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Leukemogenesis in Down Syndrome

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1. Introduction

Constitutional trisomy 21 or Down syndrome (DS) is the most common human genetic aneuploidy caused by the presence of all or part of an extra 21 chromosome. The incidence of DS is estimated at 1 per 700 births (Malinge et al., 2009) and is the most common genetic factor predisposing to childhood leukemia. People with DS present several clinical phenotypes, including cognitive impairment, craniofacial dysmorphy, gastrointestinal tract abnormalities, congenital heart defects, endocrine abnormalities, neuropathology leading to dementia and immunological defects. Concerning the hematopoietic system, children with DS frequently show abnormalities in platelet counts, macrocytosis and an increased prevalence of leukemia (Lange, 2000; Roizen & Amarose, 1993).

2. Manifestations of leukemia in Down Syndrome

The high frequency of leukemia in children with DS suggests that trisomy 21 is involved directly and functionally to the malignant transformation of hematopoietic cells. However, DS is not a classic genomic instability syndrome, since the overall risk of developing cancer, in particular solid tumors, including neuroblastoma and Wilms tumor, is lower in these people (Hasle, 2001; Malinge et al., 2009).

Newborns with DS have a risk 10 to 20 times higher of developing acute leukemia (AL) when compared with the incidence rates of leukemia in the general child population (Hitzler et al., 2003). The AL in children with DS presents an intriguing relationship between the age at onset of disease and the subtype of leukemia cell. DS children older than 4 years have predominantly acute lymphoblastic leukemia (ALL), whose incidence is approximately 20 times higher than in the general population. However the DS patients aged under 3 years are more likely to develop acute megakaryoblastic leukemia (AMKL), with an incidence 500 times higher than in children without DS (Hitzler et al., 2003; Issacs, 2003; Lange, 2000; Malinge et al., 2009).

The condition of patients with DS awakens, therefore, a special interest in studies on leukemogenesis not only by the high prevalence of AMKL, usually rare in the general

pediatric population, but also by another form of clonal proliferation called transient myeloproliferative disorder (TMD) which affects between 5 and 10% of newborns with DS. The TMD is a clonal disease characterized by accumulation of immature megakaryoblasts in fetal liver and peripheral blood, a picture indistinguishable from AL (Hitzler et al., 2003; Malinge et al., 2009; Pine et al., 2007; Rainis et al., 2003; Zipursky, 2003). It is unclear whether all AMKLs are preceded by TMD, since several TMD cases are underdiagnosed. One study suggests that the prognosis for AMKLs preceded by TMD is better than de novo AMKL (Klusmann et al., 2008).

In contrast to AMKL, TMD usually evolves to spontaneous remission within the first three months of life and therefore is considered a pre-leukemic syndrome. This spontaneous remission can vary from 59 to 64% (Kanezaki et al., 2010; Massey et al., 2006). However, approximately 20% of children diagnosed with TMD will develop AMKL after 2 to 3 years of TMD spontaneous remission, which does not regress without chemotherapy (Malinge et al., 2009).

The biological mechanism of TMD spontaneous remission is not clear. Holt et al. (2002) showed that telomerase activity was decreased at the beginning of congenital leukemia and suggested that this deficiency could explain the spontaneous regression. Furthermore, the factors underlying the transformation of the TMD "benign" status for "evil" in AMKL are unknown (Izraeli et al., 2007; Malkin et al., 2000; Rainis et al., 2003).

In rare cases, the TMD is fatal due to poor prognostic factors such as liver fibrosis or liver dysfunction, manifested by jaundice, bleeding diathesis, fetal hydrops, cardiopulmonary failure, high white blood cell (WBC) and failure of spontaneous remission within the first 3 months (Malinge et al., 2009; Massey et al., 2006; Pine et al., 2007; Shimizu et al., 2008). Most of these variants were found in all reports. However, the risk factors for the progression to AMKL remain unclear (Kanezaki et al., 2010). Three studies in the United States, Japan and Europe reported the natural course of TMD in 264 children with DS. These studies confirmed the transient course of this disease that usually resolved spontaneously within the first 3 months of life. However, these studies revealed that the disease is not benign, since early deaths have been reported in 15 to 20% of the cases (Klusmann et al., 2008; Massey et al., 2006; Muramatsu et al., 2008). Kanezaki et al. (2010) also reported early death in 24.2% of the DS patients with TMD.

3. Mutations in *GATA1 g*ene and leukemogenesis in Down Syndrome

The *GATA1* (globin transcription factor 1) gene located on the X chromosome in the region Xp11.23 encodes the GATA binding protein 1 (GATA-1) belonging to the family of transcription factors with zinc finger structural motifs for DNA binding. GATA-1 is essential for survival of erythroid progenitor cells and for proper maturation of megakaryocytes, so in this way this protein has an essential rule in the erythrocytic and megakaryocytic differentiation (Wechsler et al., 2002; Yu et al., 2002).

