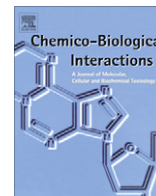


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Perspectives on the causes of childhood leukemia

Joseph Wiemels

Department of Epidemiology and Biostatistics, University of California San Francisco, Helen Diller Cancer Center Research Building, 1450 3rd Street, HD274, San Francisco, CA 94158, United States

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ABSTRACT

Acute leukemia is the most common cancer in children but the causes of the disease in the majority of cases are not known. About 80% are precursor-B cell in origin (CD19+, CD10+), and this immunophenotype has increased in incidence over the past several decades in the Western world. Part of this increase may be due to the introduction of new chemical exposures into the child's environment including parental smoking, pesticides, traffic fumes, paint and household chemicals. However, much of the increase in leukemia rates is likely linked to altered patterns of infection during early childhood development, mirroring causal pathways responsible for a similarly increased incidence of other childhood-diagnosed immune-related illnesses including allergy, asthma, and type 1 diabetes. Factors linked to childhood leukemia that are likely surrogates for immune stimulation include exposure to childcare settings, parity status and birth order, vaccination history, and population mixing. In case-control studies, acute lymphoblastic leukemia (ALL) is consistently inversely associated with greater exposure to infections, via daycare and later birth order. New evidence suggests also that children who contract leukemia may harbor a congenital defect in immune responder status, as indicated by lower levels of the immunosuppressive cytokine IL-10 at birth in children who grow up to contract leukemia, as well as higher need for clinical care for infections within the first year of life despite having lower levels of exposure to infections. One manifestation of this phenomenon may be leukemia clusters which tend to appear as a leukemia "outbreak" among populations with low herd immunity to a new infection. Critical answers to the etiology of childhood leukemia will require incorporating new tools into traditional epidemiologic approaches – including the classification of leukemia at a molecular scale, better exposure assessments at all points in a child's life, a comprehensive understanding of genetic risk factors, and an appraisal of the interplay between infectious exposures and the status of immune response in individuals.

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1. Introduction

Our objective with this report is to highlight recent advances and provide a perspective on the current understanding of the etiology of childhood leukemia rather than being an all-inclusive review. Childhood leukemia is a group of diseases with varied immunophenotypes and genetic changes. By all measures, the leukemia cases that comprise the Fallon leukemia cluster do not differ from a typical set of leukemia cases found anywhere in the US [1]. As this review paper consists of a part of a special issue on the Fallon cluster, we comment on all subtypes of childhood leukemia with a focus on the most common – acute lymphoblastic leukemia.

Childhood acute leukemia is the most common cancer in children representing 31% of all cancers and about 3250 new cases per year in the US [2]. Numerous breakthroughs in the past 50 years have increased survivability of the disease to greater than 80%, but survivors face long term morbidities [3]. The identification of causes and prevention/early intervention is clearly a worthwhile

goal. Known causes include ionizing radiation and congenital genetic syndromes such as Down's, neurofibromatosis, Fanconi's anemia, and Bloom's Syndrome, all of which together explain less than 10% of cases. Incidence of the disease has increased close to 1% per year in the past two decades [4] with similar rates of increase decades earlier [5,6], indicating that causal factors for the disease are likely to have become more prevalent in the population in the past several decades. The most notable feature of this period of time is the rise of the "common acute lymphocytic leukemia" (or CD19+, CD10+, B-cell cALL) peak in 2–6 year olds, a peak absent in some populations such as Africa and India, and in an ecological sense associated with countries that have higher socioeconomic status [7]. It is also notable that this peak may vary by ethnicity within the United States, with Hispanic:white:black ratio being 1.2:1.0:0.6 [8,9]. Whether this is related to genetic or environmental reasons is unknown.

The disease is comprised of several subtypes that vary in phenotype and age incidence patterns (Fig. 1). The broadest division for phenotyping leukemia is the lymphoid and myeloid split, with about 80% of leukemias being lymphocytic. Infant leukemias (<1 year of age) predominantly exhibit 11q23 *MLL* gene rearrangements and

E-mail address: joe.wiemels@ucsf.edu

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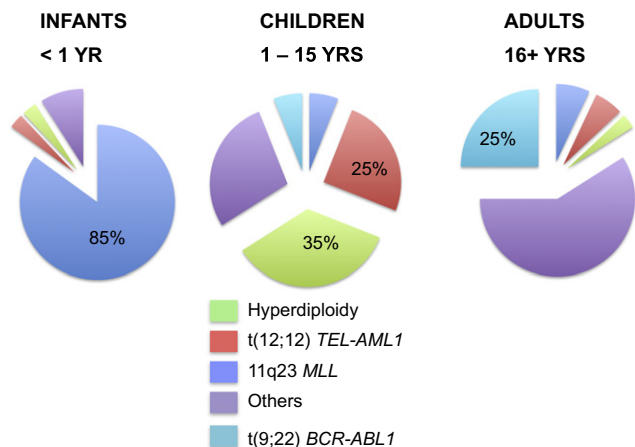


