

Epidemiological and Experimental Evidence for an Infection-Mediated Childhood Leukemogenesis

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B-ALL (B-cell acute lymphoblastic leukemia) is the most common childhood cancer, characterized by a distinctive age distribution with a peak onset between 2 and 5 years of age¹. The first genetic driving event (e.g., a germline variant or a somatic translocation) occurs prenatally, and it is present in up to 5% of healthy newborns, though the disease eventually affects less than 1% of those children². This latent and silent pre-leukemic phase (the initiating leukemogenic genetic hit is present but leukemia does not develop) is a key biological characteristic of this disease³, which offers a potential room to interfere with the pathogenetic mechanism. Epidemiological evidences exist linking the peak of B-ALL to the age when children are first exposed to common infections⁴⁻⁶. The International Agency for Research on Cancer, in collaboration with the International Association of Cancer Registries, using quality-assured data collected from cancer registries, revealed an overall increase in registered B-ALL comparing 1980's to 2001–2010 (International Incidence of Childhood Cancer volume 3 (IICC-3))⁶. During this period, the overall WSR (age-standardised rate (world standard)) for all tumours in children aged 0–14 years increased from 124.0 per million person-years (95% CI 123.3–124.7) in the 1980s to 140.6 per million person-years (140.1–141.1) in 2001–10. Leukaemia, the most common cancer in children worldwide, had the largest impact on this total increase of cancer incidence. This was particularly pronounced in sub-Saharan Africa and North Africa, where the age-standardized incidence rates had doubled⁶. Less pronounced increases were also seen in South, Southeast, and West Asia as well as in Eastern Europe⁶. B-ALL appeared to be among the childhood cancer types that are highly underestimated, compared to solid cancers with more visible symptoms⁷. At this stage, it is impossible to disentangle the various factors contributing to geographical and time trends differences. Variations in the completeness of case ascertainment—how thoroughly cancer cases are identified and recorded—are almost certainly a key factor influencing these trends. However, it might also reflect differences in susceptibility to leukemia in different racial or ethnic groups as seen in the IICC-3 data, where the highest leukemia rates in the USA were seen in white Hispanic children whereas it was less common in USA black children⁶. Exposure to environmental factors may also differ between low-, middle- and high-income countries. In order to solve these issues, global research efforts are essential.

Indeed, identifying the factors that contribute to the irreversibly transformed state has been particularly difficult, because of the inherent challenge of detecting pre-malignant cells in what appear to be otherwise healthy children. To this end, preclinical mouse models recapitulating genetic leukemia predisposing conditions have been instrumental in uncovering a “gene/environment cooperation” as a requirement for the genesis of B-ALL⁸⁻¹⁰. A “gene/environment cooperation” refers to the increased sensitivity of individuals carrying a specific germline or acquired alteration to certain environmental exposures^{11, 12}. How to stop a pre-cancerous cell from developing into cancer remains unsolved, mainly because the early events that determine the conversion are largely unknown^{11, 12}. Clearly, the most critical point of cancer development is the transition from a normal target cell to a cancer cell. B-ALL is an obvious candidate for the study of this process, as it develops fast and unfolds without the accumulation of large numbers of somatic mutations. Thus, it can be the forefront of preventing cancer development in genetically predisposed individuals. The trend of increasing childhood cancer incidence¹ underscores the urgency in addressing cancer disease prevention.

stressors has been supported by epidemiological data for several decades¹³⁻¹⁷. The role of infections as the key risk factor in the etiology of B-ALL has been considerably strengthened in recent years, with the strongest support coming from mouse models of *Pax5* heterozygous and *ETV6-RUNX1*⁺ leukemias, showing that B-ALL was initiated in these genetically predisposed mice only when they were exposed to common pathogens⁹⁻¹⁰. Interestingly, the immune stress does not act by selecting a pre-leukemic clone that already harbours the second hit; on the contrary, infection itself promotes the acquisition of the second hit itself, leading to full-blown B-ALL¹⁸. These preclinical mouse models where the disease emerge naturally will be able to make useful predictions in this scenario: these models can consider and predict such dynamic changes, while traditional genetics only can assess the change after it has already happened. This is relevant because many of the observations obtained previously using these mouse models have later been mirrored in pediatric B-ALL patients, as illustrated by the case where the B-cell alterations found in preleukemic *Pax5* heterozygous mice⁸ were later confirmed in children carrying *PAX5* germline variants^{19, 20}, or by the discovery that B-ALL driver genes are not targeted by AID in mice, which was subsequently validated in human