The *GATA1* gene is 6.857 kb long with 6 exons and an open reading frame of 1,239 nucleotides starting in exon 2. The protein GATA-1 consists of 413 amino acids and 42.75 kDa with an N-terminal transactivation domain and two zinc finger domains. These two fingers are functionally distinct and cooperate to achieve specific, stable DNA binding. The first finger (NF) is necessary only for full specificity and stability of binding, whereas the second one (CF) is required for DNA binding (Martin & Orkin, 1990, Shimizu et al., 2008).

GATA1 mutations prevent the synthesis of heavy chain of GATA-1 (translated from the first ATG codon of exon 2) but not the synthesis of truncated protein, with 330 amino acids and 34.23 kDa called GATA-1s. GATA-1s is also expressed starting at codon 84 in exon 3 in consequence of an alternative translation initiation site or alternative splicing that eliminates exon 2. This truncated protein lacks the transactivation domain, but retains both zinc finger domains, as shown in figure 1. The function of GATA-1s is still quite unclear. Several experiments suggest that GATA-1s helps the megakaryocytic and erythrocyte differentiation (Weiss et al., 1997). However, studies of in vivo gene rescue indicated that only the endogenous GATA-1s expression would not be enough to restore definitive erythropoiesis unless this gene is hyper expressed (Shimizu et al., 2001). Even being detected both forms of GATA-1 in mouse embryonic tissue, their relative proportions vary during development, suggesting that the transcriptional activity of GATA1 can be modulated by the relative rate of the two forms (Calligaris et al., 1995).

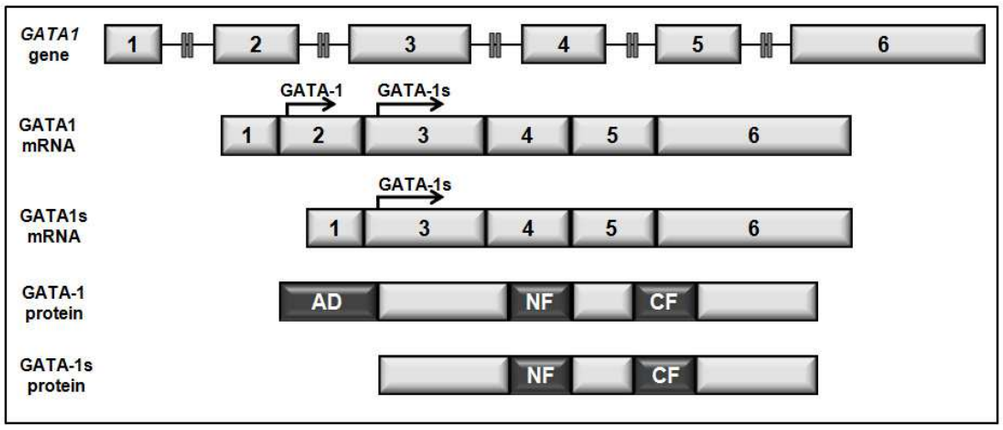


Fig. 1. Models for the expression of GATA-1 isoforms. The GATA-1 protein is translated from the GATA1 mRNA, whereas the GATA-1s protein can be translated either from the GATA-1 mRNA or from the alternative spliced GATA1s mRNA lacking exon 2.

The analysis of megakaryocyte-specific knockdown of *GATA1* in vivo has revealed a critical role for this factor in megakaryocytic development. Reduced expression (or complete absence) of GATA-1 in megakaryocytes leads to increased proliferation and deficient maturation as well as a reduced number of circulating platelets (Vyas et al., 1999; Wechsler et al., 2002). Mice harboring a heterozygous *GATA1* knockdown allele frequently develop erythroblastic leukemia (Shimizu et al., 2004).

Mutations in *GATA1* gene are described in TMD as well as in AMKL, and occur mainly in the 5' end of the gene in exon 2, and less commonly in exon 3 (Xu et al., 2003). Mutations as insertions, duplications, deletions and point mutations, are responsible to abrogate splicing of exon 2 or to generate a stop codon prior to the alternative translational start codon at position 84. According to Rainis et al. (2003), the most frequent mutations in TMD and AMKL were deletions and insertions in exon 2 of *GATA1* corresponding to 65, 7% followed by 25.7% of point mutations and the remaining 8.6% is due to failure to identify the mutation.

Mutations in *GATA1* are frequently associated with TMD and occur in utero (Taub et al., 2004). The true frequency of TMD is unknown because it is likely that a significant proportion of these patients are not routinely diagnosed (Malinge et al., 2009; Rainis et al., 2003). Ongoing studies in Europe and North America combining screening for *GATA1*

mutations and examination of neonatal blood smears will present a more precise picture of the true incidence of TMD (Malinge et al., 2009). Pine et al. (2007) examined DNA from Guthrie cards of 585 DS infants, and reported that *GATA1* mutations were detected in 3.8% of them. However, *GATA1* mutations may have been missed in patients with minor preleukemic clones, subclonal mutations, low numbers of cells on Guthrie cards, or extramedullary TMD without circulating blasts. In addition, a significant higher frequency of *GATA1* mutations in male newborns was observed. Malinge et al. (2009) presumed that it is likely that the frequency of TMD is not higher than 5% of DS newborns.