Fig. 1. Distribution of acute lymphoblastic leukemia subtypes by age. The figure demonstrates remarkable differences in the frequencies of cytogenetic features of leukemias by age.

may have lymphocytic (pro-B), myeloid, or undifferentiated features (Fig. 2). Leukemia among young children (2–10 years) are dominated by a pre-B lymphocytic phenotype, mostly the cALL subtype. Teenagers tend to trend towards adult-like leukemias, with an increasing frequency of myeloid types and a disappearance of cALL with increasing age. An appreciation of these phenotypes is critical as risk factors and immune dysfunction in particular are likely to affect their relative incidence differentially. Furthermore, within these subgroups are further groups defined by specific genetic features such as particular translocations, the presence of extra chromosomes, and gene mutations; the formation of each of these

mutations appear to occur within specific time periods during the child's life with the mechanistic formation likely having distinct causes.

The genetic and epigenetic aberrations frequent in the childhood leukemias are often important prognostic indicators, and identification of several of these are critical to modern disease classification protocols [10]. The uniform characterization of childhood leukemias under modern clinical protocols also provides relevant subgroup information for etiologic studies and will increasingly become a critical component of leukemia epidemiology studies.

2. The timing of initiating events in leukemia

Childhood leukemia like all cancers is a product of two or more molecular changes in stem-like cells that have the ability to divide while maintaining an immature state. The majority of leukemias are pre-B cell phenotype, meaning that they exhibit cell surface markers of normal pre-B cells, and appear to be clonal outgrowths of normal pre-B cells "frozen" at a particular differentiation stage (Fig. 2). Less common are leukemias with myeloid or T-cell lineage. Being blood cells, leukemias have an inherent capacity for mobilization in the bloodstream and extravasation. Precursor blood cells also have an enormous capacity for "blast-like" growth with their normal function to produce 10^{11} cells per organism per day. These attributes are among the six "hallmarks of cancer" [11], and the fact that hematopoietic precursors harbor these "cancer-like" attributes may be a reason by which leukemias seem to need far fewer genetic aberrations compared to solid tumors, which need to evolve these metastatic capacities through genetic mutations. The genetic simplicity of leukemia combined with the young age of the childhood leukemias and the availability of archived biological resources has allowed researchers to delineate the timing of

