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Mini Review

Clonal Origin Investigation in Pre-Leukemia Condition

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ABSTRACT

Whatever the mechanisms governing chromosomal changes in utero, it is evident that for most cases of childhood leukemia, the crucial etiologic bottleneck is the postnatal 'promotional' events or exposures that precipitate the secondary genetic changes, including TEL deletion. Uncovering the nature of these exposures is the objective of major case/control epidemiologic studies in some countries. Although no consensus view has yet emerged, there is now a body of evidence implicating infections in childhood Acute Lymphoblastic Leukemia (ALL). In other words, the infection can be leading at immune response deregulation in a pre-leukemic child minimally. After secondary mutation(s), the children go to changing into ALL which leads to clonal expansion ultimately.

Keywords: Acute Lymphoblastic Leukemia; Hematopoietic Stem Cell (HSC); Single Nucleotide Polymorphism arrays (SNP arrays)

INTRODUCTION

Genomic sequence analysis of ETV6/RUNX1 (E/R) and other fusion genes suggests that the predominant mechanism of chromosome translocation is double-stranded DNA breakage followed by normal but error-prone repair by non-homologous recombination [1]. However, this begs the question of what causes the initial DNA damage. For MLL gene fusions, there are some experimental genetic and epidemiologic, in evidence that transplacental chemical carcinogenesis may be involved [2]. However, what might be responsible for the relatively high frequency (1%) of E/R fusion gene generation in normal fetal hematopoiesis? Presumably, nonfunctional fusion genes (in non-stem cells) occur at an even higher rate. One possibility is that these are 'normal' developmental errors of DNA maintenance reflecting the complexity of embryo and fetal tissue engineering in which cell death, DNA damage and oxidative stress are ubiquitous. The initiation of other pediatric cancers has similarly been ascribed to developmental accidents [3]. Even if E/R fusion is, in effect, a spontaneous error, the risk of this event occurring may be modified by other factors. There is dietary and genetic evidence that folate has an impact on the risk of infant and childhood leukemia, and this could well be operative during pregnancy in utero, influencing the likelihood of chromosomal breaks.

DISCUSSION

Recently, some researchers have used a similar experimental approach but focused on identifying the early or pre leukemic effects of E/R expression [4]. E/R fusion gene found to inhibit B-cell differentiation that leading to an accumulation of early B-cell progenitors and a corresponding decrease in mature B-cells. Detailed examination of this partial differentiation arrest reveals effects from the very earliest pro-B cells in the mouse. The size of the Hematopoietic Stem Cell (HSC) compartment was larger in the animals and also continued to increase with time. This raises the possibility that this very primitive compartment may be responsible for the maintenance in the model and/or in addition to developing a pre-leukemic clone minimally. Despite some increase in myeloid progenitor activity, no block to myeloid differentiation was observed. Wholly, the pre leukemic phenotype displays many of the features seen in the common precursor B-cell ALL. Therefore, there are some points as follows:

- A selective differentiation block in the B-cell pathway
- In both cases the block is at an early progenitor cell level (although differences in murine and human B-lymphoid development complicate direct comparison
- Differentiation block is incomplete, resulting in the presence of mature B cells in both cases

B-cell-specific results have been reported as well who have analysed the effects of enforced E/R expression in fatal liver-derived progenitors [5]. They observed enhanced self-renewal capacity of B-cell progenitors evidenced by increased of efficiency in colony-forming assays *in vitro* and an increased repopulating activity on competitive reconstitution assays *in vivo*. Despite the

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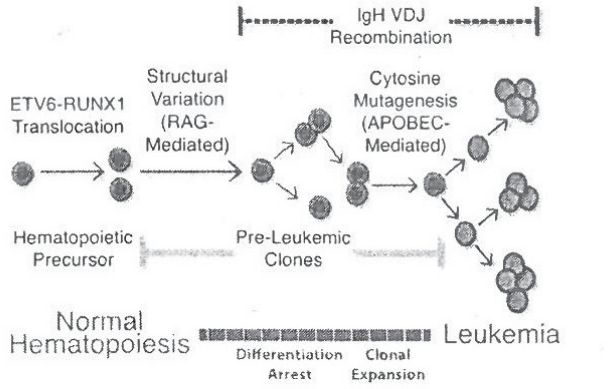
similarities, some detailed aspects of these two murine models (e.g. differentiation block at the B precursor stage) appear different. While this will require further investigation, it seems likely that the use of developmentally distinct stem cell populations in these two studies may be accountable for any differences observed partially. Collectively, these studies endorse the view that E/R fusion gene can transform early B-lineage progenitors and initiate a pre leukaemia condition [6-8].

