association of IL-6Rα to gp-130 is not required to trigger signaling. Therefore, sIL-6R has agonist properties for IL-6 and confers IL-6 responsiveness to cells expressing gp-130 but lacking IL-6Rα, a process called *transsignaling* [17]. In bone, sIL-6R is required for IL-6 effects on osteoclast