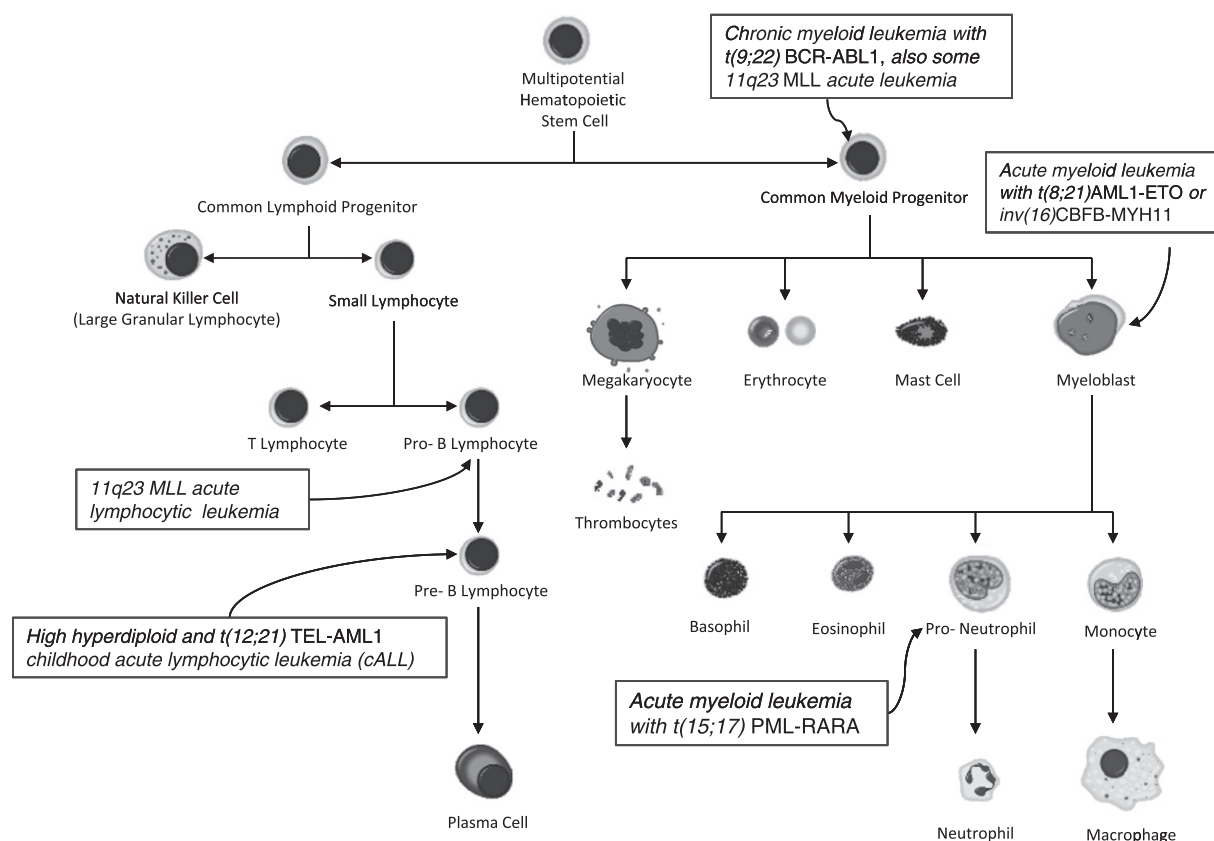


Fig. 2. Hematopoiesis. Blood cells are derived from multipotential progenitors. Nearly every cell noted here has a neoplastic counterpart which exhibits morphological features of its cell of origin. Those leukemia subtypes discussed extensively in the text are noted.

the formation of genetic aberrations within the lifetime of the child.

Most of the common genetic mutations in leukemia have been assessed for their formation during the fetal period using unique genetic tools and archived patient materials [12]. This research was made possible by the availability of neonatal heel-prick blood spots, or archived newborn blood spots (ANB cards) for children with leukemia. Several common translocations assessed on Guthrie cards, including t(12;21)*TEL-AML1*, t(8;21)*AML1-ETO*, inv(16)*CBFB-MYH11*, have indicated a clear presence of the mutations on neonatal blood spots at birth in children who contract leukemia later [13–16]. Several other mutations, including t(1;19)*E2A-PBX1*, *FLT3*, and *RAS* mutations are clearly postnatal [17–19]. *MLL* translocations (11q23) appear to occur within temporal proximity to diagnosis, meaning that infants (<1 year old) have prenatal translocations, and children beyond 2 years of age at diagnosis have postnatal translocations [20,21].

The mutations associated with leukemia are insufficient to cause disease by themselves. This is the case for *TEL-AML1* and *AML1-ETO*, the most common translocations for ALL and AML, respectively. Studies using cord bloods from normal born children indicate that these translocations may occur at a rate of 1% or more in the normal population [22,23]. This result suggests that a significant proportion of the population carries preleukemic clones, and the vast majority of these clones are self-limiting and do not result in disease. This also suggests that the critical rate-limiting step in the genesis of leukemia occurs during childhood (i.e., after birth), and that harboring initiating genetic translocations does not result in an inevitable diagnosis of leukemia; hence, interventions may be possible.

3. Causes of mutations in leukemia

Fetal and child hematopoiesis exhibits a remarkably high rate of cellular kinetics, and blood cell formation takes place within several organs – the aorta–gonad–mesonephros region, followed by the liver, spleen, and ultimately the bone marrow. The high degree of cellular proliferation creates a situation whereby perturbation via environmental insults including chemicals may induce mutations. The epidemiology of mutation-specific subtypes of leukemia is barely beginning, but there is evidence of progress. Children with t(12;21)*TEL-AML1* translocations were more than 4-fold more likely to be born from mothers who were exposed to paints during their pregnancy when compared to controls; this increased risk was not noted for other cytogenetic subtypes of leukemia [24]. Future leukemia epidemiology studies should consider genetic and cytogenetic subsets and combine cases of rare subgroups from multiple studies worldwide to gain statistical power.

