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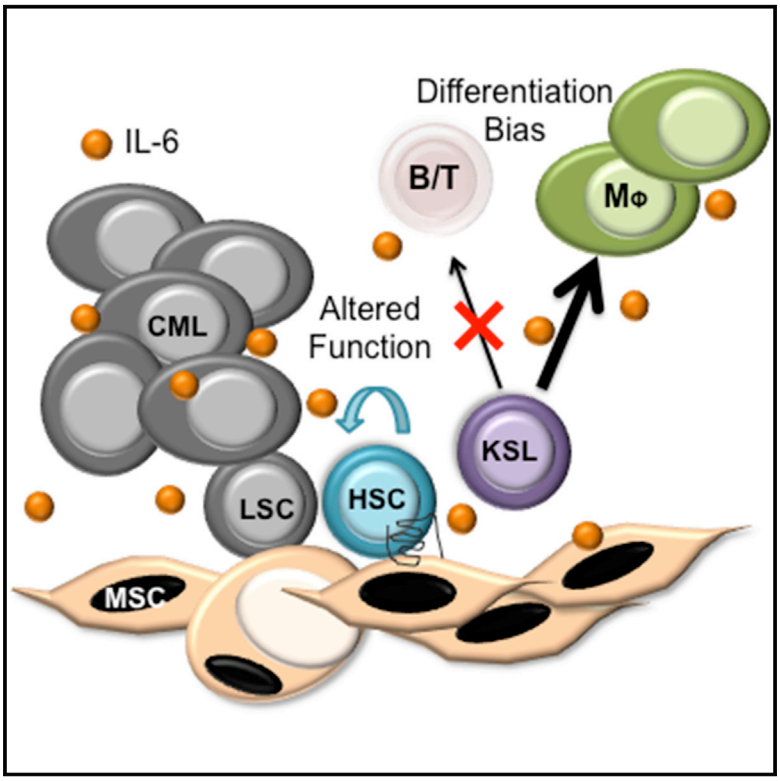
Treatment of Chronic Myelogenous Leukemia by Blocking Cytokine Alterations Found in Normal Stem and Progenitor Cells

Graphical Abstract



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In Brief

Welner et al. investigated whether chronic myelogenous leukemia (CML) cells alter normal hematopoietic stem/progenitor cells (HSPCs) in addition to outcompeting them. They show that CML cells promote proliferation, alter differentiation, and reduce self-renewal capacity of neighboring normal HSPCs via IL-6.

Highlights

- Leukemic cells alter neighboring non-transformed hematopoietic progenitor cells
- Imprinting of the leukemia on the normal progenitor cell counterparts mimics CML
- The pro-inflammatory cytokine IL-6 mediates these changes in normal hematopoiesis
- Treatment eliminates the leukemia upon targeted therapy against the IL-6 cytokine

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Treatment of Chronic Myelogenous Leukemia by Blocking Cytokine Alterations Found in Normal Stem and Progenitor Cells

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SUMMARY

Leukemic cells disrupt normal patterns of blood cell formation, but little is understood about the mechanism. We investigated whether leukemic cells alter functions of normal hematopoietic stem and progenitor cells. Exposure to chronic myelogenous leukemia (CML) caused normal mouse hematopoietic progenitor cells to divide more readily, altered their differentiation, and reduced their reconstitution and self-renewal potential. Interestingly, the normal bystander cells acquired gene expression patterns resembling their malignant counterparts. Therefore, much of the leukemia signature is mediated by extrinsic factors. Indeed, IL-6 was responsible for most of these changes. Compatible results were obtained when human CML were cultured with normal human hematopoietic progenitor cells. Furthermore, neutralization of IL-6 prevented these changes and treated the disease.

INTRODUCTION

Most hematopoietic stem cells (HSCs) reside in the bone marrow and self-renew as necessary to maintain their numbers (Mercier et al., 2012). Additionally, a fraction of HSCs develop into progenitor cells that become lineage restricted and that undergo extensive proliferation and differentiate to produce mature hematopoietic cells (Mayle et al., 2013; Venezia et al., 2004; Wilson et al., 2008). However, these normal processes are severely compromised with leukemia (Colmone et al., 2008; Hartwell et al., 2013; Hu et al., 2009; Krause et al., 2013; Schepers et al., 2013). While this could result from overcrowding by leukemic cells, it has been shown to occur with even low leukemic burden (Colmone et al., 2008). Considerable progress has been made in defining cells within marrow that support normal hematopoiesis (Morrison and Scadden, 2014). Referred to as niches, these environments are thought to include multipotent stromal cells (MSCs), osteoblasts, and endothelial cells. Additionally, there is now evidence that leukemia alters their functions (Raaijmakers et al., 2010; Reynaud et al., 2011; Schepers et al., 2013; Zhang et al., 2012). However, consequences of those changes and the direct impact of the leukemic cells on stem and progenitor cells have not been adequately explored.

Myeloproliferative neoplasms are clonal disorders propagated by transformed HSCs. Chronic myelogenous leukemia (CML) is one such disorder, and it is characterized by a reciprocal translocation of the t(9;22)(q34;q11) loci. As a result, transformed cells express the BCR/ABL fusion protein (Ben-Neriah et al., 1986; Hooberman et al., 1989; Levine and Gilliland, 2008; Savona and Talpaz, 2008; Sawyers, 1999; Witte, 1988). This deregulated

Significance

It has generally been assumed that normal hematopoietic stem and progenitor cells (HSPCs) are simply out-competed for space by malignant cells. We have shown that the leukemic cells are able to modify the differentiation potential of non-transformed cells while promoting their own maturation. The leukemic environment imprints functional and transcriptional programs onto the non-transformed progenitors. However, by specifically blocking the IL-6 cytokine, we could inhibit the differentiation bias and eliminate the bulk of the disease. Additionally, these observations were also found in human CML cells, and leukemic-exposed human progenitors could be protected by anti-IL-6. These findings implicate a drug-targetable mechanism that could account for significant malignancy-related abnormalities in CML.