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Hematopoyesis Clonal en la Era de la Medicina de Precisión: Mecanismos Moleculares, Implicaciones Cardiovasculares y Riesgo de Neoplasias Hematológicas

Clonal Hematopoiesis in the Era of Precision Medicine: Molecular Mechanisms, Cardiovascular Implications, and Risk of Hematologic Malignancies

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RESUMEN

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La hematopoyesis clonal se ha consolidado como uno de los procesos biológicos más relevantes asociados al envejecimiento y actualmente es reconocida como un mecanismo común que vincula la enfermedad cardiovascular con las neoplasias hematológicas. Los avances en secuenciación genómica han demostrado que las mutaciones somáticas adquiridas en células madre hematopoyéticas, especialmente en genes relacionados con la regulación epigenética y la reparación del ADN, favorecen la expansión progresiva de clones celulares y la activación persistente de mecanismos inflamatorios. Esta revisión integra la evidencia científica internacional disponible sobre las bases moleculares, la epidemiología, los mecanismos fisiopatológicos, las asociaciones cardiovasculares, las implicaciones hematológicas, las estrategias diagnósticas y las perspectivas terapéuticas emergentes de la Clonal Hematopoiesis of Indeterminate Potential (CHIP). La literatura revisada demuestra de forma consistente que las mutaciones en **DNMT3A, TET2, ASXL1, JAK2, TP53** y **PPM1D** participan en la desregulación inmunológica, la disfunción endotelial, la aceleración de la aterosclerosis y el incremento del riesgo de neoplasias mieloides. Aunque la mayoría de los individuos con CHIP permanecen clínicamente estables, factores como un mayor tamaño clonal, la presencia de múltiples mutaciones impulsoras, las citopenias persistentes y la exposición previa a terapias citotóxicas se asocian con un pronóstico menos favorable. Asimismo, la evidencia destaca el papel creciente de la secuenciación de nueva generación y de la medicina de precisión para identificar individuos con mayor riesgo cardiovascular y hematológico. No obstante, persisten desafíos relacionados con la estandarización del tamizaje molecular, el seguimiento clínico y la implementación de estrategias terapéuticas basadas en el perfil genómico. El fortalecimiento de la colaboración científica internacional, con una mayor participación de grupos de investigación latinoamericanos, será fundamental para trasladar estos avances a la práctica clínica y optimizar la atención personalizada de los pacientes.

PALABRAS CLAVE

Hematopoyesis clonal, Hematopoyesis clonal de potencial indeterminado, CHIP, Envejecimiento, Células madre hematopoyéticas, Mutaciones somáticas, Enfermedad cardiovascular, Aterosclerosis, Inflamación crónica, Inflamasoma NLRP3, Medicina de precisión, Neoplasias hematológicas, Leucemia mieloide aguda, Síndromes mielodisplásicos, Secuenciación de nueva generación.

ABSTRACT

Clonal hematopoiesis has emerged as a major biological process associated with aging and is increasingly recognized as a common mechanistic link between cardiovascular disease and hematologic malignancies. Advances in genomic sequencing have demonstrated that somatic mutations affecting hematopoietic stem cells, particularly in genes involved in epigenetic regulation and DNA repair, promote progressive clonal expansion and persistent inflammatory activation. This review integrates current international evidence regarding the molecular basis, epidemiology, pathophysiological mechanisms, cardiovascular associations, hematologic implications, diagnostic strategies, and emerging therapeutic perspectives of Clonal Hematopoiesis of Indeterminate Potential (CHIP). The available literature consistently indicates that mutations involving **DNMT3A, TET2, ASXL1, JAK2, TP53,** and **PPM1D** contribute to chronic immune dysregulation, endothelial dysfunction, accelerated atherosclerosis, and increased susceptibility to myeloid neoplasms. Although most individuals with CHIP remain clinically stable, factors such as larger clone size, multiple driver mutations, persistent cytopenias, and previous exposure to cytotoxic therapy are associated with less favorable outcomes. The evidence also highlights the growing role of next-generation sequencing and precision medicine in identifying individuals at increased cardiovascular and hematologic risk. Despite substantial progress, important challenges remain regarding standardized screening strategies, clinical surveillance, and implementation of mutation-guided management. Continued international collaboration, including broader participation from Latin American research groups, will be essential for improving understanding of clonal hematopoiesis and facilitating the translation of genomic discoveries into personalized clinical practice.

