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The Polycomb group protein L3MBTL1 represses a smad5-mediated hematopoietic transcriptional program in human pluripotent stem cells

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Epigenetic regulation of key transcriptional programs is a critical mechanism of hematopoietic development and, aberrant epigenetic patterns and mutations frequently occur in hematologic malignancies perturbing hematopoietic stem cells. We demonstrate that the Polycomb protein L3MBTL1, which is monoallelically deleted in 20q- myeloid malignancies, represses the ability of stem cells to drive hematopoietic-specific transcriptional programs by regulating the expression of smad5 and impairing its recruitment to target regulatory regions. Indeed, knock-down of L3MBTL1 promotes the development of hematopoiesis and impairs neural cell fate in human pluripotent stem cells. Furthermore, we found that regulation of smad5 targets by L3MBTL1 also occurs in mature hematopoietic cell populations, affecting erythroid differentiation. Altogether, these findings define an epigenetic mechanism underlying priming of hematopoietic-specific transcriptional networks and provide rationale for development of therapeutic approaches for patients with anemia.

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