While the incorporation of genetic classifications in epidemiology studies is only just beginning, the causes of broadly classified childhood leukemia have been under investigation for decades as reflected by dozens of studies. The only consistent and confirmed environmental cause is ionizing radiation from sources such as diagnostic imaging during pregnancy or atomic bomb exposure during childhood and young adulthood [25]. Other suspected contributors of leukemogenesis include diet of the mother and child, parental smoking, pesticides and household chemicals, traffic fumes, and immunologic modifiers, which we will cover in the next section. Smoking and pesticides have been recently and comprehensively reviewed and will not be further covered here [26,27].

As we are currently in the age of the genome-wide association study (GWAS), the contribution of genetic modifiers is of great current interest. To date, variation in several genes implicated in B-cell development (*ARID5B*, *IKZF1*, *CEBPA*) and cell cycle regulation/DNA repair (*CDKN2A/B*) are confirmed genetic risk factors for childhood ALL [28–31], but published GWAS studies are small and dozens of

other genetic risk factors are certain to emerge in the coming years. Besides these confirmed risk factors, candidate gene studies have implicated dozens of other genetic risk factors in candidate gene studies assessing pathways such as DNA repair, folic acid metabolism, and carcinogen detoxification. A recent meta-analysis of the multitude of studies has been published [32], but results of candidate gene studies must be taken with caution since publication bias and influence of underpowered studies may lead to false conclusions. Besides the standard GWAS, additional fine scale genotyping efforts in the major histocompatibility genes are of particular interest because of associations between patterns of infection and leukemia risk. Several HLA haplotype associations with childhood leukemia have been noted (e.g., [33–36]); however, a recent SNP-based analysis suggested no associations within the greater HLA region [37]. HLA alleles are complex and different genotypes can share the same peptide binding pockets, requiring nonconventional analytic approaches. Also, the capacity of HLA alleles to support immune reactions against particular epitopes varies greatly, so the ultimate HLA-leukemia association study should account for specific infectious exposures as well as tumor genetic profiles of leukemias.

4. Patterns of infection and acute lymphocytic leukemia

As noted above, most subtypes of childhood leukemia have their initial genetic mutations before birth, but only a fraction of those “initiated” preleukemic clones will progress to leukemia. By far, the most critical epidemiologic modifiers identified to date for the majority of childhood leukemias that will influence the progression of leukemia pertain to immunological development. The idea that exposure to infections and the development of the immune system might influence the etiology of leukemia in children grew out of two observations and led to two related hypotheses. Kinlen noted that leukemia incidence was often increased when children and families were moved and mixed in a new setting, such as the removal of children from central London during World War II, and the creation of “new towns” in Britain in the decades following that war [38,39]. Kinlen proposed a “population mixing” hypothesis on the origins of leukemia and posited a specific viral infection as potentially causative in the leukemia “outbreaks” which occurred soon after mixing. In examining data from the perspective of individuals rather than the population as a whole, Greaves noticed that children who received lower levels of immune stimulation during childhood developed a higher risk for leukemia and posited that a normal course of infections via early childhood contacts were protective [40,41]. A specific viral cause is not involved in this hypothesis; rather, the lack of immune stimulation in children who are relatively isolated followed by an aberrant over-response to common infections later in childhood is thought to induce leukemia in children who harbor preleukemic mutations. Several common childhood leukemia aberrations are prenatal in origin and occur at a much higher frequency than the disease [15,23], and those children who have a preleukemic mutation combined with aberrant immune development will be at the greatest risk. This is the essence of the “two-hit” natural history of leukemia elucidated by Greaves (Fig. 3) [40]. Given the generally sporadic patterning of leukemia incidence among populations, one could argue that prevailing evidence favors Greaves’ hypothesis of abnormal immune development rather than the involvement of a specific leukemia virus for the induction of the second “hit”.

Since it is a rare disease, nearly all childhood leukemia studies gather information on cases and controls after children are diagnosed with leukemia. Immunological development is quite difficult to assess in these retrospective studies. Data is typically questionnaire-based and variables include those that are easily remembered without bias by families enrolled in such studies. These