The association between B-ALL incidence and infectious

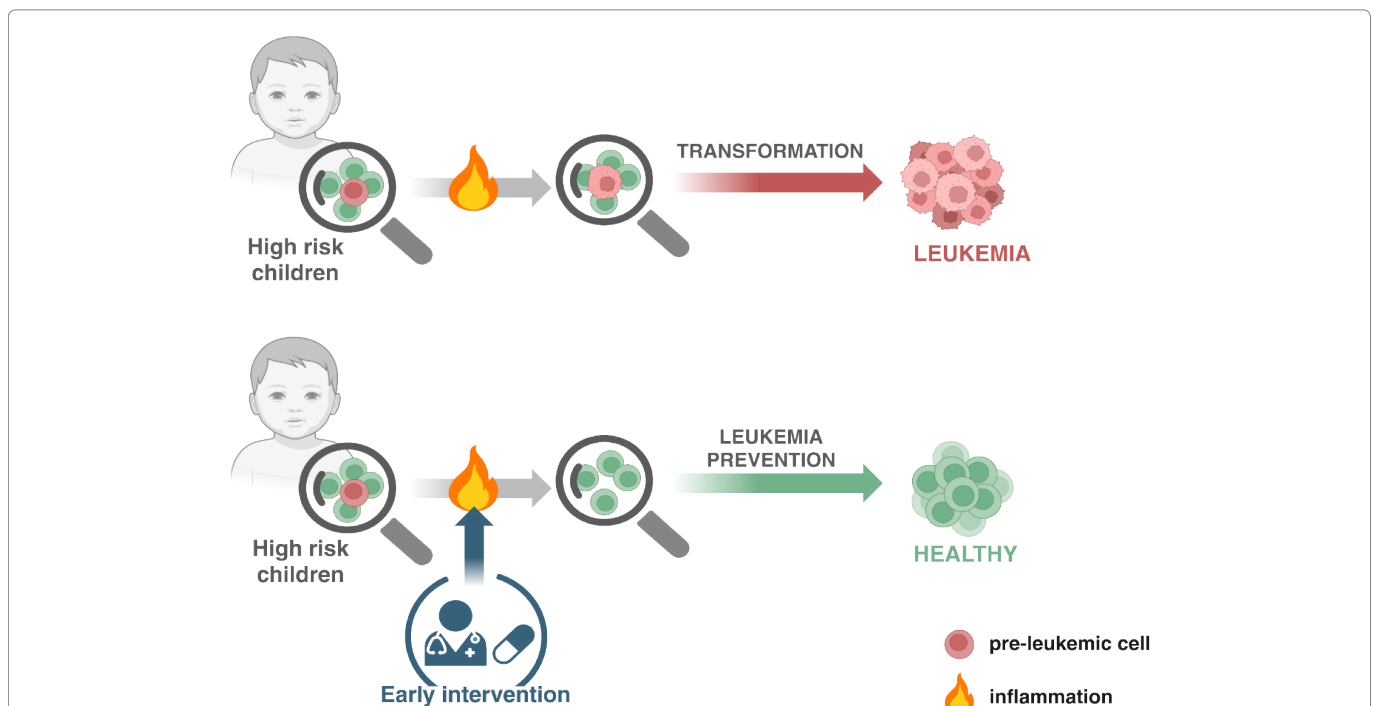


Figure 1. B-ALL development and potential avenues for prevention.

A) In B-cell acute lymphoblastic leukemia (B-ALL), the first genetic driver mutation typically occurs prenatally and is detectable in up to 5% of healthy newborns. These genetically predisposed children carry a latent, pre-leukemic phase characterized by a silent but chronic inflammatory environment. This immune-stressed state affects pre-malignant B-cell precursors, promoting their irreversible transformation into leukemic cells. B) The existence of this clinically silent, pre-leukemic phase—where the initiating genetic lesion is present but full-blown leukemia has not yet developed—represents a critical biological feature of B-ALL. This window provides a unique opportunity for early therapeutic intervention. Strategies that either eliminate pre-leukemic cells influenced by inflammation or prevent their environmentally driven transformation may help reduce leukemia onset in high-risk individuals. (Figure created in BioRender; <https://BioRender.com/undefined>)

ALL blasts¹⁸, or by the identification of gut microbiome immaturity in B-ALL predisposed mice¹⁸, which was also later corroborated in children with B-ALL^{21,22}. Hence, these preclinical mouse models, in which B-ALL occurs naturally, are indispensable for elucidating the early phases of B-ALL development, which are typically unnoticed in children¹¹, making it nearly impossible to study the initial phases of leukemic transformation in humans. Nevertheless, it has remained unclear how extrinsic factors, including immune stressors such as infection, facilitate the clonal evolution of pre-leukemic cells.

Recent findings revealed that an inflammatory state characterizes immune-stressed pre-malignant B-cell precursors in both children and predisposed mice²³⁻²⁶. Further, genetic induction of such inflammatory state in *Pax5* mutant pre-leukemic cells led to a significant increase in the incidence of B-ALL through an inflammation-dependent mechanism²⁷. Altogether, these findings show that pre-leukemic mutations induce a cell-intrinsic pro-inflammatory profile with implications for therapeutic targeting of the pre-leukemic state in children. The results highlighted above suggest that elimination of the pre-leukemic cells rewired by the inflammatory state, or protection against this environmentally mediated change, might help curtail leukemic development in genetically predisposed carriers. Likewise, recent investigations demonstrate that the incidence of B-ALL is reduced in *Pax5* heterozygous mice in an infectious environment following transient and early inhibition of inflammatory signalling in pre-leukemic cells through the administration of the JAK inhibitor ruxolitinib²⁸. These findings support the hypothesis that children who are genetically predisposed to B-ALL may also benefit from early transient inhibition of inflammatory signalling as a preventive strategy. Because an inflammatory state characterizes pre-leukemic cells from different genetic subtypes, it is possible that such an approach might prove useful for other forms of B-ALL prevention—*ETV6* mutations or the *ETV6-RUNX1* fusion gene. Overall, these findings provide evidence for a potential strategy to prevent B-ALL development in children with a genetic predisposition to leukemia. However, the challenge now is to find a way to identify children with a high risk of conversion of a pre-leukemic clone into an irreversible transformed state in order to develop new strategies to prevent this conversion and further progression. This will represent a paradigm shift for the field, helping us to move towards a future where we could identify and target potential aggressive leukemias by intervening at their earliest detection before they become an intractable clinical challenge. Achieving the prevention of the development of leukemia should lead to a substantial increase in child survival rates and might also open up new avenues for reducing complications from the late effects of current treatments. We anticipate

that the technologies and findings generated in the field of childhood leukemia will also be applicable across other cancer disorders arising in individuals carrying a genetic predisposition, yielding novel conceptual frameworks to address the central challenge of malignant transformation and tumor evolution.

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