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EDITORIAL

Age-related differences in leukemia biology and prognosis: the paradigm of *MLL-AF4*-positive acute lymphoblastic leukemia

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Chromosomal rearrangements can fuse the *MLL* (mixed lineage leukemia) gene to any of more than 50 different partner genes in both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia. The prognosis of leukemias with an *MLL* rearrangement varies widely according to the partner gene, the leukemia cell lineage, age of the patient and the treatment administered.[1] The most prevalent *MLL* rearrangement in ALL generates the *MLL-AF4* fusion gene owing to the t(4;11)(q21;q23) chromosomal translocation. *MLL-AF4*-positive ALL has a bimodal age distribution with a major peak incidence in early infancy, and accounts for over 50% of ALL cases in infants less than 6 months of age, 10–20% in older infants, 2% in children and up to 7% in adults.[1–4] In an early study of childhood t(4;11)-positive ALL, we observed that treatment outcome differed by age group with infants having the worst outcome,[5] a finding that has since been confirmed by many other studies including one published in this issue of *Leukemia*.[6–8] Despite recent improvements in the overall treatment outcome for ALL patients, *MLL-AF4* fusion is still associated with a dismal prognosis in infants (especially those younger than 6 months) and adults.[4,6–8] Of note, a difference in outcome by age has also been observed in cases with the t(9;22)(q34;q11.2) and *BCR-ABL* fusion.[9]

The underlying basis of age differences in outcome among leukemias with the same primary genetic abnormality remains unknown, but has been the subject of many investigations that raise several intriguing hypotheses. The very short latency period in infant leukemias suggests that leukemogenic events in these cases occur prenatally, during the early stages of hematopoietic cell development. Two studies reported in this issue of *Leukemia* demonstrate a high prevalence of immature, nonproductive and/or oligoclonal antigen-receptor gene rearrangements in infant ALL with *MLL* fusions.[8,10] Overall, infant leukemias had gene rearrangement patterns that were different from those of leukemias diagnosed in older children (including those with *MLL* fusions),[8,10] suggesting that infant cases originated mostly from a lymphoid progenitor with germline or incompletely rearranged antigen-receptor genes.[8,10] Leukemogenic events during fetal development may also result in distinct *MLL* breakpoints. Thus, Reichel *et al*.[11] found that 13 of 24 infants less than 1 year of age had breakpoints in the telomeric part of the *MLL* breakpoint cluster region, whereas 29 of 34 children and adults had breakpoints in the centromeric part of the *MLL* breakpoint cluster region. They suggested that certain chromosomal areas of the *MLL* breakpoint cluster region are more susceptible to DNA damage at particular stages of embryonic or hematopoietic development.

Despite these advances in knowledge, further elucidation of the biologic features between *MLL*-rearranged leukemias diagnosed at different ages is required. The gene expression profile of primary leukemic cells with *MLL* rearrangements fits with that of cells at a very early stage of differentiation, but whether this pattern differs between cases diagnosed in infants or in older age groups remains unclear.[12] Also unclear is whether the molecular pathways needed for lymphoid cell differentiation are altered in cases with an *MLL* rearrangement and, if so, whether these alterations differ between the leukemias of infants and older children. These issues can now be addressed by novel methods for large-scale screening of molecular events that might be involved in leukemia pathogenesis (Mullighan *et al., Blood* 2006; 108: 68A). Although *MLL*-rearranged leukemias are thought to arise from the oncogenic subversion of undifferentiated hematopoietic cells, it was recently shown that that enforced *MLL-AF9* expression in discrete populations of more differentiated hematopoietic progenitors can also initiate leukemia.[13,14] Importantly, the leukemic cells in these two studies differed in immunophenotype and in the aberrant expression of 'stem-cell genes.' Hence, the characteristics of leukemic cells with the same primary genetic abnormality may vary according to the developmental stage of the target cells. If these findings extend to *MLL-AF4*-induced transformation, one could hypothesize that such leukemias arise from different target cells in infants compared with older children, leading to different responses to chemotherapy.