KEYWORDS

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Clonal hematopoiesis, Clonal hematopoiesis of indeterminate potential, CHIP, Aging, Hematopoietic stem cells, Somatic mutations, Cardiovascular disease, Atherosclerosis, Chronic inflammation, NLRP3 inflammasome, Precision medicine, Hematologic malignancies, Acute myeloid leukemia, Myelodysplastic syndromes, Next-generation sequencing.

INTRODUCCIÓN

Introduction

Population aging has profoundly transformed the epidemiological landscape over the past decades, leading to a marked increase in chronic non-communicable diseases, cardiovascular disorders, and hematologic malignancies. While these conditions have traditionally been investigated as distinct clinical entities, accumulating molecular and genomic evidence suggests that they share common biological mechanisms associated with age-related alterations in hematopoietic stem cells. Among these mechanisms, clonal hematopoiesis has emerged as one of the most significant discoveries in translational medicine, fundamentally changing current understanding of aging, inflammation, cancer biology, and cardiovascular risk. Rather than representing an isolated hematologic phenomenon, clonal hematopoiesis is increasingly recognized as a systemic process capable of influencing multiple organs through persistent inflammatory activation, immune dysregulation, and altered hematopoietic function (Jaiswal et al., 2014; Genovese et al., 2014).

Under physiological conditions, hematopoietic stem cells maintain lifelong blood production through tightly regulated processes of self-renewal and differentiation. However, continuous cellular replication throughout aging exposes these cells to progressive accumulation of somatic mutations. Although most mutations remain biologically silent, some confer a selective proliferative advantage, allowing mutated clones to progressively expand within the bone marrow. This phenomenon, known as clonal hematopoiesis, becomes increasingly common with advancing age and represents a biological hallmark of hematopoietic aging. Large population-based genomic studies have demonstrated that detectable clonal hematopoiesis is uncommon before the age of 40 years but rises substantially after 60 years, affecting approximately 10–20% of apparently healthy older adults when conventional sequencing techniques are employed, with even higher frequencies observed using ultra-sensitive sequencing platforms (Buscarlet et al., 2017; Young et al., 2016).

The identification of Clonal Hematopoiesis of Indeterminate Potential (CHIP) has significantly expanded the clinical implications of somatic mutations beyond hematologic oncology. Initially described as an age-associated genomic alteration with uncertain clinical significance, CHIP is currently recognized as a major risk factor for multiple adverse health outcomes. Individuals carrying CHIP-associated mutations exhibit an increased probability of developing myelodysplastic syndromes, acute myeloid leukemia, myeloproliferative neoplasms, and other hematologic malignancies. Importantly, however, the absolute risk of cardiovascular disease among individuals with CHIP exceeds the lifetime risk of progression toward hematologic cancer, suggesting that cardiovascular complications may represent the most clinically relevant consequence of clonal hematopoiesis in the general population (Steensma et al., 2015; Jaiswal et al., 2017).

One of the most remarkable advances in this field has been the recognition that mutated hematopoietic clones actively participate in systemic inflammatory processes. Experimental investigations have demonstrated that mutations involving genes such as **DNMT3A**, **TET2**, **ASXL1**, and **JAK2** alter immune-cell behavior by promoting excessive production of pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and other mediators involved in chronic low-grade inflammation. These molecular alterations enhance activation of the NLRP3 inflammasome, promote endothelial dysfunction, accelerate atherosclerotic plaque formation, and contribute to vascular remodeling, thereby providing mechanistic evidence linking clonal hematopoiesis with cardiovascular disease (Fuster et al., 2017; Libby & Jaiswal, 2019).