Studies have shown that *GATA1* mutations in TMD activate the proliferation of progenitor cells required to promote AMKL, featuring a multi-step disease. This process is likely to involve the participation of unidentified genes/proteins. These megakaryocytic progenitors quickly disappear after birth. Until now the molecular and cellular basis of this natural remission is unknown, but it may be related to changes in the hematopoietic microenvironment that occur during growth and neonatal development. Affected megakaryoblasts with additional genetic hits are probably subjected to clonal evolution, making them susceptible to malignant transformation to leukemic cells, leading to the development of AMKL (Shimizu et al., 2008) (figure 2).

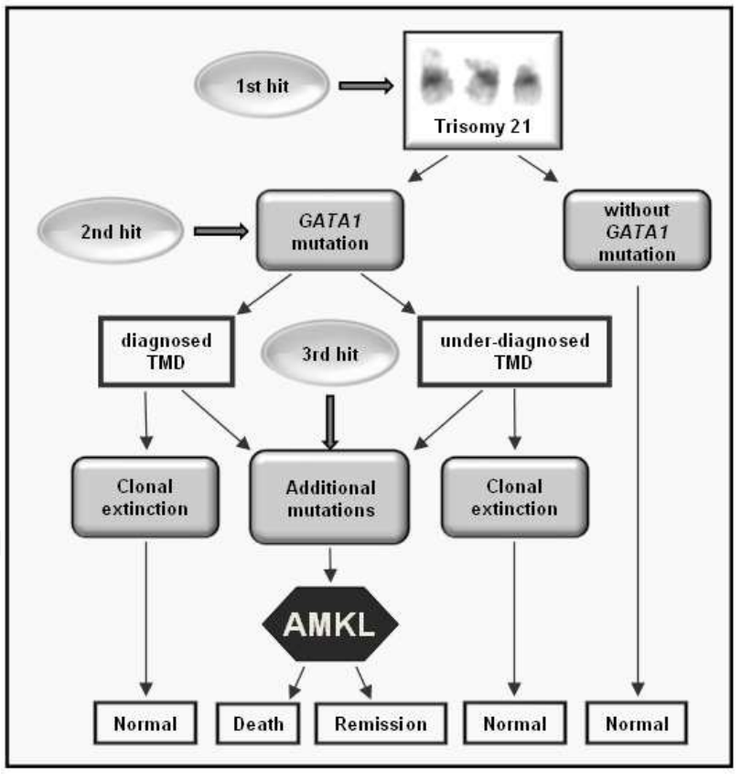


Fig. 2. A model for multi-step leukemogenesis in DS. The accumulation of hits (multiple genetic abnormalities) characterizes the evolution of TMD for AMKL.

Somatic mutations in the N-terminus activation domain of *GATA1* are found in most cases of TMD and AMKL, suggesting these mutations have a significant role in the process of leukemogenesis (Wechsler et al., 2002). *GATA1* mutations with trisomy 21 may be sufficient to promote the expansion of transient megakaryoblasts seen in TMD (Mundschau et al., 2003).

The expression levels of GATA-1 isoforms are crucial for the proper development of erythroid and megakaryocytic cells and compromised GATA-1 expression is a causal factor in leukemia (Shimizu et al., 2008). These findings strongly suggest that the qualitative deficit of GATA-1 contributes to the genesis of TMD and AMKL (Kanezaki et al., 2010). The selection of mutations that retain GATA-1s may result in disruption of normal balance between GATA-1 and GATA-1s, which probably would be involved in regulating normal development of megakaryocytes (Izraeli et al., 2007), but pass to act as an oncogene directly in the presence of trisomy 21. Alternatively, GATA-1s may be required for survival of leukemic blasts and the oncogenic effect may be purchased by the loss of the heavy chain of GATA-1. Another possibility is that this type of mutation may reflect specific mechanisms of selection or generation of this mutation in the presence of trisomy 21 (Rainis et al., 2003).

According some evidences the arising of AL is due to the cooperation between one class of mutations which interferes with differentiation (class II mutations) and another class which confers a proliferative advantage to cells (class I mutations) (Deguchi & Gilliland, 2002). It has been shown that high level expression of exogenous GATA-1 lacking the N-terminus induced differentiation rather than decreased the aberrant growth of GATA1-null megakaryocytes (Kuhl et al., 2005; Muntean & Crispino, 2005). This observation suggested that abundant GATA-1s functions like a class I mutation in TMD blasts. In contrast, reducing GATA-1 expression leads to differentiation arrest and aberrant growth of megakaryocytic cells (Vyas et al., 1999). The present data suggest that GATA-1s is expressed at very low levels in TMD blasts with GATA-1s low mutations. These levels may not be sufficient to provoke normal maturation. Together, these findings suggest that the low expression of GATA-1s might function like class II mutations in TMD blasts. Additional class I mutations or epigenetic alterations might be more effective in the development of leukemia in blast cells expressing GATA-1s at low levels (Kanezaki et al., 2010).