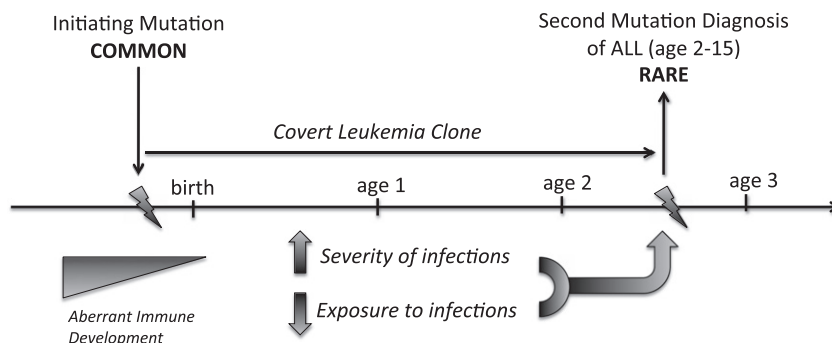


Fig. 3. A model illustrating key events in the development of childhood acute lymphoblastic leukemia. Genetic events are shown above the horizontal line, and immune development below the line. Initiating mutations are quite common, perhaps in 1% of normal live births, but among these births a second mutation after birth in the same initiated cell is rare. Epidemiologic exposures linked to the initiating mutation are not well established but chemical causes are a possibility (Scelo paper cite). Occurrence of the secondary post-natal mutation is enhanced by features of immune development – namely, a higher propensity to overreact to common infections early in life, and a lower overall exposure to infections and other immune stimuli. Figure modeled after Fig. 1, [40].

include: childcare history, vaccinations, infections, and allergies/asthma. Childcare history, or daycare, is considered a proxy measure for exposure to infection – the more contacts a child has in daycare setting, the better chance for exposure to new infections. Studies of daycare and leukemia sometimes demonstrated no difference in frequency, or more often a reduced level of daycare in children who contract leukemia compared to controls. A recent meta-analysis by Urayama and colleagues compiled evidence from 15 studies and yielded a combined OR = 0.76, 95% confidence interval (CI): 0.67–0.87, indicating a reduced level of prior childhood contacts in leukemia patients via daycare setting in the majority of studies, which is interpreted as a reduced level of immune stimulation/modulation in those children [42]. This epidemiologic result supports Greaves' "delayed infection" hypothesis elucidated above [40]. Other support for Greaves' hypothesis has come from studies showing an inverse relationship between childhood ALL and higher birth order [43,44] along with the daycare attendance studies, which both indicate that an increased opportunity for early childhood infections protects against leukemia. Additional support is provided by studies of normal childhood vaccinations. While vaccinations are largely ubiquitous making it difficult to assess their role in a population (very few unexposed persons) studies of Haemophilis Influenza (Hib), a vaccination phased in over the past two decades, indicates that vaccination reduces risk to leukemia [45,46]. This is not likely to be a specific effect; rather, the Hib vaccination is another example of an immunomodulatory stimulation which will help moderate future responses to new infections.

Greaves' hypothesis is similar to the "hygiene hypothesis" proposed by Strachan to explain the rising prevalence of allergy in the western population [47]. Strachan hypothesized that early childhood infections may be protective against allergy, but that declining family size and improved sanitation may have reduced exposure to infectious agents during early childhood thus resulting in the rising prevalence of allergy [47]. The hygiene hypothesis has been supported by epidemiologic studies that reported an inverse association between allergy and higher birth order [48–50] or early daycare attendance [51,52], similar to the associations seen with childhood leukemia. Allergies and asthma have generally been associated in an inverse relationship with leukemia as detailed in a recent meta-analysis on the subject [53]. On the face of it, this contradicts the data above on allergies; if allergies and leukemia share the same risk factors related to immune development, should not their incidence patterns be similar? The case-control studies that assess allergy do so by assessing parental recall of allergies. Case parents may be more likely to ruminate about factors that may have affected their child's risk to leukemia leading to false positive associations. In addition, control families tend to

misreport allergies that may have occurred after a "reference date" (diagnostic date for the corresponding leukemic children), therefore, over-reporting exposures, infections, and medical conditions [54]. The two studies that utilized medical record abstraction rather than patient interview found that allergy was a risk factor for leukemia [55,56], which is more plausible given the similar risk factors for these two diseases. This illustrates a situation whereby systematic bias may affect a series of case-control studies and produce an aberrant conclusion.

The leukemia cluster at Fallon exhibited a similar age and immunophenotype profile as any typical cohort of childhood leukemias, and it is likely that infection patterns affected the incidence and timing of the cluster. Given the geographic patterning and narrow time window of the cluster, it is likely that a specific infection was involved, closely emulating Kinlen hypothesis [57]. Further details are outlined below in Section 7 and in an accompanying paper in this issue [58].