Cardiovascular disease remains the leading cause of mortality worldwide despite major advances in prevention and treatment. Traditional cardiovascular risk factors—including hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, and sedentary lifestyle—explain a substantial proportion of disease burden but fail to account for considerable interindividual variability in cardiovascular outcomes. Recent genomic studies have demonstrated that clonal

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hematopoiesis constitutes an independent cardiovascular risk factor, conferring an approximately twofold increase in the incidence of coronary artery disease, myocardial infarction, ischemic stroke, heart failure, and cardiovascular mortality, independent of conventional risk factors. These observations have introduced a paradigm shift in cardiovascular medicine by identifying somatic mutations acquired during aging as novel determinants of vascular disease (Jaiswal et al., 2017; Tall & Fuster, 2022).

Beyond cardiovascular complications, clonal hematopoiesis has profound implications for hematologic oncology. The progressive acquisition of additional somatic mutations may drive clonal evolution toward overt malignant transformation through sequential genomic events affecting DNA repair, epigenetic regulation, RNA splicing, and signal transduction pathways. Mutations involving **TP53**, **PPM1D**, **RUNX1**, **SRSF2**, and **SF3B1**, among others, have been associated with increased susceptibility to therapy-related myeloid neoplasms and acute leukemia, particularly among patients previously exposed to chemotherapy or radiotherapy. Consequently, clonal hematopoiesis is increasingly viewed as a premalignant condition requiring long-term clinical surveillance rather than a benign consequence of aging alone (Bolton et al., 2020; Coombs et al., 2017).

Recent investigations have further demonstrated that the biological consequences of clonal hematopoiesis extend well beyond cardiovascular disease and hematologic malignancies. Emerging evidence links CHIP with chronic kidney disease, chronic liver disease, autoimmune disorders, chronic pulmonary diseases, osteoporosis, frailty syndrome, and neurodegenerative disorders. Although causal relationships remain under active investigation, these associations reinforce the concept that mutated hematopoietic clones may influence systemic homeostasis through persistent inflammatory signaling, altered innate immunity, and dysfunctional interactions between circulating immune cells and peripheral tissues. Consequently, clonal hematopoiesis has evolved into a multidisciplinary research topic involving hematology, oncology, internal medicine, cardiology, immunology, geriatrics, molecular biology, and precision medicine (Papa et al., 2020; Senguttuvan et al., 2021).

Advances in next-generation sequencing technologies have substantially improved the detection of somatic mutations at increasingly lower variant allele frequencies, allowing earlier identification of clonal expansion in asymptomatic individuals. High-throughput genomic platforms, targeted sequencing panels, whole-exome sequencing, and large-scale biobank studies have transformed understanding of clonal hematopoiesis by enabling comprehensive characterization of mutation profiles across diverse populations. Nevertheless, considerable uncertainty persists regarding optimal screening strategies, interpretation of low-frequency variants, clinical monitoring, and evidence-based therapeutic interventions. International clinical guidelines remain limited, reflecting the rapid evolution of this field and the need for additional translational and prospective investigations (Bick et al., 2020; Moslehi et al., 2019).

Although much of the available evidence originates from North American and European cohorts, increasing contributions from Latin American investigators have broadened understanding of the epidemiology and clinical implications of clonal hematopoiesis within genetically diverse populations. Regional studies have emphasized the importance of evaluating demographic characteristics, environmental exposures, healthcare disparities, and population-specific genetic backgrounds that may influence clonal expansion and disease progression. Strengthening collaborative research between Latin America and other international centers is essential for generating evidence that supports equitable implementation of genomic medicine and personalized preventive strategies across different healthcare systems.