GATA1 mutations have not been identified in normal children, in children with DS and other types of leukemia, or in acute myeloid leukemias (AML) of children without DS. Mutations restricted to leukemic clones were not detectable in samples in remission. They were therefore selected and acquired, probably because they granted a clonal advantage (Pine et al., 2007; Wechsler et al., 2002).

Rainis et al. (2003) reported two patients with identical *GATA1* mutations in TL and subsequently in AMKL, showing that the AMKL was originated from the clone of TMD. Thus, *GATA1* is mutated in most patients with TMD, but that is not enough to generate leukemia after remission. Moreover, it has been reported that monozygotic twins that developed AMKL associated with acquired trisomy of chromosome 21 in blast cells have the same mutation that was not detected during remission. Because it was an identical mutation in the leukemic cells of twins, so it is likely that the mutation has occurred in one twin in utero and that his pre-leukemic cells have migrated to the other twin by blood embryological anastomoses.

Wechsler et al. (2002) analyzed the X chromosome inactivation in cell lysates from BM of women carrier from AMKL. Since the female leukemic cells showed the X chromosome inactivation due to monoclonality, and the mutant allele was detected only in leukemic cells, they predicted that the wild-type allele should be on the inactive X chromosome. As expected, only the truncated protein GATA-1s was observed. On the other hand Rainis et al. (2003) proposed that if there was no process of X chromosome inactivation, *GATA1* mutation would be involved in a higher frequency of patients with DS and TMD. Therefore, this inactivation of the *GATA1* mutation is considered a key event for non-occurrence of the TMD transformation to AMKL (Rainis et al., 2003).

Ahmed et al. (2004) described for the first time multiple independent *GATA1* mutations in four of 12 patients that developed AMKL, showing multiple *GATA1* mutant clones in the same individual. In these patients, analysis of mutant clones by automated sequencing allowed to confirm that each clone contained a different mutation in *GATA1*. Interestingly, at the diagnosis of AMKL only one of the three mutations was present. The presence of these multiple *GATA1* mutations suggests that mutations are a frequent event in hematopoietic cells of DS children. Using cell surface markers, Groet et al. (2005) showed the presence of several independent clonal expansions in different stages of megakaryocytic differentiation in a single patient with TMD. Probably this was due to independent clones that acquired the respective mutations in different stages of differentiation.

GATA-1s is no different from wild type in their ability to bind to DNA and interact with its co-factor friend of GATA-1 (FOG-1), but shows a reduction in their ability to transcriptional activation since it was truncated to its activation domain N-terminal (Rainis et al., 2003; Wechsler et al., 2002).

FOG-1 binds specifically to the NF zinc finger motif of GATA-1, and is expressed abundantly in erythroid and megakaryocytic cells (Crispino et al., 1999). FOG-1 is encoded by the gene *ZPFM1* as a protein of 998 amino acids which contains nine zinc finger motifs, four of them (ZFS 1, 5, 6 and 9) mediate the interaction with GATA-1 (Fox et al., 1999; Muntean & Crispino, 2005). Studies using point mutations in *GATA1* lead to a protein with a remarkable reduction of the affinity to FOG-1, but with ability of DNA binding, demonstrating that direct interaction FOG-1 and GATA-1 is required for normal erythropoiesis in vitro (Crispino et al., 1999).

A missense mutation in the *GATA1* gene was described in members without DS of a family affected with congenital dyserythropoietic anemia and thrombocytopenia. The megakaryocytes of these patients had similar changes in the megakaryocytes of mice deficient in expression of *GATA-1* suggesting that the interaction GATA-1/FOG-1 is also crucial in late stages of megakaryopoiesis (Nichols et al., 2000).

4. Other mutations associated with DS leukemia

The occurrence of mutations in exon 2 of *GATA1* in TMD suggests that there is cooperation between increased dosage of the gene or genes on chromosome 21 with the initiation of prenatal clonal proliferation of megakaryocytic precursors (Malinge et al., 2009).

Based on numerous studies with mutations in *GATA1* by several research groups, Malinge et al. (2009) concluded that the TMD and AMKL require both trisomy 21 and *GATA1* mutation but is not clear if only these alterations are enough to promote the TMD. Furthermore, the specific secondary mutations that promote the evolution of TMD to AMKL are still unknown. It has been identified cooperating mutations including *JAK3, TP53, FLT3* and *JAK2* mutations whose frequencies are shown in table 1 (Malinge et al., 2009).

The identification of activating mutations in tyrosine kinase genes in TMD and AMKL specimens has provided new insights into the evolution of AMKL. *JAK3* mutations have been detected in a small but significant fraction of DS-leukemia samples. Among the mutations found, most were considered as gain of function. JAK3 was also found in the CMK cell line (cells that do not express GATA-1 wild type and are removed from patients with AMKL) inducing a lethal biphenotypic hematopoietic disorder in mice with features of AMKL (Walters et al., 2006). Other mutations in *JAK3* have been proposed to be loss of function (De Vita et al., 2007). Additional experiments are necessary to determine how these different *JAK3* variants affect hematopoiesis and megakaryocyte development (Malinge et al., 2009).

