Leukemia in human infants often begins with an in utero chromosomal translocation resulting in an MLL fusion oncogene that is most frequently MLL-AF4 or MLL-AF9. Recent gene expression studies suggest that human infant MLL fusion gene leukemia originates in cells that differ from both infant leukemia without the fusion gene and non-infant childhood leukemia. However, the cell of origin remains undefined.

Mouse models of human MLL leukemia have proven to be informative. An example is the MLL-AF9 knock-in model, in which the fusion gene is expressed at physiologic levels. In this model, hematopoietic stem cells (HSCs) from postnatal murine marrow are readily transformed and leukemias develop that resemble human myeloid postnatal MLL leukemias.

The current study was designed to model human fetal–originated infant MLL leukemia. We compared the leukemia that developed from MLL-AF9 fetal liver cells with that arising from adult marrow cells. Mice were transplanted with fetal MLL-AF9 liver cells (sorted HSCs or unsorted cells) or HSC cells from adult MLL-AF9 bone marrow. We found that the time to development of leukemia was significantly longer after transplantation of fetal liver HSCs than that from marrow HSCs (Figure 1A). Extensive analysis of the leukemias by histopathology, immunohistochemistry, and flow cytometry showed important differences in recipients of adult marrow HSCs (Figure 1B) compared with recipients of fetal liver HSCs (Figure 1C) and unsorted fetal liver cells (Figure 1D). When donor cells were from adult marrow, the leukemia was always myeloid in character with myeloperoxidase (MPO) positivity but negative for CD45R/B220, a phosphatase that appears early in hematopoietic cellular differentiation. However, when fetal liver cells (either sorted HSCs in Figure 1C or unsorted in Figure 1D) were used as donor cells, the leukemia often showed more undifferentiated cells. In some cases fetal liver–derived leukemia cells were positive for CD45R/B220 (Figure 1C-D) and either positive or negative for MPO.

The delay in overt murine MLL leukemia from both fetal liver and bone marrow compared with many human infants with MLL fusion gene leukemia suggests that secondary cooperating events (genetic or epigenetic) may differ between species. The shorter latency of onset of leukemia in bone marrow compared with fetal liver cells suggests that by the time the targeted cells have progressed in maturity to the marrow stem/progenitor stage secondary changes have already developed. Our previous observation that MLL-AF9–transformed fetal liver had limited replating capacity compared with MLL-AF9 marrow is consistent with this hypothesis.

The MLL fusion partner, AF9, may also be important in the timing of the onset of leukemia. Human infant MLL fusion gene leukemia involving an AF9 partner occurs with greater delay than with other partners as another group has observed.

Overall, these results provide further impetus for the study of the cellular origins of human and murine MLL leukemia.

References


Contribution: W.C. conducted cell experiments; M.G.O. studied histopathology and immunohistochemistry; W.H. conducted experiments in mice; and J.K. planned and provided oversight for all of the experiments.

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References

Modeling human infant MLL leukemia in mice: leukemia from fetal liver differs from that originating in postnatal marrow

Weili Chen, M. Gerard O'Sullivan, Wendy Hudson and John Kersey