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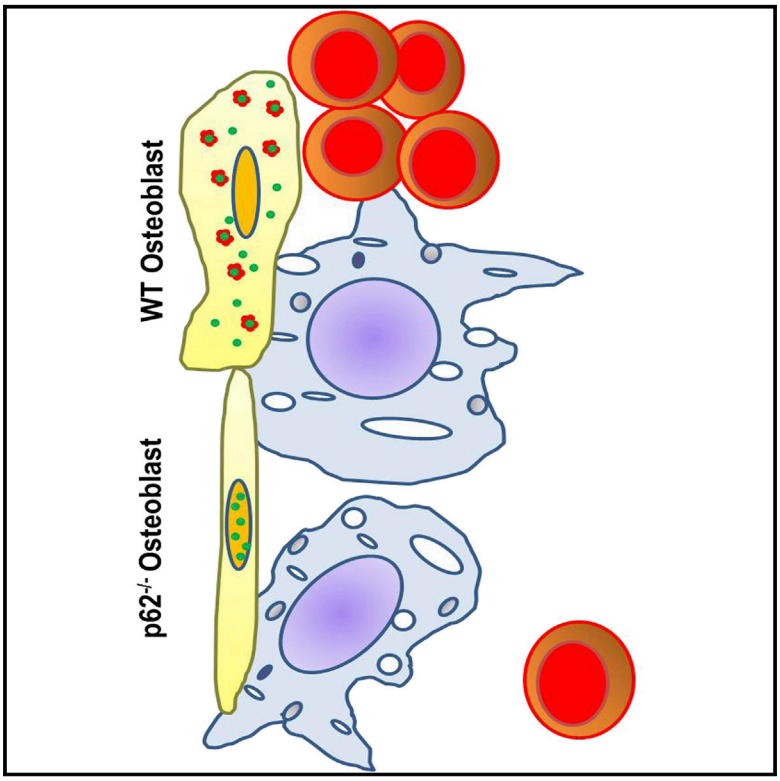
p62 Is Required for Stem Cell/Progenitor Retention through Inhibition of IKK/NF-κB/Ccl4 Signaling at the Bone Marrow Macrophage-Osteoblast Niche

Graphical Abstract



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In Brief

Chang et al. describe crosstalk between macrophages and osteoblasts that regulates bone formation and hematopoietic progenitor retention and homing to the marrow cavity. The authors find that p62 is required to maintain macrophage-dependent, osteoblast NF-κB repression, osteogenesis, and hemopoietic stem cell/progenitor trafficking.

Highlights

- Macrophages activate osteoblastic NF-κB, resulting in osteopenia and HSC/P egress
- Autophagic p62 negatively regulates osteoblastic NF-κB activation at several levels
- Nbr1 deficiency rescues the bone and HSC/P egress associated to p62 deficiency

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p62 Is Required for Stem Cell/Progenitor Retention through Inhibition of IKK/NF-κB/Ccl4 Signaling at the Bone Marrow Macrophage-Osteoblast Niche

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SUMMARY

In the bone marrow (BM), hematopoietic progenitors (HPs) reside in specific anatomical niches near osteoblasts (Obs), macrophages (MΦs), and other cells forming the BM microenvironment. A connection between immunosurveillance and traffic of HP has been demonstrated, but the regulatory signals that instruct the immune regulation of HP circulation are unknown. We discovered that the BM microenvironment deficiency of p62, an autophagy regulator and signal organizer, results in loss of autophagic repression of macrophage contact-dependent activation of Ob NF-κB signaling. Consequently, Ob p62-deficient mice lose bone, Ob Ccl4 expression, and HP chemotaxis toward Cxcl12, resulting in egress of short-term hematopoietic stem cells and myeloid progenitors. Finally, Ccl4 expression and myeloid progenitor egress are reversed by deficiency of the p62 PB1-binding partner Nbr1. A functional "MΦ-Ob niche" is required for myeloid progenitor/short-term stem cell retention, in which Ob p62 is required to maintain NF-κB signaling repression, osteogenesis, and BM progenitor retention.

INTRODUCTION

Steady-state blood formation during most adulthood depends on long-lived hematopoietic progenitors (HPs) (Sun et al., 2014). Constitutive egress of bone marrow (BM)-resident HP into the blood is a well-established phenomenon. Circulating HP can survey peripheral organs and foster the local production of tissue-resident innate immune cells under both steady-state conditions and in response to inflammatory signals (Baldridge et al., 2010; Essers et al., 2009; Massberg et al., 2007). Dysregulation of stromal components of the HP niches within the BM, such as changes in the levels of chemokines from osteoblasts (Obs) and other mesenchymal cells, has been associated with HP egress (Ding and Morrison, 2013; Greenbaum et al., 2013; Méndez-Ferrer et al., 2010; Omatsu et al., 2010; Petit et al., 2002; Sugiyama et al., 2006; Visnjic et al., 2004). Specifically, the deletion of the major hematopoietic stem cell and progenitor (HSC/P) traffic regulator Cxcl12 (Peled et al., 1999, 2000) from Cxcl12-abundant reticular cells and Ob results in constitutive HP mobilization and a loss of B-lymphoid progenitors, whereas their HSC function is normal (Greenbaum et al., 2013). Physiological regulation of these mesenchymal components modulates HP trafficking and is afforded by several mechanisms, including signals derived from BM-resident macrophages (MΦs) (Casanova-Acebes et al., 2013; Chow et al., 2011; Christopher et al., 2011; Winkler et al., 2010). Cellular crosstalk between MΦs and Obs in the HP niche may critically regulate the response of HP to cytokines and chemokines.

The transcription factor NF-κB has a key role in inflammation and immune responses (Ghosh and Karin, 2002; Silverman and Maniatis, 2001; Sun et al., 2013) and has been recently shown to play a role in the response of myeloid progenitors to stress hematopoiesis (Zhao et al., 2014). NF-κB can also control mesenchymal-derived osteogenesis, and mice with a loss of function of NF-κB signaling show osteopetrosis (Iotsova et al., 1997). IκB