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Is Genomic Imprinting Involved in the Pathogenesis of Hyperdiploid and Haploid Acute Lymphoblastic Leukemia of Childhood?

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Biological and cytogenetic features of hyperdiploid and haploid acute lymphoblastic leukemia (ALL)

Hyperdiploidy with a chromosome number between 51 and 65 and a mean peak at 55 occurs as a distinct karyotype pattern in approximately 25-30% of ALLs in childhood [l, 2]. It is considered a favorable prognostic factor. The most intriguing cytogenetic peculiarities of these leukemias are the nearly exclusive presence of nonrandom numerical abnormalities due to the gain of chromosomes 4, 6, 10, 14, 17, 18, 20, 21 and X [1, 2]. In contrast, chromosomes 1, 2, 3, 12 and 16 are rarely involved [1, 2]. Typically, the affected chromosomes are present in three copies, with chromosome 21 also often being tetrasomic.

Near-haploid cases, on the other hand, are extremely rare and have a bad prognosis [1, 2]. They contain at least one copy of each chromosome, a second copy of one of the sex chromosomes and both chromosomes 21 in most instances. In addition, two copies of chromosomes 10, 14 and 18 are commonly found.

In the majority of cases of hyperdiploid ALL, the mechanism leading to the increased number of chromosomes is unknown. However, once formed, the abnormal karyotype is uniform and stable in the malignant cell population. Molecular genetic studies performed by Onodera et al. [3] revealed that the hyperdiploid karyotype usually arises by a simultaneous event during a single abnormal cell division from a diploid karyotype. Occasionally, this can also occur by doubling of the chromosomes from a near-haploid karyotype [4]. In virtually all cases, tetrasomy of chromosome 21 was generated by a duplication of both the maternally and paternally derived homolog. This finding was one of the main arguments for the notion that hyperdiploidy cannot be caused by stepwise or sequential gains from a diploid karyotype or by consecutive losses from a tetraploid karyotype.

Prenatal origin of hyperdiploid ALL

Recently, Wassermann et al. [5] provided the first evidence suggesting that the majority of ALL presenting within the first 3 years of life probably arise from an in utero transforming event. This notion derived from the fact that N regions are generally present in the DJ_H joinings of adult B cells but are often absent in fetal B cells [5]. The vast majority (nearly 90%) of precursor B-ALL in children who were younger than 3 years had a fetal type of rearrangement, whereas the older ones usually harbored the adult type [5]. Thus, in accordance with many other childhood neoplasms, such as pseudotriploid neuroblastoma, transient myeloproliferative disorder (TMD) associated with constitutional trisomy 21, Wilms tumor and tumors occurring in the Beckwith-Wiedemann syndrome, these leukemias may be considered as originating from a kind of premalignant "residual embryonic tissue" [6, 7].

Epignenetic disturbances as a possible pathogenetic factor

Despite the preferential involvement of the same set of additional chromosomes, namely X, 10, 14, 18 and 21, the good prognosis of hyperdiploid ALL contrasts sharply with the bad prognosis of near-haploid ALL. The pathogenetic role of such exclusively numeric karyotype abnormalities is still an enigma [8]. However, the general lack of gross structural chromosome abnormalities in hyperdiploid and haploid ALL can be taken as an indication that specific DNA alterations are rather rare. On the other hand, imprinting defects in the form of epigenetic DNA alterations, such as disturbed DNA methylation, are the earliest and most ubiquitous changes preceding malignant transformation [9]. Onodera et al. [3] proposed that a gene mutation or mutations may not be critical to the development of hyperdiploidy. Instead, trisomies of certain chromosomes may either enhance the proliferation capacity of early lymphoid cells through a change in dosage or relative dosage of a set of genes or in a similar process block differentiation [3]. Such an imbalance may occur between chromosomes with and without putative oncogenes and antioncogenes [8]. For example, it has been demonstrated that the introduction of an additional normal copy of particular chromosomes, such as chromosomes 1, 2, 16, 17, 19 and 21, can control tumorigenic expression of malignant cells [10, 11] and others, such as chromosomes 1, 6 and 7, can induce cellular senescence [12-14].

The accumulating evidence that the neoplastic growth may be rather due to epigenetic imbalances than to an excessive mutational perturbance invokes the necessity to strongly consider the possibility that imprinting phenomena may be important in the pathogenesis of these specific subsets of leukemias. Growth and differentiation control mechanisms may thus be deregulated by the unequal distribution of paternally and maternally derived chromosomes and/or by changes in the DNA methylation and expression patterns of particular imprinted genes.

In general, the maintenance and progression of a neoplastic tissue depends on ectopic and intrinsic factors. During pregnancy, the response towards maternally derived growth promoters or differentiaton inhibitors may differ between diploid, hyperdiploid and haploid B lymphocyte precursors and, therefore, lead to the prolonged survival, delayed maturation and/or overgrowth of the abnormal cell line. The cessation of the maternal

influence after birth together with a postnatal change of gene expression, the expansion of the B cell immune system as well as its response to the increasing antigenic challenge may then trigger the development of overt ALL in young children [15]. The more benign behavior of hyperdiploid ALL versus the more aggressive one of haploid ALL may be explained by the lack of a trans-acting gene expression control in the latter.

All the above-described factors are certainly also responsible for the rather extraordinary in vitro behavior of these ALL cells. They are difficult to propagate, it is virtually impossible to stimulate them and they rapidly undergo apoptosis. Moreover, gross alterations of the DNA methylation pattern may also be responsible for the visible changes in chromatin configuration [9, 16], and may therefore be responsible for the contracted, fuzzy and difficult-to-band chromosomes which are often encountered in cytogenetic preparations of hyperdiploid ALL.

Possibilities for verification of the presented model

If my model is valid, it can be expected that analysis of the chromosomal compositions of haploid and hyperdiploid leukemias should reveal nonrandom patterns with regard to the parental origin of the extra or lost chromosomes, similar to the concordant parental origin of the deleted chromosome 13 and the duplicated 6p in retinoblastoma [17]. Whether the additional chromosomes are of uniparental or mixed biparental origin can be easily studied with molecular genetic means. Such studies will also help to elucidate the mechanisms leading to these abnormal karyotypes.

Considering the common occurrence of premalignant neoplasms in very young children, an epigenetic first step in these diseases is a particularly appealing one, as conventional mutational mechanisms probably do not occur at high frequency. This notion also implies that treatment strategies pursued in such neoplasms with exclusive epigenetic changes should differ from those in neoplasms with abundant DNA alterations. In line with the current successful treatment concepts which include primarily antimetabolite drugs and already try to avoid the more mutagenic alkylating drugs, therapy could be optimized with nonmutagenic agents that may modify epigenetic effects, influence gene expression and stimulate differentiation [18].

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