5. Fetal immune development

Leukemia is a cancer of the immune system, and while immune stimulation by a normal course of infections and vaccinations appears to be protective, there are other data suggesting that children who contract leukemia may be born with an aberrant immunity that makes them respond to infections more vigorously. The United Kingdom Childhood Cancer Study (UKCCS) reported that children diagnosed with ALL had significantly more clinically diagnosed infectious episodes in the first year of life compared to controls [59]; this result was replicated in an independent study [60]. The number of infectious episodes in children with ALL increased with increasing indices of infectious exposure (birth order, regular social activity outside the home, and social deprivation at birth), a phenomenon not observed among healthy control children [61]. The UKCCS also clearly demonstrated fewer social contacts for children contracting leukemia, indicating that overall exposure to infections were likely lower than controls [62]. This suggests that there may be two separate phenomena influencing leukemia risk: (i) a lower repertoire of infections during early immune development which will increase risk (i.e., daycare, see the last section); (ii) an altered congenital responder status to infection resulting in a functionally aberrant clinical presentation of occasional infections in these same children (i.e., greater propensity to need clinical care when contracting infections). In support of this, we recently discovered that a key cytokine is severely deficient among children who grow up to contract leukemia, a greater than 10-fold difference when comparing the highest tertile to the lowest [63]. Interleukin-10 (IL-10) is a key regulator for modulating the

intensity and duration of immune responses to infections [63]. IL-10 is a strong anti-inflammatory cytokine secreted by monocytes and lymphocytes and is critical in limiting cell-mediated immune reactions. It has been reported that an increased risk for repeated respiratory infections during infancy and childhood associated with an elevated production of IL-5 by T cells at birth could be attenuated by IL-10 production [64]. It is possible that children with dysregulated immune function at birth are at higher risk for developing leukemia due to constitutively lower expression of IL-10, a cytokine that is critical to prevent an overactive inflammatory response to pathogenic infections. Biological stress from postnatal infection in combination with a dysregulated immune response may confer a growth advantage for a preleukemic clone leading to its rapid expansion and an increased opportunity for the occurrence of a second mutation required for the development of childhood leukemia [40]. The mechanism behind this constitutive lower IL-10 expression at birth will be a critical research question in discovering the causes of childhood leukemia.

6. Infant leukemias and MLL translocation

The infants are quite marked among childhood leukemias due to their nearly singular association with one particular genetic mutation – translocations at the *MLL* gene in chromosome 11q23. Mutations in this gene occur in more than 85% of infant leukemias and close to 100% of prenatal and congenital leukemias. These leukemias can harbor lymphoid or myeloid and occasionally undefined lineage characteristics but share a common transcription profile [65]. *MLL* has been termed a “promiscuous” gene as its translocation to nearly 100 different partners has been associated with leukemia [66]. As noted above, *MLL* translocations in infants are typically prenatal events. One may ask whether *MLL* translocation is simply more common than other translocations in the fetus, resulting in its more frequent presence in infants. Several observations counter this, however. First, infant leukemias with *MLL* appear to have more mature immunoglobulin gene rearrangement pattern than the common childhood ALLs of older children, indicating that the leukemia cells actually were initiated later, possibly in the third trimester of pregnancy [67–69]. Second, *MLL* translocations are highly transforming and the human disease has an extremely short latency, indicating that secondary mutations in this leukemia subtype may not be the rate-limiting event for full disease, and the leukemia incidence rate may mirror the translocation frequency [70]. *TEL-AML1* translocations, for instance, are present at a 1% frequency among neonates and the vast majority of translocation-positive cells do not progress to leukemia [22,23], compared to 10^{-5} frequency for infant leukemia with *MLL* translocations.

MLL translocations are common in another set of leukemia patients – iatrogenic leukemias induced by cancer chemotherapy of other cancer sites. Interestingly, 11q23/*MLL* translocations were first reported in adult therapy-related leukemias only after the introduction of cancer chemotherapy drugs which target topoisomerase II, including the epidophyllotoxins, during the 1980s [71]. This observation resulted in a theory that *MLL* translocations in idiopathic leukemias may be a product of dietary, medicinal, or environmental chemicals which target topoisomerase II [72]. The intense research interest that followed described many possible mechanisms by which drugs and other conditions might enhance breakage of *MLL* gene. Specific topoisomerase II sequences in the *MLL* gene, chromosomal scaffold attachment sites, apoptotic nucleases, and unique structures derived from transcriptional torsional forces may contribute to *MLL* breakage [73–79]. The mechanism is still not fully clear and the exact chemical constituents that might contribute to the formation of *MLL* translocations in infants has not been fully elucidated. An intriguing report from

Brazil and another international study implicated a type of insecticide and a therapeutic analgesic as potential agents [80,81]. While the epidemiology of *de novo* (i.e., not treatment-related) infant leukemias in the US has not yet found consistent culprits [82,83], the strong epidemiologic associations with specific clinical therapies in iatrogenic leukemias continues to focus interest on topoisomerases in the causes of infant ALLs. Efforts at examination of *MLL* breakpoints at the molecular scale have identified a translocation hotspot in therapy-related leukemias [73,74]; interestingly about half of infant breakpoints have the same molecular phenotype as therapy-related breakpoints suggesting that diverse mechanisms of formation (more than simply topoisomerase II inhibition) may play a role in infants [84–86].