Types of leukemia	Mutated gene	Localization	Frequencies recorded
TMD	*GATA1*	Xp11.23	97,3%
	JAK3	19p13.1	12,5%
	TP53	17p13.1	7,7%
AMKL	*GATA1*	Xp11.23	89,2%
	JAK3	19p13.1	13,2%
	FLT3	13q12.2	5,7%
	TP53	17p13.1	21,4%
	JAK2	9p24.1	6,2%

Table 1. Genetic abnormalities identified in leukemia associated SD.

5. Trisomy 21 influence on hematopoiesis

The functional contribution of the trisomy 21 in hematologic malignancies is supported by several observations such as the high incidence of leukemia in DS patients, the fact that TMD and AMKL blasts present trisomy 21 (even in children without DS), and that acquired trisomy or tetrasomy of chromosome 21 is frequently observed in blasts of different types of leukemia, including hyperdiploid ALL and de novo AML (Vyas & Crispino, 2007).

It is assumed that the cells of DS complete or partial trisomy of Hsa21, approximately 33.7 Mb, promote an overexpression of at least one of the 364 known genes, 31 antisense transcripts, and five different miRNAs (miR-99a, let-7c, miR-155, miR-125b-2, and miR-802), which could cooperate with the loss of GATA-1 in the pathogenesis of AMKL. Mutations in several genes on chromosome 21 have been identified in leukemia, and many of them recognized as encoding transcription factors acting at various stages of hematopoiesis. There should be contribution of genes present on chromosome 21 that cooperate with mutations of the *GATA1* to cause leukemogenesis (Look, 2002; Malinge et al., 2009).

The identification of the Down Syndrome Critical Region (DSCR) on the 21q22 band based in the genotype-phenotype correlations of partial trisomy in children suspected of having DS disclosed a list of genes potentially implicated in the clinical phenotype. However no specific genes have been certainly linked to the increased incidence of leukemia in DS. Few strong candidates include *ERG*, *ETS2*, and *RUNX1* (Lyle et al., 2009; Malinge et al., 2009).

Since the TMD is originated in a fetal liver progenitor and is restricted to children with DS (or to rare cases of acquired trisomy 21), it is presumed that trisomy 21 directly affects the development of hematopoietic cells during gestation. It has been shown that *GATA1* mutations can appear in 21-week-old embryos (Taub et al., 2004). To define the cellular context in which *GATA1* mutations occur, two groups studied hematopoiesis in trisomy 21 human fetal livers (FLs) (Chou et al., 2008; Tunstall-Pedoe et al., 2008). They found that although trisomy 21 did not alter the proportion of CD34+ and CD38- cells, trisomy 21 FLs showed a 2 to 3 fold increase of megakaryocyte erythroid progenitors (MEPs), which appeared to increase over time (35% at 16 weeks to 65% at 18 weeks).

The functional perturbations induced by trisomy 21 probably induce a highly susceptible cellular environment to additional transformations such as *GATA1* mutagenesis in TMD. The FL cell-based assay is a powerful tool to determine the specific Hsa21 genes that

participate in TMD. Preliminary quantitative reverse transcription-polymerase chain reaction (qRT-PCR) studies have shown that there are no significant differences in expression of *ERG, ETS2, RUNX1*, and *SON,* top-ranked candidate leukemia oncogenes, in trisomic versus euploid FLs (Chou et al., 2008; Tunstall-Pedoe et al., 2008). However, functional studies, such as knockdown of one or more of these candidates genes in FL progenitors followed by colony assays and transplantation experiments, are necessary to determine the requirements for these genes in leukemia (Malinge et al., 2009).

6. Specific chromosome 21 genes in DS-associated leukemia

Two microarray studies comparing AMKL versus non-DS AML have recently been reported (Bourquin et al., 2006; Ge et al., 2006) and 76 genes were described that discriminate between DS AMKL and non-DS. For example, genes encoding erythroid markers, glycophorin A and CD36, were found meaningly overexpressed in AMKL, as confirmed by immunophenotypic analysis of blasts (Langebrake et al., 2005).

Analysis of the gene expression data also revealed that there is an overall increase in expression of chromosome 21 genes in AMKL, relative to non-DS AMKL. By gene set enrichment analysis, 47 Hsa21 genes, including *BACH1, SON, C21orf66*, and *GABPA*, contributed for this observed enrichment score, but the distinction between the 2 types of AMKL was not driven by differences in expression of chromosome 21 genes (Bourquin et al., 2006). By qRT-PCR and microarray analyses, Ge et al. (2006) found that 7 of 551 genes were up or down-regulated in AMKL relative to non-DS AMKL and not encoded by chromosome 21, including *BST2, DUSP6, KRT18*, and *CD36.* Differences in these two data might be explained by differences in the samples or different protocols and methods used to analyse the expression of the genes.

