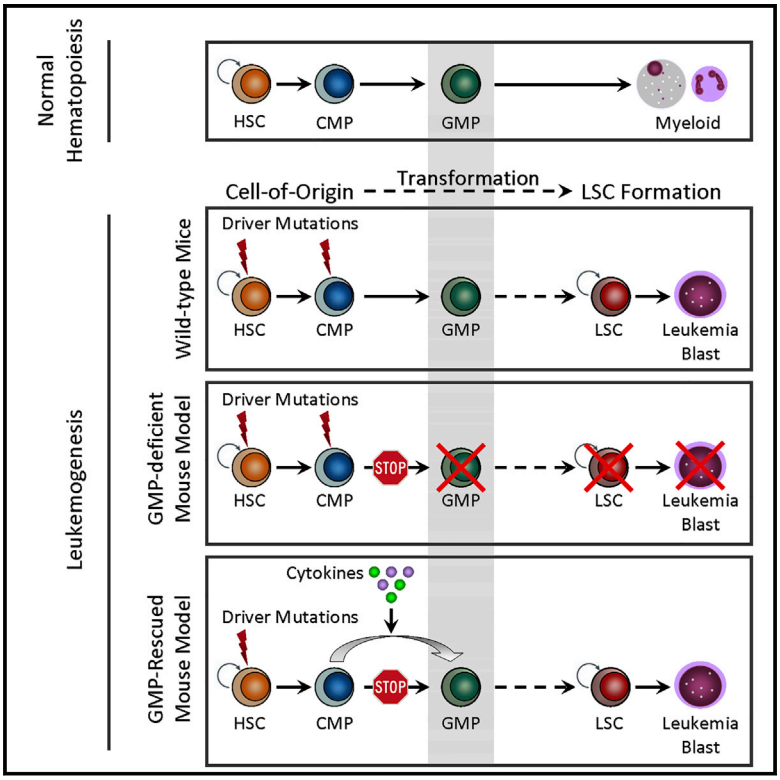
Article

Cell Stem Cell

Hematopoietic Differentiation Is Required for Initiation of Acute Myeloid Leukemia

Graphical Abstract



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In Brief

Ye et al. show that myeloid differentiation is required for acquiring a leukemia stem cell (LSC) phenotype and AML initiation and that blocking GMP formation abrogates leukemic transformation. Cytokine-induced bypass of this block restores LSC and AML development, with GMPs providing a genomic environment permissive for activating LSC transcriptional programs.

Highlights

- Myeloid differentiation to GMPs is required for LSC formation and AML initiation
- Bypassing disrupted GMP differentiation restores AML LSC generation
- Normal GMPs and L-GMPs share a minimal transcriptional program
- GMPs provide a genomic environment permissive for L-GMP formation

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Hematopoietic Differentiation Is Required for Initiation of Acute Myeloid Leukemia

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SUMMARY

Mutations in acute myeloid leukemia (AML)-associated oncogenes often arise in hematopoietic stem cells (HSCs) and promote acquisition of leukemia stem cell (LSC) phenotypes. However, as LSCs often share features of lineage-restricted progenitors, the relative contribution of differentiation status to LSC transformation is unclear. Using murine MLL-AF9 and MOZ-TIF2 AML models, we show that myeloid differentiation to granulocyte macrophage progenitors (GMPs) is critical for LSC generation. Disrupting GMP formation by deleting the lineage-restricted transcription factor C/EBPa blocked normal granulocyte formation and prevented initiation of AML. However, restoring myeloid differentiation in C/EBPa mutants with inflammatory cytokines reestablished AML transformation capacity. Genomic analyses of GMPs, including gene expression and H3K79me2 profiling in conjunction with ATAC-seq, revealed a permissive genomic environment for activation of a minimal transcription program shared by GMPs and LSCs. Together, these findings show that myeloid differentiation is a prerequisite for LSC formation and AML development, providing insights for therapeutic development.

INTRODUCTION

Leukemia stem cells (LSCs) are thought to be responsible for leukemia initiation, maintenance, and recurrence in acute myeloid leukemia (AML). Consequently, understanding the step-wise formation of LSCs might help overcome AML's resistance to current chemotherapy and disease relapse. Initial studies suggested that LSCs are restricted to a small sub-fraction of human AML cells phenotypically resembling normal hematopoietic stem cells (HSCs) (Bhatia et al., 1997). However, further characterization of LSCs using improved xenotransplantation models revealed the presence of functional LSCs sharing the surface phenotype of committed progenitors (McKenzie et al., 2005; Taussig et al., 2008). Recent studies of a large cohort of AML patients demonstrated enriched LSC activity within subsets phenotypically resembling normal lymphoid-primed multipotential progenitors (LMPPs) and granulocyte macrophage progenitors (GMPs) (Goardon et al., 2011). Leukemic LMPPs gave rise to leukemic GMPs (L-GMPs), but not vice versa, mirroring the hierarchy of normal hematopoiesis. Global gene expression profiles revealed that leukemic LMPPs and L-GMPs resembled their respective normal counterparts at the molecular level (Goardon et al., 2011). The similarities between LSCs and their normal counterparts both phenotypically and molecularly suggested that transformation to LSCs was completed at the progenitor stage. Therefore, LSCs may directly arise from progenitors that acquire aberrant self-renewal capacity. Alternatively, LSCs may originate from HSCs, yet full transformation occurs only upon progression to a more committed stage of differentiation.

A number of studies of human AML have suggested that HSCs are the likely cell of origin, but functional LSCs reside in more differentiated populations (Fialkow et al., 1989; Jan et al., 2012; Miyamoto et al., 1996; Shlush et al., 2014). Studies of murine leukemia models using retroviral expression of leukemia-associated fusion oncogenes MF9 and MOZ-TIF2 or a knockin mouse model carrying patient-derived CEBPA biallelic mutations demonstrated that both HSC and committed myeloid progenitor cells can be transformed and potentially serve as the cell-of-origin of LSCs (Huntly et al., 2004; Krivtsov et al., 2006; Bereshchenko et al., 2009). Regardless of cell-of-origin, LSCs from MF9 or MOZ-TIF2 mouse models phenotypically and molecularly resemble committed myeloid progenitor cells (Bereshchenko et al., 2009; Kirstetter et al., 2008; Kvinlaug et al., 2011; Somervaille and Cleary, 2006), consistent with features of LSCs in human AML patients. Therefore, the question remains to what extent differentiation impacts the complete transformation of LSCs from their cell-of-origin.

We and others have shown that C/EBPa plays a non-redundant role in the transition from common myeloid progenitors (CMPs) to GMPs (Zhang et al., 2004). Deletion of C/EBPa leads to a complete loss of GMPs and downstream progeny. Mice transplanted with C/EBPa knockout (KO) cells do not develop