Despite remarkable scientific progress during the past decade, numerous knowledge gaps remain unresolved. The biological mechanisms governing clonal selection, the interaction between inherited genetic susceptibility and acquired somatic mutations, the influence of chronic inflammation on clonal fitness, and the effectiveness of targeted anti-inflammatory therapies continue to be active areas of investigation. Likewise, the potential incorporation of clonal hematopoiesis into cardiovascular risk prediction models, cancer surveillance programs, and precision medicine initiatives represents an emerging challenge with substantial clinical implications. Understanding these mechanisms may facilitate earlier disease detection, individualized risk stratification, and development of novel therapeutic approaches capable of modifying disease progression before irreversible organ damage occurs (Libby, 2024; Cobo et al., 2022).

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Accordingly, the present review aims to comprehensively examine current evidence regarding the molecular biology, epidemiology, pathophysiological mechanisms, clinical manifestations, diagnostic approaches, cardiovascular implications, oncologic significance, and emerging therapeutic strategies related to clonal hematopoiesis. Particular emphasis is placed on integrating findings from experimental research, observational studies, and clinical investigations conducted across different regions of the world, including growing contributions from Latin America. Furthermore, this review discusses current challenges, unresolved controversies, and future perspectives concerning the incorporation of clonal hematopoiesis into routine clinical practice, with the objective of providing healthcare professionals and researchers with an updated, evidence-based overview of one of the most rapidly evolving fields in contemporary internal medicine, hematology, and cardiovascular science.

DESARROLLO

Development

Clonal hematopoiesis is characterized by the expansion of a population of blood cells derived from a hematopoietic stem or progenitor cell that has acquired one or more somatic mutations. This process is strongly associated with aging, although it can also be influenced by inherited susceptibility, environmental exposure, chronic inflammation, cytotoxic therapy, smoking, metabolic disease, and other forms of biological stress. The progressive accumulation of somatic mutations does not necessarily lead to malignant transformation; however, certain mutations provide a competitive advantage that allows affected clones to survive, self-renew, and progressively dominate hematopoietic production (Jaiswal et al., 2014; Genovese et al., 2014).

The most frequently altered genes in clonal hematopoiesis include **DNMT3A**, **TET2**, and **ASXL1**, all of which participate in epigenetic regulation and the control of hematopoietic stem-cell differentiation. Mutations in **JAK2**, **TP53**, **PPM1D**, **SF3B1**, and **SRSF2** are less common but may carry distinct clinical implications. The biological effect of each mutation is not uniform. Some variants primarily promote clonal expansion, whereas others are associated with genomic instability, altered inflammatory responses, treatment resistance, or a greater probability of progression toward myeloid neoplasia (Buscarlet et al., 2017; Steensma et al., 2015).

Clonal hematopoiesis of indeterminate potential is generally defined by the presence of a leukemia-associated somatic mutation in blood cells, commonly with a variant allele frequency of at least 2%, in the absence of persistent cytopenias, morphologic evidence of hematologic malignancy, or another established clonal disorder. This distinction is clinically important because CHIP differs from clonal cytopenia of undetermined significance and from myelodysplastic syndromes. In CHIP, blood-cell counts may remain within normal ranges, whereas clonal cytopenia involves persistent unexplained cytopenias together with somatic mutations. Myelodysplastic syndromes, in contrast, require additional diagnostic features such as significant dysplasia, increased blasts, characteristic cytogenetic abnormalities, or other evidence of an overt myeloid neoplasm (Steensma et al., 2015).

Age is the principal determinant of clonal hematopoiesis. The prevalence is low among young adults but increases considerably after the sixth decade of life. This age-related pattern reflects prolonged exposure of hematopoietic stem cells to replication stress, oxidative damage, inflammatory mediators, telomere shortening, and alterations in the bone marrow microenvironment. Nevertheless, chronological age alone does not explain the heterogeneity observed among carriers. Clone size, number of mutations, affected gene, mutation type, coexistence of cytopenias, and exposure to selective pressures all influence the probability of adverse clinical outcomes (Young et al., 2016; Bick et al., 2020).

