

## Editorial

# Pediatric Leukemia and Hematopoietic Microenvironment: Is Spontaneous Remission Due to Intrinsic or Extrinsic Mechanism?

**Jun Miyauchi\***

Department of Pathology &amp; Laboratory Medicine, Tokyo Dental College Ichikawa General Hospital, Japan

**\*Corresponding author:** Jun Miyauchi, Department of Pathology & Laboratory Medicine, Tokyo Dental College Ichikawa General Hospital, 5-11-13 Sugano, Ichikawa, Chiba-ken 272-8513, Japan**Received:** January 21, 2015; **Accepted:** February 13, 2015; **Published:** February 16, 2015**Keywords**

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Cancers are thought to evolve through multiple steps by accumulating mutations in the genes associated with cell growth/death control. Research in the field of pediatric cancer development has the advantage that these multi-step genetic abnormalities are confined to a relatively narrow chronological window. Acquired somatic mutations in cancers can be markers of each neoplastic cell clone. Using rearrangement of the *MLL* gene at 11q23 in infantile acute leukemias as clonal markers, pairs of identical twins with concordant leukemia were investigated and identical rearrangements were detected in the leukemic blasts in each twin pair [1], indicating that the rearrangements occurred in utero, that the leukemic progenitors with the rearrangement in one fetus passed through anastomosing blood vessels in the placenta and transferred to the other fetal twin (intra-placental “metastasis”), and that the same type of infantile leukemia developed from the cells with an identical *MLL* gene rearrangement in both twins later in their postnatal lives. In another study, a pair of twin patients with acute lymphoblastic leukemia, whose diagnoses were made at 5 and 14 years of age, was investigated and an identical *TEL-AML1* rearrangement was detected in the blasts of both of them, indicating the prenatal initiation of the leukemia but variable latency before onset even in older children [2]. Hence, it has been shown that a large proportion of pediatric leukemias have their origin in prenatal hematopoietic cells.

In mammals as well as non-mammalian vertebrates, hematopoiesis occurs in several waves in different organs in ontogeny [3]. The first wave of hematopoiesis (“primitive erythropoiesis”) begins in the extra-embryonic yolk sac. Various types of hematopoietic precursor produced later in the yolk sac, allantois, and aorta-gonad-mesonephros region migrate to the liver, where the second wave of hematopoiesis (adult-type or “definitive hematopoiesis”) begins and continues until birth. Adult-type hematopoiesis also occurs in the bone marrow in the late stage of fetal life and the bone marrow finally

becomes the major site of hematopoiesis throughout the postnatal life. Although leukemias generally arise in the bone marrow, the microenvironments of prenatal hematopoietic organs other than the bone marrow could play an important role in the development of certain pediatric leukemias, given that they may be of prenatal origin. However, the exact site of leukemogenesis in pediatric leukemias of prenatal origin remains largely undetermined. One exception may be transient leukemia (TL) in patients with Down Syndrome (DS), for which abundant data have suggested that the disease arises in the fetal liver.

TL is a myeloid neoplasm that occurs, in most cases, in neonates with DS or, on rare occasions, in non-DS infants with mosaic trisomy 21 [4,5]. In 4-10% of neonates with DS, abnormal blasts indistinguishable from acute megakaryoblastic leukemia (AMKL) blasts appear in the blood, but usually spontaneously disappear within the first 3 to 6 months of life. Because of this unique nature, a variety of names have been given to this disorder, including TL, transient abnormal myelopoiesis (TAM), and transient myeloproliferative disorder (TMD). The blasts in TL are monoclonal in origin in most cases, and TL is now considered to be a very special form of preleukemia or leukemia. Following the spontaneous remission of TL, AMKL develops in 20-30% of patients within the first 4 years of life. Somatic mutations affecting the *GATA1* gene, which encodes one member of the GATA family of zinc-finger transcription factors, can be detected in exclusively and nearly all cases of TL and AMKL in DS patients [6]. It is considered that the *GATA1* mutations in association with trisomy 21, both of which occur in utero, play an essential role in the prenatal leukemogenesis of TL and that AMKL develops from latent clones of blasts with *GATA1* mutations by acquiring additional postnatal mutations [4,5].

Although TL is usually diagnosed in neonates/infants, it has occasionally been found in stillborns with DS. In these cases, TL blasts and atypical megakaryocytes were found to be present in certain fetal organs, particularly in large numbers in the liver, with hepatic fibrosis also being present in some cases. Hepatic fibrosis has also often been found in fatal cases of TL in live-born patients [7]. Myelofibrosis is a common complication of AMKL and is thought to be caused by cytokines, including transforming growth factor  $\beta$ , that are produced by leukemic cells and stimulate fibroblasts to induce fibrosis. Since TL blasts have the features of megakaryoblasts, it is thought that hepatic fibrosis in TL is caused by cytokines produced by TL blasts in the liver in a similar manner to that of myelofibrosis in AMKL. Hence, these autopsy findings suggest that the fetal liver is a major site of leukemogenesis in TL.

It remains unknown why TL spontaneously resolves, but two major hypotheses have been proposed based on previous data

suggesting that TL originates from prenatal hematopoietic progenitors and arises in the fetal liver. Firstly, since the major organ of fetal hematopoiesis gradually shifts from the liver to the bone marrow at the late stage of prenatal life and hepatic hematopoiesis ceases shortly after birth, this may result in loss of the microenvironment necessary for the growth of TL blasts. It is also possible that unknown factors which stop the proliferation of TL blasts are present in the postnatal bone marrow. These scenarios are called the environmental or “extrinsic” theory. Secondly, there are data indicating that prenatal hematopoiesis is controlled, at least in part, by a genetic mechanism. A good example of the developmental switch is seen in hemoglobin synthesis: several types of hemoglobin, a tetramer consisting of 2 pairs of globin subunits ( $\zeta$ ,  $\alpha$ ,  $\epsilon$ ,  $\gamma$ ,  $\delta$ ,  $\beta$ ), are successively produced from the embryonal (HbE;  $\zeta_2\epsilon_2$ ) through fetal (HbF;  $\alpha_2\gamma_2$ ) to adult (HbA;  $\alpha_2\beta_2$ ) type in accordance with the hematopoietic site transition, and these hemoglobin subtype switches are mainly controlled by a genetic mechanism and not determined by the site of erythropoiesis. If TL blasts are derived from prenatal hematopoietic progenitors, they may already be destined to stop proliferating and/or disappear at an appropriate time according to the preset genetic program, even if they are neoplastic cells (the genetic or “intrinsic” theory).

Spontaneous resolution is also a well-known phenomenon in neuroblastoma, another pediatric cancer that is thought to be of prenatal origin [8]. Infantile neuroblastomas can metastasize to distant organs, leading to the death of some patients, as in the case of fatal aggressive neuroblastomas in older children, but usually regress spontaneously and the majority of patients show a favorable outcome even after distant metastasis has occurred. The distinct biology of neuroblastomas between infants and older children appears to be comparable to the relationship between TL in infants and lethal AMKL in older children with DS. Although it is currently unclear which of intrinsic or extrinsic factors, or both of them equally, play the primary role in the spontaneous resolution of infantile cancers, it

seems plausible that common environmental as well as genetic factors that physiologically influence the functions of normal counterparts of these different cell types during transition from pre- to postnatal life also influence the biological behavior of infantile cancers and are involved in their spontaneous resolution. The spontaneous cancer remission mechanism would be an important research target to deepen insight into the biological nature of these special types of pediatric cancer and develop novel therapeutic strategies for cancer patients.

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