6.1 Candidate leukemia oncogenes encoded by chromosome 21

Of the genes on chromosome 21, several are compelling candidate leukemia oncogenes. Of these, four such candidates are *RUNX1* (AML1), which encodes the heterodimeric partner of the complex of transcription factors denominated core-binding factor β (CBFβ), cooperates with GATA-1 during megakaryocytic differentiation, and the three ETS transcription factors, which are expressed and functionally involved in megakaryocytic differentiation and sensitivity to chemotherapy (*ERG, ETS2*, and *GABPA*) (Ge et al., 2008). It has been suggested that *RUNX1* is involved in the AMKL, since mutations in the DNA-binding domain of *RUNX1* was identified in 5% of sporadic leukemia and in myeloid malignancies with acquired trisomy 21 (Osato et al., 1999; Preudhomme et al., 2000). However, despite of the loss-of-function mutations in *RUNX1* are associated with leukemia, it is not known how three copies of the chromosome 21 would promote tumorigenesis in DS (Izraeli, 2004). It is possible that cells with trisomy 21 express different levels of *RUNX1* isoforms, affecting tumor development (Levanon & Groner, 2004). Despite of the fact that the total level of RUNX1 expression was lower in AMKL compared with non-DS AML, the differential expression of RUNX1 isoforms was indeed observed in human AMKL samples (Bourquin et al., 2006). In contrast, trisomy for *Runx1* was found not to be required for the development of myeloproliferative disorder (MPD) in Ts65Dn mice (model used with partial trisomy 21) (Kirsammer et al., 2008). Furthermore, the Ts16 fetuses hematopoietic phenotype was not related with an increased ratio of *Runx1* or an altered expression of its isoforms (Gjertson et al., 1999).

Inherited hypomorphic mutations in *Runx1* cause low levels of expression in hematopoietic stem cells and result in the syndrome of thrombocytopenia with familial susceptibility to leukemia. Abnormalities in *Runx1* were not detected in AMKL (Rainis et al., 2003).
In different types of cancer, it has been shown that the *ERG* proto-oncogene is dysregulated, and its overexpression in AML samples with normal or complex karyotypes involving Hsa21 was observed (Baldus et al., 2004; Marcucci et al., 2005). An overexpression of *ERG* in human K562 cells that express both forms of GATA1 induced a switch in differentiation toward the megakaryocytic lineage and showed an increased expression of the early megakaryocytic markers, as CD41 and CD61 (Rainis et al., 2005). To confirm a role of ERG in late stages of megakaryopoiesis, Loughran et al. (2008), working with homozygous and heterozygous of mutant *Erg* mice, observed that the first one died in utero, in consequence of a defect in definitive hematopoiesis, and the second one showed thrombocytopenia with normal number of BM megakaryocytes.
Overexpression of *ETS2* has also been shown in several cancers, including AML (Baldus et al., 2004), and the amount of *ETS2* transcripts are increased in both AMKL (DS or non-DS) (Ge et al., 2008). These facts and its involvement in the regulation of megakaryocytic genes suggest that *ETS2* has an important role in TMD or AMKL. As same as for *ERG*, *ETS2* overexpression in K562 cells was found to promote a switch in differentiation from erythroid to megakaryocytic fate (Ge et al., 2008).
The ETS family member *GABPA* is not considered an oncogene and its expression in the megakyocyte suggests that the GABPA protein has a role in early stages of megakaryocytic maturation (Pang et al., 2006). Recent studies have shown that GABPA directly affects the cell cycle by regulating the expression of genes required of DNA synthesis and degradation of cell-cycle inhibitors (Yang et al., 2007). Of Hsa21 genes, *GABPA* was one of the few whose expression is elevated in AMKL versus non-DS AML (Bourquin et al., 2006).

6.2 miRNAs encoded by chromosome 21

Hsa21 encode five miRNAs and overexpression of some of these has been observed in brain and heart tissues of people with DS and has been implicated in normal and pathologic hematopoiesis (Kuhn et al., 2008). For example, miR-99a is up-regulated during megakaryocytic differentiation of CD34+ cells, whereas miR-155 and let-7c are down-regulated (Garzon et al., 2006). Notably, miR-155 has been linked to myeloproliferative and B-lymphoproliferative disorders (Garzon & Croce 2008; O'Connell et al., 2008). Studies have implicated miR-125b-2, which is overexpressed in TMD and AMKL samples compared with normal megakaryocytes, in the megakaryocytic leukemia of DS (Klusmann, 2007).
Klusmann et al. (2010) showed that miR-125b-2 is an oncogene potentially involved in the pathogenesis of trisomy 21-associated leukemia. They demonstrated in mice and human that overexpression of miR-125b-2 led to specific hyperproliferation and enhanced self-renewal capacity of megakaryocytic progenitor (MPs) and megakaryocytic/erythroid progenitors (MEPs), without affecting their normal differentiation. The miR-125b was highly expressed in AMKL blasts, whereas the identified target genes of miR-125b were down-regulated. Thus, miR-125b-2 has a role in regulating megakaryopoiesis and in the pathogenesis of trisomy 21-associated TMD and AMKL, in cooperation with GATA1s. The miR-125b-2 exerts its oncogenic potential by at least two different mechanisms: blocking post-transcriptional miRNA processing through repression of *DICER1* expression, and by inhibiting tumor suppressor genes, such as *ST18*.