Novel therapies are urgently needed for infant leukemias with *MLL* rearrangements. Such patients might well be among the first candidates for cellular therapies that could enhance the efficacy of hematopoietic stem cell transplantation or even replace it.[15–17] Besides FLT3 inhibitors, options for molecularly targeted therapies for *MLL* leukemias are currently limited.[18] Hence, it is essential to elucidate the molecular pathways subverted by the gene fusion and determine their relative impact on disease aggressiveness and drug resistance, so that promising candidate targets can be identified. Finally, there is increasing evidence that the bone marrow microenvironment can protect leukemic cells from the cytotoxic effects of chemotherapy.[19] If bone marrow mesenchymal cells are found to play a major role in the different treatment responses of *MLL*-rearranged leukemias by age group, it may be possible to manipulate the interaction between the leukemic cells and their microenvironment to therapeutic advantage.

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References

1 Pui C-H, Relling MV, Downing JR. Acute lymphoblastic leukemia. *N Eng J Med* 2004; **350**: 1535–1548.
2 Pui C-H, Ribeiro RC, Campana D, Raimondi SC, Hancock ML, Behm FG *et al.* Prognostic factors in the acute lymphoid and myeloid leukemias of infants. *Leukemia* 1996; **10**: 952–956.
3 Pui C-H, Kane JR, Crist WM. Biology and treatment of infant leukemias. *Leukemia* 1995; **9**: 762–769.
4 Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M *et al.* Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): Analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/ Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*, Blood First Edition Paper, pre-published online December 14, 2006; doi:10.1182/blood-2006-10-051912 (abstract).
5 Pui C-H, Frankel LS, Carroll AJ, Raimondi SC, Shuster JJ, Head DR *et al.* Clinical characteristics and treatment outcome of childhood acute lymphoblastic leukemia with the t(4;11)(q21;q23): A collaborative study of 40 cases. *Blood* 1991; **77**: 440–447.
6 Pui C-H, Gaynon PS, Boyett JM, Chessells JM, Baruchel A, Kamps W *et al.* Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. *Lancet* 2002; **359**: 1909–1915.
7 Pui C-H, Chessells JM, Camitta B, Baruchel A, Biondi A, Boyett JM *et al.* Clinical heterogeneity in childhood acute lymphoblastic leukemia with 11q23 rearrangements. *Leukemia* 2003; **17**: 700–706.
8 Mann G, Cazzaniga G, van der Velden VHJ, Flohr T, Csinady E, Paganin M *et al.* Acute lymphoblastic leukemia with t(4;11) in children one year and older: the 'big sister' of the infant disease? *Leukemia*, (in press).
9 Pui C-H, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med* 2006; **354**: 166–178.
10 Jansen MWJC, Corral L, van der Velden VHJ, Panzer-Grümayer R, Schrappe M, Schrauder A *et al.* Immunobiological diversity in infant acute lymphoblastic leukemia is related to the occurrence and type of MLL gene rearrangement. *Leukemia*. (in press).
11 Reichel M, Gillert E, Angermüller S, Hensel JP, Heidel F, Lode M *et al.* Biased distribution of chromosomal breakpoints involving the MLL gene in infants versus children and adults with t(4;11) ALL. *Oncogene* 2001; **20**: 2900–2907.
12 Armstrong SA, Staunton JE, Silverman LB, Pieters R, den Boer ML, Minden MD *et al.* MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. *Nat Genetics* 2002; **30**: 41–47.
13 Krivtsov AV, Twomey D, Feng Z, Stubbs MC, Wang Y, Faber J *et al.* Transformation from committed progenitor to leukaemia stem cell initiated by MLL-AF9. *Nature* 2006; **442**: 818–822.
14 Somervaille TCP, Cleary ML. Identification and characterization of leukemia stem cells in murine MLL-AF9 acute myeloid leukemia. *Cancer Cell* 2006; **10**: 257–268.
15 Imai C, Mihara K, Andreansky M, Nicholson IC, Pui C-H, Geiger TG *et al.* Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. *Leukemia* 2004; **18**: 676–684.
16 Imai C, Iwamoto S, Campana D. Genetic modification of primary natural killer cells overcomes inhibitory signals and induces specific killing of leukemic cells. *Blood* 2005; **106**: 376–383.
17 Triplett B, Handgretinger R, Pui C-H, Leung W. KIR-incompatible hematopoietic-cell transplantation for poor prognosis infant acute lymphoblastic leukemia. *Blood* 2006; **107**: 1238–1239.
18 Pui C-H, Jeha S. New therapeutic strategies for the treatment of acute lymphoblastic leukemia. *Nat Rev Drug Discov*, (in press).
19 Iwamoto S, Mihara K, Downing JR, Pui C-H, Campana D. Mesenchymal cells determine the response of acute lymphoblastic leukemia cells to L-asparaginase. *J Clin Invest* (in press).