Figure 1: E/R fusion gene occur in utero and in the following it, pre-leukemic evolution can be as the more genomic variation. Initially, we have a single cell genomic and after the mutation(s), go to be continuing in the most developed clones gradually.

In fact, a recent investigation successfully identified a pre leukemic E/R-positive clone in the healthy twin of a patient diagnosed with E/R-positive ALL and also demonstrated that expression of E/R alone can mimic the pre leukemic clone but not induce leukemia in an *in vivo* model. Taken together, these data indicate that E/R positive leukemia is generated through a multi-step mechanism, and that accumulation of additional genetic changes is necessary for the development of overt leukemia. Thus, to understand fully the genetic evolution of this disorder, identification of the complete spectrum of genetic changes that accompany the E/R fusion gene is necessary. Moreover, critical genetic aberration insights may be gained from studying the correlation pattern of the different copy number changes.

Proper function of TEL gene is crucial for the establishment of hematopoiesis of all lineages in the bone marrow. The TEL defect may reveal within the first week of postnatal life [9-10]. The first cells produced, embryonic (or primitive) erythrocytes arise within the blood islands of the yolk sac at embryonic day 14. Later hematopoiesis shifts to the fetal liver and to spleen where adult red cells, as well as cells of other lineages appear- the process of granulo-, mono-lymph and mega karyocytopoiesis starts. The development ends in Bone Marrow (BM) and in lymphatic nodes. The regulation of the processes takes place at multiple levels to insure proper blood cells in proliferation, differentiation into maturation cells, viz to progenitors and precursor cells. One of them is operation of cytokines, their receptors and the transcriptional factors, affecting the correct genes expression. So, initiation of angiogenesis in the yolk sac, maintenance of life cells, their



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proper movement from fetal liver and spleen to bone marrow and processes, which work there, are controlled by TEL gene. However, TEL is not intrinsically required for the growth or differentiation of hematopoietic cells [11-14]. In spite of these facts, the disorder in adhesion and colonization of TEL/HSCs (or progenitors) in microenvironment of bone marrow may reflect the subsequent appearance and circulation in the peripheral blood of premature leukemic progenitors which proliferate excessively. This constitutes a very important element in E/R pathogenesis because the TEL loss impairs the progenitor's capacity for effective hematopoiesis in BM.

These results parallel the impact of AML1-ETO on early myeloid cell self-renewal and differentiation Thus, while expressions of both AML1/ETO and E/R within the stem cell compartment appear to inhibit differentiation, the activities of the Thus, while expressions of both AML1/ETO and E/R within the stem cell compartment appear to inhibit differentiation, the activities of the two molecules appear to be broadly selective for myeloid and B-lymphoid lineages, respectively, and are consistent with the lineage selectivity seen in t(8;21) and t(12;21)- associated leukemias. The data argue that this striking feature of fusion genes arises not because of a restrictive cell of origin of chromosome translocation itself, but rather as a consequence of cell context- dependent function of the encoded chimeric proteins. It is therefore important to understand how these different chimeric fusions involving AML1-regulated transcription function at the molecular level. One possibility supported by the available molecular evidence is that E/R functions to interfere with normal AML1 activity. While it has been appreciated for some time that AML1 is expressed in most blood cell types including B-lymphocytes, most attention has focused on its role in the specification of HSC, during ontogeny. Most recently its role in adult hematopoiesis has been addressed using a conditional knockout approach [15]. These studies reveal that AML1 function is not required for the maintenance and self-renewal of HSC, but is required for B-lymphoid differentiation. In addition, loss of AML1 activity results in an increase in multi-potent progenitors. These effects are similar to those seen as a result of enforced expression of E/R and are therefore consistent with the notion that E/R functions as an antagonist of endogenous AML1 activity.