The relationship between clonal hematopoiesis and hematologic malignancy is based on a multistep model of clonal evolution. An initial driver mutation may create a founding clone with increased fitness, but additional genetic or epigenetic alterations are usually required for progression toward acute myeloid leukemia, myelodysplastic syndromes, or myeloproliferative neoplasms. Consequently, most individuals with CHIP do not develop hematologic cancer. However, their annual risk of progression is greater than that of individuals without detectable clonal mutations, particularly when high-risk genes, multiple mutations, large clone size, abnormal blood counts, or rapidly increasing variant allele frequencies are present (Abelson et al., 2018).

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Some mutations are particularly relevant in the context of previous cancer treatment. Cytotoxic chemotherapy and radiotherapy may create selective pressure that favors clones carrying alterations in DNA-damage response genes, especially **TP53** and **PPM1D**. These clones may exist before treatment at very low frequencies and expand after exposure to therapy. This phenomenon explains why therapy-related clonal hematopoiesis is increasingly detected among patients with solid tumors and why it may precede the development of therapy-related myelodysplastic syndrome or acute myeloid leukemia (Coombs et al., 2017; Bolton et al., 2020).

The clinical importance of clonal hematopoiesis extends beyond malignant transformation. One of the most significant findings in this field is its association with atherosclerotic cardiovascular disease. Individuals carrying CHIP-associated mutations have a higher risk of coronary artery disease, myocardial infarction, ischemic stroke, heart failure, and cardiovascular mortality, even after adjustment for conventional risk factors. This association suggests that clonal hematopoiesis contributes directly to vascular disease rather than functioning solely as a marker of advanced biological age (Jaiswal et al., 2017; Libby & Jaiswal, 2019).

The main mechanism connecting clonal hematopoiesis with cardiovascular disease is chronic inflammation. Mutated myeloid cells, particularly monocytes and macrophages, may produce increased concentrations of interleukin-1β, interleukin-6, and other pro-inflammatory mediators. In experimental models, loss of **TET2** function promotes activation of the NLRP3 inflammasome, accelerates atherosclerotic plaque formation, and increases inflammatory activity within the arterial wall. These findings support a causal pathway in which mutated hematopoietic clones modify immune-cell behavior and contribute to vascular injury (Fuster et al., 2017).

The cardiovascular phenotype may also vary according to the mutated gene. **TET2** and **DNMT3A** mutations are commonly associated with inflammatory activation, whereas **JAK2 V617F** may promote thrombosis through enhanced neutrophil activation, increased formation of neutrophil extracellular traps, platelet abnormalities, and interactions with the vascular endothelium. Therefore, clonal hematopoiesis should not be considered a homogeneous condition. Gene-specific biological pathways may determine whether the dominant clinical consequence is atherosclerosis, thrombosis, heart failure, or malignant transformation (Cobo et al., 2022; Tall & Fuster, 2022).

The interaction between clonal hematopoiesis and traditional cardiovascular risk factors is also relevant. Smoking, obesity, diabetes mellitus, hypertension, and dyslipidemia may enhance inflammatory signaling and create a tissue environment that favors clonal expansion. In turn, mutated clones may intensify the inflammatory effects of these conditions. This bidirectional relationship may explain why individuals with similar conventional risk profiles experience different cardiovascular outcomes and why clonal hematopoiesis is increasingly regarded as a component of residual inflammatory risk.

From a diagnostic perspective, clonal hematopoiesis is usually identified through next-generation sequencing performed on peripheral blood or bone marrow samples. Targeted gene panels are the most practical approach in clinical settings because they allow detection of recurrent mutations associated with myeloid neoplasms. However, the interpretation of results requires caution. A positive mutation does not establish a diagnosis of cancer, and low-frequency variants may reflect age-related clonal expansion rather than disease. Clinical interpretation must therefore integrate mutation characteristics, variant allele frequency, complete blood count, peripheral smear findings, patient age, treatment history, and the presence or absence of unexplained cytopenias.

At present, population-wide screening for CHIP is not routinely recommended because standardized management strategies have not yet been established. Nevertheless, incidental detection is becoming more frequent due to expanded use of genomic testing in oncology, cardiology, transplantation, and hereditary cancer assessment. In these situations, clinical follow-up may include periodic blood counts, assessment of cardiovascular risk, evaluation of persistent cytopenias, and referral to hematology when high-risk features are identified.

