Journal of Leukemia
ISSN: 2329-6917
OPEN ACCESS Freely available online
Commentary

Clonal Hematopoiesis: Implications for Leukemia Prevention and Treatment

Shawn Chen*

Department of Pharmacology, Shantou University, Shantou, China

DESCRIPTION

The discovery of Clonal Hematopoiesis of Indeterminate Potential (CHIP) has transformed our understanding of the premalignant landscape preceding leukemia development and offers unprecedented opportunities for early intervention. CHIP is defined by the presence of somatic mutations in genes recurrently mutated in hematologic malignancies (most commonly DNMT3A, TET2, and ASXL1) in individuals without overt hematologic abnormalities. These mutations confer a selective advantage to hematopoietic stem cells, leading to clonal expansion. The prevalence of CHIP increases dramatically with age, detected in <1% of individuals under 40 years but >10% of those over 70 years. The finding that these mutations precede leukemia development by years or decades has profound implications for leukemia prevention, risk stratification, and therapeutic development.

The progression from CHIP to leukemia follows a multistep process analogous to the adenoma-carcinoma sequence in colorectal cancer. CHIP may evolve to Clonal Cytopenias of Undetermined Significance (CCUS), then to Myelodysplastic Syndrome (MDS) or Myeloproliferative Neoplasm (MPN), and eventually to Secondary Acute Myeloid Leukemia (SAML). This progression is driven by acquisition of additional mutations, with specific patterns of co-mutation and clonal evolution. For example, DNMT3A mutations often represent early events, while mutations in signaling pathways (e.g., FLT3, RAS) typically occur later in leukemic transformation. The annual risk of progression from CHIP to hematologic malignancy is approximately 0.5-1%, suggesting that while most individuals with CHIP will not develop leukemia, the cumulative risk over decades is substantial.

Beyond hematologic malignancies, CHIP has emerged as an important risk factor for cardiovascular disease, with mutation carriers demonstrating approximately 2-fold increased risk of coronary heart disease, stroke, and cardiovascular mortality. This association appears mediated through enhanced inflammation, particularly IL-1β and IL-6 production by mutant macrophages derived from CHIP clones. This finding has stimulated interest in repurposing anti-inflammatory therapies for individuals with CHIP, with pilot studies of IL-1β inhibition showing promising preliminary results in reducing cardiovascular events.

The identification of CHIP in individuals receiving cytotoxic chemotherapy or radiation therapy has particular relevance for hematologic malignancy survivors. These treatments appear to provide selective pressure favoring expansion of pre-existing mutant clones resistant to genotoxic stress. The presence of therapy-related CHIP confers substantially higher risk of therapy-related MDS/AML compared to CHIP in the general population, with annual progression rates of 5-10%. This observation has prompted inclusion of CHIP assessment in long-term monitoring protocols for patients receiving intensive chemotherapy.

Detection of CHIP mutations has important implications for stem cell transplantation, both for donors and recipients. Donor-derived CHIP has been associated with donor cell leukemia, a rare but serious complication of allogeneic transplantation. Recent studies have demonstrated that donor CHIP mutations may be transferred to recipients and expand in the post-transplant environment, with adverse impacts on outcomes including chronic GVHD and non-relapse mortality. These findings have prompted debate regarding optimal donor selection and monitoring strategies, with some centers implementing CHIP mutation screening for older donors. In autologous transplantation, pre-transplant CHIP mutations may expand following high-dose chemotherapy and predict for post-transplant MDS/AML development, suggesting a role for post-transplant maintenance strategies targeting these clones.

The recognition of CHIP as a premalignant state creates opportunities for leukemia prevention that were previously inconceivable. Prospective monitoring of CHIP evolution through serial sequencing can identify early progression based on increasing variant allele frequency or acquisition of additional mutations. This approach enables risk-adapted surveillance and early intervention before development of overt malignancy. Precision prevention strategies targeting specific mutations show promise in preclinical models. For example, vitamin C supplementation was found to suppress TET2-mutant clone expansion through enhanced function of residual wild-

Correspondence to: Shawn Chen, Department of Pharmacology, Shantou University, Shantou, China, E-mail: chens@js-p2.cn

Received: 02-Jan-2025, Manuscript No. JLU-25-37204; **Editor assigned:** 06-Jan-2025, PreQC No. JLU-25-37204 (PQ); **Reviewed:** 20-Jan-2025, QC No. JLU-25-37204; **Revised:** 27-Jan-2025, Manuscript No. JLU-25- 37204 (R); **Published:** 03-Feb-2025, DOI: 10.35248/2329-6917-24.13.420

Citation: Chen S (2025). Clonal Hematopoiesis: Implications for Leukemia Prevention and Treatment. J Leuk. 13:420.

type TET2 alleles. Similarly, IDH1/2 inhibitors demonstrated efficacy in suppressing mutant IDH clones before development of frank leukemia.

Despite these advances, several challenges remain in translating CHIP biology to clinical practice. First, optimal screening strategies remain undefined, with questions regarding target populations, testing intervals, and cost-effectiveness. Second, predictive biomarkers to identify the minority of CHIP carriers who will progress to malignancy are needed to focus preventive interventions on high-risk individuals. Integrative approaches combining mutation characteristics (variant allele frequency, co-mutations), epigenetic profiling, and inflammatory biomarkers show promise in enhancing risk stratification. Third, the design of prevention trials presents unique challenges given the long latency between CHIP detection and leukemia development, necessitating thoughtful endpoint selection and adaptive trial designs.

As our understanding of CHIP biology expands, several promising research directions emerge. Single-cell approaches are revealing remarkable heterogeneity within CHIP, with distinct subclones demonstrating differential fitness and malignant potential. Microenvironmental factors including inflammatory cytokines, stromal interactions, and immune surveillance appear crucial in determining whether CHIP progresses or remains indolent. The interaction between CHIP and aging biology, particularly cellular senescence and inflammaging, represents another frontier with therapeutic implications.

The identification of CHIP as a prevalent age-related condition with implications for leukemia development has transformed our perspective on hematopoietic malignancies from a binary state to a multistep continuum. This paradigm shift creates unprecedented opportunities for early detection, risk stratification, and preventive intervention. The development of precision prevention strategies targeting specific mutations holds promise for reducing the burden of leukemia while avoiding the toxicity of traditional approaches. As we advance toward implementation of CHIP detection in clinical practice, thoughtful integration with existing risk assessment tools and careful evaluation of interventions will be essential to realize the full potential of this breakthrough in leukemia prevention.