7. Methods of leukemia diagnosis in DS

The diagnosis of TMD usually occurs during the first weeks after birth and is observed as hydrops fetalis. The elevated blood count associated with hepatomegaly is the common symptom in an asymptomatic neonate. Infants with TMD can also display occasionally jaundice and bleeding diatheses, respiratory distress coupled with ascites, pleural effusion, signs of heart failure, and skin infiltrates. There is megakaryocytic infiltration and liver fibrosis, likely caused by excess cytokines secreted from the megakaryoblasts. The full clinical TMD may develop only at the second or third week of life. Laboratory tests are significant for either thrombocytosis or thrombocytopenia accompanied by elevated leukocytes with excess of blasts. The blood smear may show nucleated red cells, giant platelets and megakaryocytic fragments, and, most significantly, typical deeply basophilic blasts with blebs characteristic to megakaryocytic blasts. The differential diagnosis includes leukoerythroblastic reaction associated with prematurity, sepsis, or asphyxia. However, the blasts of TMD usually persist for several weeks, and *GATA1* mutations are invariably found (Malinge et al., 2009).

AMKL is preceded in 20 to 60% of cases by an indolent prephase of myelodysplasia (MDS), characterized by thrombocytopenia and dysplastic changes, BM aspiration is often dry, and fibrosis is detected in BM biopsy (Creutzig et al., 1996; Lange et al., 1998). This MDS can last several months or years before progressing to leukemia. In contrast to MDS in non-DS children, which requires stem-cell transplantation for cure, MDS in children with DS present a highly favorable response to chemotherapy alone (Lange et al., 1998). Therefore, Hasle et al. (2003) suggested that all cases of MDS and overt myeloid leukemia in DS, children should be classified as one disease entity, and referred to as ''acute myeloid leukemia of Down syndrome'' or ML DS. As this is a unique disease, it should be classified separately from other cases of AML in the WHO-classification.

Immunophenotyping characterizes the hematopoietic lineage involved and their degree of maturation by monoclonal antibodies labeled with fluorochromes. Flow cytometry reveals that blasts are positive for CD34, CD33, CD41, CD61, glycophorin A, and often CD7 and CD36 (Langebrake et al., 2005, Massey et al., 2006). Savasan & Ravindranath (2003) observed that blasts of DS children with AMKL express CD36, in contrast to the low or no expression of CD36 in AML without DS. If 25% of blast cells are not detected, the diagnosis of AMKL can be given by the megakaryocytic markers CD41, CD61 and CD42a. The immunophenotype of the blasts in AMKL is generally similar to TMD, except that the percentage of CD34 cells may be lower in AMKL (Langebrake, 2005; Malinge et al., 2009).

Pine et al. (2005) demonstrate the possibility of using specific *GATA1* mutations already identified in the diagnosis of TMD or AMKL to monitor the size of the clone of leukemic cells over time with a sensitivity level (10^{-4} to 10^{-5}) beyond the microscopic detection. The study confirmed that *GATA1* mutations in TMD and AMKL can be used as clonal markers were suitable for measurement of minimal residual disease (MRD).

This approach serves as a valuable tool in monitoring the spontaneous remission of TMD and in assessing response to treatment of AMKL subcytologic level. In addition, the MRD based GATA-1s mutations has been much in demand as a prognostic parameter for newborns with TMD. One may speculate, for example, that every group of newborns showing apparent remission of TMD can be divided into two subgroups: one in which the size of the clone of blasts in TMD after morphological remission continues to decline to become undetectable versus a second group, in which a clone of blasts in the TMD remains

detectable submicroscopic level. It is interesting to correlate these patterns of MRD kinetics in TMD with the probability of developing AMKL later (Hitzler & Zipursky, 2005).
Additional copies of chromosome 8 and 21 in addition to the constitutional trisomy 21 are the most frequent in AMKL, and are found in approximately 10 to 15% for each chromosome. Cytogenetic findings associated with a high rate of relapse in non-DS AML, such as monosomy 7 and deletion 5/5q- also occur in DS patients but do not seem to have a negative impact on prognosis in the rare cases (Gamis et al., 2003, 2005; Rainis et al., 2003).
The approach of molecular techniques including: PCR amplification of *GATA1* exons 2 and 3, followed by direct sequencing or analysis by denaturing high performance liquid chromatography (DHPLC), and cloning allow greater sensitivity and specificity of detection and have become essential for the identification of gene alterations in leukemias. The ability to detect mutations depends on the proportion of mutant cells in the sample. In general, for direct sequencing, approximately 20% of the sample has to have mutant cells. The sensitivity of DHPLC is higher at around 2 to 5%. Once a mutation has been identified, mutation-specific probes and primers for mutation detection by qRT-PCR can be designed that allow for more sensitive detection of mutant cells, which may be used for MRD detection (Pine et al., 2005).
Until recently, there were no reports on the expression levels of GATA-1s in TAM blasts, and the risk factors for the progression to AMKL. In 2010, Kanezaki et al. tested whether the spectrum of transcripts derived from the mutant *GATA1* genes affects the expression levels. They classified the mutations according to the types of transcripts, and investigated the modalities of expression by in vitro transfection experiments using GATA-1 expression constructs harboring mutations. They have shown that the mutations altered the amount of mutant protein. Based on the evaluation of GATA-1s expression, the mutations were classified into two groups: high and low GATA-1s expression. Phenotypic analyses of 66 TMD patients with *GATA1* mutations revealed that GATA-1s low expression mutations were significantly associated with a high risk of progression to AMKL and lower counts of both WBC and blast cells. These results suggest that quantitative differences in mutant protein levels have significant effects on the phenotype of TMD.
Nevertheless, neither mice nor humans with germline mutations expressing GATA-1s develop TMD or AMKL without trisomy 21 (Hollanda et al., 2006; Li et al., 2005). Therefore, the role of the trisomy 21 in the cellular transformation in AMKL seems to be fundamental (Klusmann et al., 2010). It remains unknown which factors on chromosome 21 cooperate with the oncogenic GATA-1s and which factors are involved in this transition from preleukemia to AMKL in only a part of these children (Kanezaki et al., 2010; Klusmann et al., 2007; Langebrake et al., 2006; Malinge et al., 2009).