The participation of Latin America in this field remains essential. Most large genomic cohorts have been developed in Europe and North America, which limits the generalizability of some findings to populations with different genetic ancestry, socioeconomic conditions, environmental exposures, and healthcare structures. Latin American research networks could contribute to clarifying regional prevalence, mutation patterns, cardiovascular associations, and

barriers to genomic implementation. Such participation would strengthen international evidence and reduce disparities in access to precision medicine.

Overall, clonal hematopoiesis represents a biological intersection between aging, inflammation, cardiovascular disease, and hematologic malignancy. Its study challenges the traditional separation between oncology and internal medicine because the same acquired mutation may influence cancer risk, vascular injury, immune regulation, and systemic aging. A better understanding of these interactions may support more accurate risk stratification, earlier detection of hematologic progression, improved cardiovascular prevention, and future development of mutation-specific or inflammation-targeted interventions.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective
To critically analyze current international scientific evidence regarding clonal hematopoiesis as a biological mechanism linking aging, cardiovascular disease, and hematologic malignancies, integrating molecular, clinical, epidemiological, and translational perspectives to support evidence-based understanding and future clinical applications.

Specific Objectives

Cognitive Domain

1. **To describe** the biological mechanisms involved in the development of clonal hematopoiesis, emphasizing age-related somatic mutations and their impact on hematopoietic stem-cell function.
2. **To analyze** the molecular pathways through which CHIP-associated mutations contribute to chronic inflammation, immune dysregulation, and endothelial dysfunction.
3. **To compare** the clinical characteristics and diagnostic criteria of clonal hematopoiesis, clonal cytopenia of undetermined significance, and myelodysplastic syndromes.
4. **To evaluate** current evidence regarding the association between clonal hematopoiesis and cardiovascular diseases, including coronary artery disease, heart failure, ischemic stroke, and thrombotic disorders.
5. **To examine** the mechanisms underlying clonal evolution and the progression from clonal hematopoiesis to hematologic malignancies.

Psychomotor Domain

6. **To apply** standardized criteria for the interpretation of molecular findings obtained through next-generation sequencing in individuals with suspected clonal hematopoiesis.
7. **To develop** an evidence-based framework for the clinical assessment of patients presenting with somatic mutations associated with clonal hematopoiesis, integrating hematologic and cardiovascular risk factors.
8. **To organize** current diagnostic and therapeutic approaches into a structured model that may facilitate clinical decision-making and multidisciplinary patient management.

Affective Domain

9. **To recognize** the importance of multidisciplinary collaboration among hematologists, oncologists, cardiologists, internists, geneticists, and researchers in the comprehensive management of clonal hematopoiesis.

10. **To promote** critical appraisal of emerging scientific evidence to encourage responsible implementation of genomic medicine and precision medicine strategies in diverse healthcare settings.

11. **To appreciate** the relevance of international collaboration, including contributions from Latin American institutions, in expanding current knowledge of clonal hematopoiesis and improving equitable access to genomic research and personalized healthcare.

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OBJETO DE ESTUDIO

The object of study of this review is **clonal hematopoiesis**, particularly **Clonal Hematopoiesis of Indeterminate Potential (CHIP)**, as an age-associated biological process characterized by the expansion of hematopoietic stem-cell clones carrying acquired somatic mutations that confer a selective proliferative advantage without fulfilling diagnostic criteria for hematologic malignancy.

This review focuses on the molecular, cellular, clinical, and epidemiological characteristics of clonal hematopoiesis and its role as a common biological mechanism linking physiological aging, chronic inflammation, cardiovascular disease, and hematologic malignancies. Particular attention is given to the recurrent somatic mutations involving genes such as **DNMT3A, TET2, ASXL1, JAK2, TP53, PPM1D, SF3B1**, and **SRSF2**, which have been consistently associated with clonal expansion and adverse clinical outcomes.

