Similar MLL-associated leukemias arising from self-renewing stem cells and short-lived myeloid progenitors

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We have used the hematopoietic system as a model to investigate whether acute myeloid leukemia arises exclusively from self-renewing stem cells or also from short-lived myeloid progenitors. When transduced with a leukemogenic MLL fusion gene, prospectively isolated stem cells and myeloid progenitor populations with granulocyte/macrophage differentiation potential are efficiently immortalized in vitro and result in the rapid onset of acute myeloid leukemia with similar latencies following transplantation in vivo. Regardless of initiating cell, leukemias displayed immunophenotypes and gene expression profiles characteristic of maturation arrest at an identical late stage of myelomonocytic differentiation, putatively a monopotent monocytic progenitor stage. Our findings unequivocally establish the ability of transient repopulating progenitors to initiate myeloid leukemias in response to an MLL oncogene, and support the existence of cancer stem cells that do not necessarily overlap with multipotent stem cells of the tissue of origin.

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