8. Treatment outcome

DS children with AMKL have an excellent prognostic, with an approximately 80% cure rate, in relation to children without DS who develop AML (Arico et al.; 2008; Creutzig et al., 2005; Gamis et al., 2003; Rao et al., 2006; Taub et al., 1996). This outcome is possible on contemporary AML protocols which based in reducing treatment intensity regimens has considerably reduced the mortality rates in children with DS (Creutzig et al., 2005; Gamis et al., 2003; Whitlock et al., 2005; Zeller et al., 2005).
AMKL blasts have shown hypersensitivity to varied chemotherapeutic drugs (Zwaan et al., 2002). Probably the hypersensibility of the blasts to cytarabine (ARA-C) is due of the effect

of *GATA1* mutations and Hsa21 on the levels of cytarabine-metabolizing enzymes (Ge et al., 2005). ARA-C sensitivity is restricted to the leukemic population and may be caused by increased expression levels of the cystathionine-beta-synthase gene, which is located on Hsa21 (Taub et al., 2000). Despite of many patients respond favorably to a simple regimen including low-dose of ARA-C, this is not currently the standard of care. Since many problems have been occurred in treating of AMKL like toxic deaths, infections, and cardiac toxicity, thereby new and less-intensive protocols have been initiated in the United States and Europe (Creutzig et al., 2005; International Cooperative Pediatric AML Study Group Myeloid Leukemia DS 2006 [European Clinical Trials Database (EUDRACT) no. 2007-006219-22]; Children's Oncology Group: The Treatment of Down Syndrome Children with AML and MDS under the age of 4 Years [COG-AAML0431]; low dose cytarabine in treating infants with DS and TMD [COG-AAML0532]).

Researchs in prospective clinical trials are trying to demonstrate whether treatment of TMD by low-dose cytarabine could prevent the arise of AMKL. Another related question to be clarified is whether treatment of clinically silent disease, identified by molecular detection of *GATA1* mutations in patients who recovered from TMD, can prevent the future development of AMKL (Malinge et al., 2009).

9. Conclusion

In conclusion, many questions remain unanswered concerning the factors that contribute to the progression of TMD and AMKL in DS-patients. Progress in research to unravel these questions will improve diagnosis and treatment. Furthermore, ensuring the diagnosis of *GATA1* mutations to the DS child to monitor the progression of the disease is essential to enable better clinical decision for the treatment regimen and, consequently, better quality of life to the patients.

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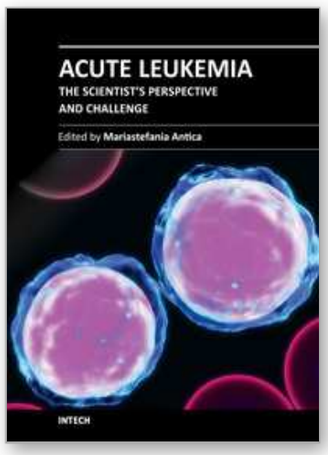
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Acute Leukemia - The Scientist's Perspective and Challenge
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This book provides a comprehensive overview of he basic mechanisms underlying areas of acute leukemia, current advances, and future directions in management of this disease. The first section discusses the classification of acute leukemia, taking into account diagnoses dependent on techniques that are essential, and thankfully readily available, in the laboratory. The second section concerns recent advances in molecular biology, markers, receptors, and signaling molecules responsible for disease progression, diagnostics based on biochips and other molecular genetic analysis. These advances provide clinicians with important understanding and improved decision making towards the most suitable therapy for acute leukemia. Biochemical, structural, and genetic studies may bring a new era of epigenetic based drugs along with additional molecular targets that will form the basis for novel treatment strategies. Later in the book, pediatric acute leukemia is covered, emphasizing that children are not small adults when it comes to drug development. The last section is a collection of chapters about treatment, as chemotherapy-induced toxicity is still a significant clinical concern. The present challenge lies in reducing the frequency and seriousness of adverse effects while maintaining efficacy and avoiding over-treatment of patients.

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