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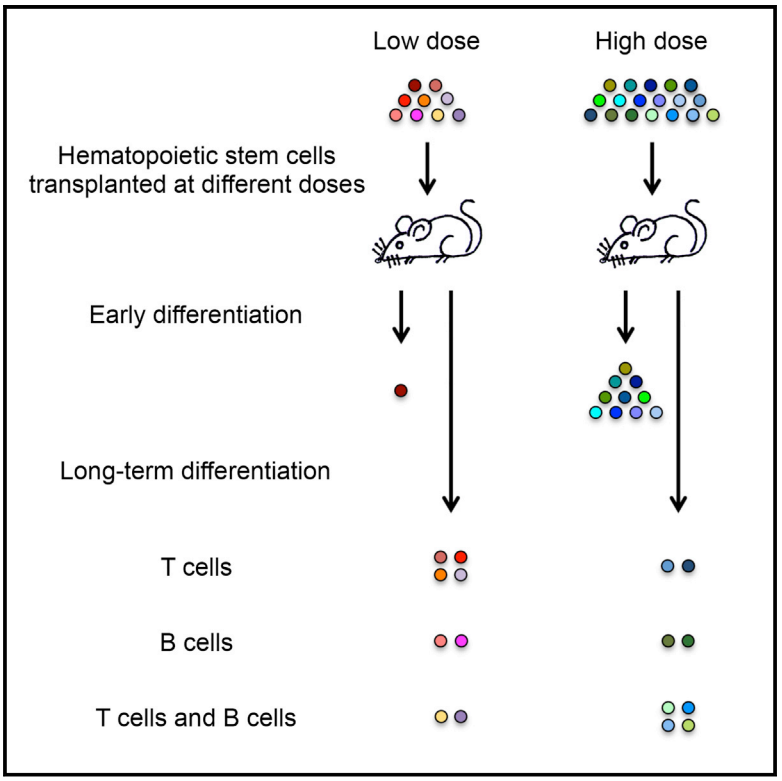
Transplantation Dose Alters the Differentiation Program of Hematopoietic Stem Cells

Graphical Abstract



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In Brief

HSCs are thought to supply all blood cell types after transplantation. Brewer et al. show that most HSCs specialize in producing only a subset of blood cell types post transplantation. They also find that transplantation dose alters differentiation specialization and dynamics.

Highlights

- 70%–80% HSC clones do not supply every blood cell type in the presence of other HSCs
- HSC differentiation changes with the transplantation dose
- Maximum blood production by a single HSC is unaffected by transplantation dose
- High transplantation doses increase the number of short-term differentiating clones

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Transplantation Dose Alters the Differentiation Program of Hematopoietic Stem Cells

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SUMMARY

Hematopoietic stem cell (HSC) transplantation is the most prevalent stem cell therapy, but it remains a risky procedure. To improve this treatment, it is important to understand how transplanted stem cells rebuild the blood and immune systems and how this process is impacted by transplantation variables such as the HSC dose. Here, we find that, in the long term following transplantation, 70%–80% of donor-HSC-derived clones do not produce all measured blood cell types. High HSC doses lead to more clones that exhibit balanced lymphocyte production, whereas low doses produce more T-cell-specialized clones. High HSC doses also produce significantly higher proportions of early-differentiating clones compared to low doses. These complex differentiation behaviors uncover the clonal-level regeneration dynamics of hematopoietic regeneration and suggest that transplantation dose can be exploited to improve stem cell therapy.

INTRODUCTION

Hematopoietic stem cells (HSCs) replenish the blood and immune systems. Residing in the bone marrow, each HSC is capable of generating every blood and immune cell type (Barker et al., 2010; Bryder et al., 2006). Since the mid-20th century, scientists have recognized HSCs as a potential cure for patients suffering from hematologic diseases or injuries (Copelan, 2006). HSC transplantation, also known as bone marrow transplantation, is currently used to treat a variety of blood diseases, to reset the immune system during organ transplantation, and to regenerate blood systems destroyed by radiation and chemotherapy during cancer treatment (Kondo et al., 2003). It remains the only cure option for many diseases. Although millions of patients could potentially benefit from HSC transplantation, only a small fraction of these patients undergo the procedure due to high treatment-related mortality (Copelan, 2006). Most adverse incidents arise from infection or from graft-versus-host complications following the procedure. In addition, patients with hematological malignancies such as leukemia often suffer relapse following disease remission. A better understanding of how HSCs rebuild the blood and immune system post transplantation will help develop a safer and more effective therapy.

Although much has been learned about HSC transplantation in recent years, most of our knowledge comes from population-level analyses. In these studies, a population of HSCs is isolated using cell-surface markers, and their progeny are analyzed at the population level. Limiting dilution assays of HSC transplantation suggest that the number of donor HSCs quantitatively determines the fraction of blood cells that they produce (Eaves et al., 1997; Purton and Scadden, 2007). These experiments support a simple model for HSC coordination in which individual HSCs play equal roles and uniformly alter their blood production in response to changes in hematopoiesis. This simple, homogeneous model was challenged by recent work from our group and others indicating the heterogeneity of HSC differentiation at the single-cell level (Beerman et al., 2010; Benz et al., 2012; Dykstra et al., 2007; Ergen et al., 2012; Lu et al., 2011; McKenzie et al., 2006; Sieburg et al., 2006; Yamamoto et al., 2013). For instance, individual HSC clones supply differential amounts of blood cells in mice and in human patients (McKenzie et al., 2006; Weksberg et al., 2008; Fehse and Roeder, 2008; Roeder et al., 2005; Nienhuis, 2008; Yamamoto et al., 2013). They also exhibit distinct differentiation preferences for myeloid or lymphoid lineages post transplantation (Beerman et al., 2010; Cho et al., 2008; Dykstra et al., 2007; Lu et al., 2011; Sieburg et al., 2006). In addition, recent studies of native hematopoiesis suggest that different blood cell types have distinct clonal origins as well (Pietras et al., 2015; Sun et al., 2014). These findings raise the question of how the diverse differentiation programs of individual HSCs are coordinated following transplantation. Manipulating this coordination may provide alternative approaches to controlling HSC differentiation and to improving stem cell therapy.

Previous studies showed that the regeneration of the blood supply post transplantation occurs in two phases (Camargo et al., 2006; Eaves, 2015; Morrison and Weissman, 1994). Immediately after transplantation, HSCs and short-term hematopoietic progenitors collectively supply blood cells. 4 months later, HSCs are thought to be the only cells to supply every blood cell type as short-term progenitor cells lack the capacity for long-term self-renewal. This two-phase mode of blood supply suggests that the coordination of HSC blood production changes during the blood reconstitution process. Immediately after transplantation, HSC clones must respond to the presence of short-term progenitors and to the urgent need for blood cells, while 4 months later, HSCs only have to contend with themselves. A full understanding