MLL leukemias are not alone in harboring a chemical etiology. Certain myeloid subtypes are also suggestive for this. The *AML1* gene is involved in many translocations and has also been linked to anti-topoisomerase II agents, similar to the *MLL* gene [87,88]. Additional chemicals such as Classical clastogenic chemotherapy and environmental alkylating agents are associated with leukemias that have less precise breakpoints but commonly exhibit broken chromosomes and aneuploidy [89].

7. Leukemia clusters

Perhaps no other cancer type has captured both public and scientific attention in the same way that childhood leukemias have in the topic of cancer clusters. The most famous clusters include the Seascale cluster in the Lake District, UK; the Woburn cluster in Massachusetts, and the Fallon cluster in Nevada. Typically, chemo-physical “causes” are blamed with local culprits being ionizing radiation from a new nuclear plant (Seascale), trichloroethylene (Woburn) and tungsten alloy dust or petroleum fuels (Fallon). Only one of these factors approached a legal standard of proof (Woburn) at this writing, but scientific proof has been elusive. Studies of radiation exposure in the Seascale cluster were negative; however, it has been noted that the children who got leukemia were preferentially migrants to the area and experienced the most population mixing, providing credence to the population mixing hypothesis or infectious causes of this cluster [90,91]. In Fallon, the unique exposure environment includes arsenic and ^{210}Po Polonium in the water [92](in this issue), a tungsten/cobalt refinery [93], and a Navy flight and aircraft carrier base with its attendant exposures including jet fuel and other organics [94]. The leukemias from the Fallon cluster share a unique profile – nearly all cases were from children who lived near agriculture fields and open irrigation ditches forming an annulus around the town [58](in this issue). This indicates a possible scenario whereby an infection transmitted through a water-borne means might influence the disease. The US armed forces exhibited a similar peak incidence of leukemia at the same time suggesting transmission of an infectious agent throughout the armed services branches [58]. The timing was coincident with an adenovirus epidemic throughout the military [95,96]; however, no concrete link between adenovirus and leukemia is currently available.

8. Adult leukemias

Any discussion about the causes of childhood leukemias should consider adults, who represent about 90% of all leukemias diagnosed or about 40,000 individuals per year in the US. Adult leukemias are different diseases from their childhood counterparts. First of all, some subtypes exist in adults and not children and vice versa. The most common leukemia in adults is chronic lymphocytic leukemia (CLL), which is not seen in children [97]. Adults also display a wider range of leukemia subtypes with lower incidence of B and T-cell ALL but much higher chronic lymphocytic leukemia

(CML), AML, and myelodysplastic and myeloproliferative syndromes [98]. These latter four subtypes are myeloid in nature, meaning that they are derived from the precursors to cells critical in innate immunity rather than adaptive immunity. These cells, particularly neutrophils and their precursors, produce large amounts of enzymes that can both produce cytotoxic mediators as part of their normal function (e.g., myeloperoxidase), but also can activate environmental chemicals that reach the bone marrow, producing genotoxic intermediates [99]. A prime example of this phenomenon is exposure to benzene, which is metabolized in the liver to produce various phenols and quinone intermediates (which themselves are not leukemogenic when ingested). The zonal localization of Phase I and II enzymes in the liver facilitate the formation of these benzene metabolites, which enter the hepatic vein and general circulation; whereas phenol and hydroquinones themselves are detoxified by conjugation in the liver prior to entering general circulation [100]. Benzene metabolites are activated to nucleophilic compounds by myeloperoxidase in the bone marrow causing DNA damage and also may be subsequently reduced by quinone oxidoreductases [101,102]. Benzene is a confirmed cause of both leukemia and lymphoma [103,104] and has been linked to the formation of chromosome rearrangements typical of leukemia even in normal healthy, exposed persons as well as hematopoietic defects [105–107]. Other causes of leukemia in adults are chemicals associated with the rubber industry (butadiene, etc.), radiation, smoking, and chemotherapies for cancer [108].

A second difference between adult and childhood cancers is the molecular phenotype of some of the same disease classifications. The *TEL-AML1* and hyperdiploid subtypes, which together account for half of childhood leukemias, are rare if not absent among adult ALLs, the latter of which are dominated by more complex chromosome aberrations as well as a different dominant repertoire of translocations including *BCR-ABL1* (the “Philadelphia chromosome”) [109]. Unlike the childhood leukemias, there is some specific viral involvement of some types of adult leukemias. HTLV1 causes T-cell leukemia, rarely, in individuals infected in endemic areas [110].

