Congenital asplenia in mice and humans with mutations in a Pbx/Nkx2-5/p15 module.

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Public Summary: This article describes the molecular pathways in progenitor cells involved in spleen formation in the developing embryos.

Scientific Abstract: The molecular determinants of spleen organogenesis and the etiology of isolated congenital asplenia (ICA), a life-threatening human condition, are unknown. We previously reported that Pbx1 deficiency causes organ growth defects including asplenia. Here, we show that mice with splenic mesenchyme-specific Pbx1 inactivation exhibit hyposplenia. Moreover, the loss of Pbx causes downregulation of Nkx2-5 and derepression of p15Ink4b in spleen mesenchymal progenitors, perturbing the cell cycle. Removal of p15Ink4b in Pbx1 spleen-specific mutants partially rescues spleen growth. By whole-exome sequencing of a multiplex kindred with ICA, we identify a heterozygous missense mutation (P236H) in NKX2-5 showing reduced transactivation in vitro. This study establishes that a Pbx/Nkx2-5/p15 regulatory module is essential for spleen development.