High resolution Single Nucleotide Polymorphism arrays (SNP arrays) and Comparative Genomic Hybridization arrays (CGH arrays) have provided powerful tools for identifying genetic changes in childhood leukemia. Recent studies of childhood ALL using such genome-wide techniques have revealed the presence of several submicroscopic genetic changes [16-21]. Importantly, these studies have shown that genes involved in the regulation of B-cell' development, such as PAX5 and EBF I, are targeted by deletions in around 40% of B-lineage ALL.

In contrast to AML1 transiently expressed E/R fusion proteins generally repress the activities of reporter constructs driven by regulatory regions derived from hematopoietic-specific genes and/or antagonize their AML1-dependent activation [22-25]. Work from several laboratories has shown that the transcriptional activities of E/R involve recruitment of nuclear receptor co-repressor/HDAC complexes to the TEL moiety of the fusion gene similar findings have been reported for other AML1 fused genes.

CONCLUSION

The t(12;21) is the most frequent chromosomal aberration in childhood ALL being present in approximately 20%-25% of all newly diagnosed children [26-27]. Patients with the E/R fusion gene form relatively homogenous group of ALL. These children are diagnosed mostly in the pre-school age with B cell precursor immunophenotype of leukemic blasts and they have favorable treatment outcome. Studies on identical twins and triplets with concordant ALL and retrospective scrutiny of neonatal blood spots have provided evidence that fusion of E/R often arises prenatally, possibly as the first or initiating event [28-29]. The "pre-leukemic" clone with E/R fused gene can persist post natally for extended periods and another post-natal genetic event is required for overt leukemia. It has been suggested that some late relapses of E/R positive ALL might be in fact "new leukemias" arising from the same "pre-leukemic" E/R positive clone but triggered by a new post-natal hit possibly by deletion of the non-translocated TEL allele which can be an important potential parameter in next investigations [30-31].