9. Environmental causes: Synthesis of the evidence

Like most cancers, leukemia has been linked to certain environmental chemicals and ionizing radiation. Chemicals with specific capacity to target the bone marrow via selective accumulation and metabolic activation are the prime candidates. The myeloid series harbors higher levels of enzymes with metabolic activation and are more consistently linked to chemical exposures such as cigarette smoking, occupational solvent exposures, and alkylator chemotherapies in therapy-related leukemias [111]. The 11q23 *MLL* translocation is linked to chemicals with topoisomerase-II inhibition activity and result in leukemias of both myeloid and lymphoid subtypes. Benzene is a confirmed cause of myeloid leukemias with some evidence of causing lymphoid hematologic neoplasms [112], and there is some epidemiologic evidence that chemicals may impact lymphoid subtypes of childhood leukemia as well [24,113].

As leukemia is a neoplasm of the immune system, it is highly plausible that immune modulators will also modulate risk, particularly for the leukemias derived from adaptive immune branches including pre-B and pre-T leukemias. Infections, vaccinations, population mixing, and birth order are linked to lymphocytic leukemias, in particular the pre-B cell childhood ALLs. The discovery of causes of childhood leukemia clusters has been vexing to the research community, but evidence best implicates patterns of infections, possibly specific infections, spreading through naïve communities as an ultimate cause. Prior to an infection being the ultimate stimulus, a normal series of early infections appears to

be protective for leukemia. Recent evidence from epidemiology and the laboratory suggests that newborns who grow up to get leukemia may be born with low IL-10 levels and a propensity to react to normal infections in a hyper-responsive manner during their first year of life, which may induce a progression of preleukemic clones via inflammatory processes related to infection.

10. Conclusion

Childhood leukemia like all cancers is currently being subjected to intensive analysis by the “new genetics,” meaning genome-wide association studies (GWAS), high dimension expression and copy number variation, mutation analysis, and array-based intensive DNA methylation analyses. The power of GWAS studies is clear but limited due to the modest effect sizes of “genome-wide significant” SNPs. The small effect sizes of the handful of GWAS genes discovered so far limit the potential for the genes to be useful in prevention or clinical modalities; however, the identities of such genes illuminate cellular pathways that may otherwise not be known to be involved in these diseases. Just as environmental epidemiology studies will become more powerful with precise disease classifications, GWAS studies will become more powerful when larger numbers of diseases in precise classifications are studied, such as those described by recurrent chromosomal abnormalities such as *TEL-AML1*, high hyperdiploidy, and *PML-RARA*. Indeed a *TEL-AML1* GWAS has just been completed and shows larger effect sizes than the original, mixed phenotype GWAS studies [114]. Additional GWAS studies will require consortiums involving international pooling of samples to obtain required sample sizes.

Next generation sequencing analyses will certainly discover new genes and pathways in leukemia. The transformative potential of this technology is evident in the discovery of *IDH1/2* and *TET2* mutations in adult acute myeloid leukemia and brain cancer and the discovery of the critical nature of DNA methylation pathways in these two diseases [115,116]. Mutations in these genes are not present in childhood AML or ALL, which, besides having several common translocations, mutations, and deletions, have not been fully vetted for genetic and epigenetic architecture. Coordinated analyses involving gene expression, gene copy number change, and epigenetic modifications such as the TARGET initiative will help to complete knowledge of the range of modifications in leukemia cells [117].

These high technology initiatives must ultimately be linked up to population-based epidemiologically-derived data on infections, exposures, diet, and other environmental factors for true clarity to be reached on the causes of childhood leukemias. Clearly these studies must be very large to support the investigation of infrequent genetically-described subtypes of leukemia. This is not possible for investigations of leukemia clusters which are finite in space and time, sometimes statistically remarkable like the Fallon leukemia cluster but in practical terms very small. The Fallon cluster is a situation which demands a fresh study design that incorporates investigation of individual samples to assess viral or chemical involvement. Traditional case-control surveys do not make sense for small clusters unless they focus on the overall community from which the leukemia cases are derived. Future studies would benefit from earlier identification of cancer clusters via active surveillance at cancer registries, the capture of complete residential histories for cancer patients, and prospective population-level archiving of biological materials to permit accurate environmental and viral testing.

Conflict of interest statement

None declared.

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