SUPPLEMENTARY INFORMATION

SUPPLEMENTAL DISCUSSION

Further analysis of the entire set of 104 DE genes and their protein-protein interactors, encompassing a core transcriptional program of LSCs, may identify novel regulators of stemness, as well as putative therapeutic targets. This idea is supported by recent evidence that CDK6, one of the LSC17 genes, governs stem cell quiescence in normal human HSCs. Indeed, low levels of CDK6 are associated with dormancy in HSCs and the negative regression coefficient of CDK6 in the LSC17 score is consistent with a link between lower CDK6 levels, a higher score, dormancy, therapy resistance, and poorer outcome. Conversely, higher expression of genes with a positive regression coefficient in the LSC17 score would be predicted to confer increased stemness properties to LSCs, leading to worse outcomes. For example, high expression of GPR56 has recently been shown to enrich for LSC activity in AML.

Of the other genes in the LSC17 score, many do not have a clear function in AML or stem cell biology in humans (i.e., SMIM24, AKR1C3, NGFRAP1, EMP1, CPXM1, KIAA0125, DPYSL3, MMRN1, ARHGAP22, NYNRIN). In the normal hematopoietic hierarchy, CD34+ cell populations are well known to be enriched with stem and progenitor cells including functional HSCs capable of long-term repopulation and self-renewal. In the mouse, SOCS2 deficiency leads to initial enhanced but transient bone marrow reconstitution with expansion of short term HSCs and MPPs, followed by long term HSC exhaustion. Thus, SOCS2 expression may support the maintenance of the LSC and long term HSC pool. In a mouse cell line comprising primitive hematopoietic progenitor cells, LAPTM4B was found to be a target gene of HOXB4, a transcription factor well known to enhance HSC self-renewal. Thus, LAPTM4B expression may also support LSC and HSC maintenance. ZBTB46 was implicated to be required for
establishment of dendritic cells and their committed precursor cells\textsuperscript{58}, and may be a marker of differentiation, consistent with its negative regression coefficient in the LSC17 score calculation. Silencing of \textit{DNMT3B} leads to reduced clonal expansion of human embryonic stem cells\textsuperscript{59}. \textit{DNMT3A} is frequently mutated in AML, and is implicated in clonal expansion of pre-leukemic HSCs\textsuperscript{60}. Since \textit{DNMT3A} and \textit{DNMT3B} may function in a multimeric complex\textsuperscript{61}, increased expression of \textit{DNMT3B} is likely to affect function and may contribute to clonal dominance of LSCs in AML. It is our hope that the genes reported to be associated with LSC function through this study will motivate further investigation of their roles in AML and stem cell biology in mechanism-focused studies.