REFERENCES

1. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer. 2003;3(9):639-649.
2. Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC, et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res. 2001;61(6):2542-2546.
3. Maris JM, Denny CT. Focus on embryonal malignancies. Cancer cell. 2002;2(6):447-450.
4. Tsuzuki S, Seto M, Greaves M, Enver T. Modeling first- hit functions of the t (12;21) TEL/AML_1 translocation in mice. Proc Natl Acad Sci.2004;101(22):8443-8448.
5. Morrow M, Horton S, Kioussis D, Brady HJ, Williams O. TEL-AML1 promotes development of specific hematopoietic lineages consistent with preleukemic activity. Blood. 2004;103(10):3890-3896.
6. Gu J, Reynolds A, Fang L, DeGraffenreid C, Sterns K, Patel KP, et al. Coexistence of iAMP21 and ETV6-RUNX1 fusion in an adolescent with B cell acute lymphoblastic leukemia: literature review of six additional cases. Mol Cytogenet. 2016;9(1):1-10.
7. Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. J Clin Oncol. 2017;35(9):975-983.
8. Sood R, Kamikubo Y, Liu P. Role of RUNX1 in hematological malignancies. Blood. 2017;129(15):2070-2082.
9. Wang LC, Swat W, Fujiwara Y, Davidson L, Visvader J, Kuo F, et al. The TEL/ETV6 gene is required specifically for hematopoiesis in the bone marrow. Genes Dev. 1998;12(15):2392-2402.
10. Wiemels JL, Greaves M. Structure and possible mechanisms of TEL/AML_1 gene fusion in childhood ALL. Cancer Res, 1999; 59:4075-4082.
11. Golub TR, Goga A, Barker GF, Afar DE, McLaughlin J, Bohlander SK, et al. Oligomerization of the ABL tyrosine kinase by the Ets protein TEL in human leukemia. Mol Cell Biol. 1996;16(8):4107-4116.
12. Graves BJ, Petersen JM. Specificity within the Ets family of transcription factors. Adv Cancer Res. 1998; 75:1-57.
13. Wasylyk B, Hahn SL, Giovane A. The Ets family of transcription factors. Eur J Biochem.1994;211(2):7-18.
14. Yergeau DA, Hetherington CJ, Wang Q, Zhang P, Sharpe AH, Binder M, et al. Embryonic lethality and impairment of haematopoiesis in mice heterozygous for an AML1-ETO fusion gene. Nat Genet. 1997;15(3):303-306.
15. Ichikawa M, Asai T, Saito T, Yamamoto G, Seo S, Yamazaki I, et al. AML_1 is required for megakaryocytic maturation and lymphocytic differentiation, but not for maintenance of hematopoietic stem cells in adult hematopoiesis Nat Med. 2004;10(3):299-304.
16. Penther D, Preudhomme C, Talmant P, Roumier C, Godon A, Mechinaud F, et al. Amplification of AML1 gene is present in childhood acute lymphoblastic leukemia but not in adult, and is not associated with AML1 gene mutation. Leukemia. 2002;16(6):1131-1134.
17. Nucifora G, Rowley JD. AML_1 and the t (8;21) and t (3:21) translocations in acute and chronic myeloid leukemia. Blood. 1995;86(1):1-14.
18. Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan Smith E, Dalton JD, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007;446(7137):758-764.
19. Parker H, An Q, Barber K, Case M, Davies T, Konn Z, et al. The complex genomic profile of ETV6-RUNX1 positive acute lymphoblastic leukemia highlights a recurrent deletion of TBL1XR1. Genes Chromosom Cancer. 2008;47(12):1118-1125.
20. Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature. 2008;453(7191):110-114.
21. Tsuzuki S, Karnan S, Horibe K, Matsumoto K, Kato K, Inukai T, et al. Genetic abnormalities involved in t(12;21) TEL-AML1 acute lymphoblastic leukemia: Analysis by means of array-based comparative genomic hybridization. Cancer Sci. 2007;98(5):698-706.
22. Hiebert SW, Sun W, Davis JN, Golub T, Shurtleff S, Buijs A, et al. The t(12;21) translocation converts AML-1B from an activator to a repressor of transcription. Mol Cell Biol. 1996;16(4):1349-1355.
23. Romana SP, Mauchauffe M, Le Coniat M, Chumakov I, Le Paslier D, Berger R, et al. The t(12;21) of ALL results in TEL/AML_1 gene fusion. Blood. 1995;85(12):3662-3670.
24. Fenrick R, Amann JM, Lutterbach B, Wang L, Westendorf JJ, Downing JR, et al. Both TEL and AML-1 contribute repression domains to the t (12;21) fusion protein. Mol Cell Biol. 1999;19(10):6566-6574.
25. Lilljebjörn H, Soneson C, Andersson A, Heldrup J, Behrendtz M, Kawamata N, et al. The correlation pattern of acquired copy number changes in 164 ETV6/RUNX1-positive childhood acute lymphoblastic leukemias. Hum Mol Genet. 2010;19(16):3150-3158.
26. Kaindl U, Morak M, Portsmouth C, Mecklenbräuker A, Kauer M, Zeginigg M, et al. Blocking ETV6/RUNX1-induced MDM2 overexpression by Nutlin-3 reactivates p53 signaling in childhood leukemia. Leukemia. 2014;28(3):600-608.
27. Halalsheh H, Abuirmeileh N, Rihani R, Bazzeh F, Zaru L, Madanat F. Outcome of childhood acute lymphoblastic leukemia in Jordan. Pediatr Blood Cancer. 2011;57(3):385-391.
28. Horsley SW, Colman S, McKinley M, Bateman CM, Jenney M, Chaplin T, et al. Genetic lesions in a preleukemic aplasia phase in a child with acute lymphoblastic leukemia. Genes Chromosom Cancer. 2008;47(4):333-340.
29. Wiemels JL, Cazzaniga G, Daniotti M, Eden OB, Addison GM, Masera G, et al. Prenatal origin of acute lymphoblastic leukaemia in children. Lancet. 1999;354(9189):1499-1503.
30. Gawad C, Koh W, Quake SR. Dissecting the clonal origins of childhood acute lymphoblastic leukemia by single-cell genomics. Proc Natl Acad Sci. 2014;111(50):17947-17952.
31. Woo JS, Alberti MO, Tirado CA. Childhood B-acute lymphoblastic leukemia: a genetic update. Exp Hematol Oncol. 2014;3(1):1-4.