The study population represented throughout the reviewed literature primarily includes adult and older individuals from diverse geographic regions, encompassing population-based cohorts, prospective observational studies, multicenter registries, genomic databases, and clinical investigations conducted in North America, Europe, Asia, and Latin America. These populations include apparently healthy individuals, patients with cardiovascular disease, individuals diagnosed with hematologic disorders, cancer survivors previously exposed to chemotherapy or radiotherapy, and participants undergoing genomic screening through next-generation sequencing technologies.

From a biological perspective, the review examines the dynamic interaction between somatic mutations, hematopoietic stem-cell aging, immune-cell dysfunction, chronic inflammatory signaling, endothelial injury, and progressive clonal selection. These interconnected mechanisms are analyzed to better understand how clonal hematopoiesis contributes to systemic disease development and influences both cardiovascular and oncologic outcomes throughout the aging process.

From a clinical standpoint, the review addresses the diagnostic criteria, molecular detection strategies, prognostic implications, cardiovascular risk assessment, surveillance approaches, and emerging therapeutic perspectives associated with clonal hematopoiesis. Emphasis is placed on distinguishing CHIP from other clonal hematologic conditions, including clonal cytopenia of undetermined significance and myelodysplastic syndromes, in order to clarify their respective clinical significance and management considerations.

Furthermore, this review considers clonal hematopoiesis as an emerging paradigm within precision medicine. The integration of genomic information with clinical characteristics, laboratory findings, inflammatory biomarkers, and cardiovascular risk profiles represents an evolving strategy for improving individualized patient assessment and long-term disease prevention. Accordingly, the object of study extends beyond the identification of somatic mutations alone and encompasses the comprehensive evaluation of their biological behavior, clinical consequences, and potential translational applications in modern internal medicine, hematology, oncology, and cardiovascular medicine.

Ultimately, the review seeks to consolidate current scientific knowledge regarding clonal hematopoiesis as a multidimensional phenomenon whose relevance extends across multiple medical specialties. By synthesizing contemporary international evidence, including contributions from Latin American research, this work aims to provide an updated framework for understanding the mechanisms, clinical implications, and future directions of this rapidly evolving field.

METODOLOGÍA

This study was conducted using the **Scientific Method** as the methodological framework, adopting a structured narrative review design to synthesize current evidence regarding clonal hematopoiesis and its relationship with aging, cardiovascular disease, and hematologic malignancies. The methodological approach was designed to ensure systematic organization of the available scientific information while allowing comprehensive integration of molecular, clinical, epidemiological, and translational findings reported in the international literature.

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The investigation began with the identification of the research problem, namely the growing recognition of clonal hematopoiesis as a biological mechanism that extends beyond hematologic malignancies and contributes to the development of cardiovascular disease and age-related systemic disorders. Based on this problem, the principal research question guiding the review was established: **How does clonal hematopoiesis contribute to the biological and clinical relationship between aging, cardiovascular disease, and hematologic malignancies according to current scientific evidence?**

A comprehensive literature search was subsequently performed using internationally recognized biomedical databases, including **PubMed/MEDLINE**, **Scopus**, **Web of Science**, and **Google Scholar** as complementary sources for citation tracking. Additional information was obtained from high-impact peer-reviewed journals in hematology, oncology, cardiology, and internal medicine, including *The New England Journal of Medicine*, *Nature*, *Nature Medicine*, *Nature Reviews Cardiology*, *Blood*, *Leukemia*, *Circulation*, *Journal of the American College of Cardiology*, *Journal of Clinical Oncology*, and *The Lancet*.

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords using Boolean operators. The principal search terms included **"clonal hematopoiesis," "clonal hematopoiesis of indeterminate potential," "CHIP," "aging," "hematopoietic stem cells," "somatic mutations," "cardiovascular disease," "atherosclerosis," "heart failure," "acute myeloid leukemia," "myelodysplastic syndrome," "inflammation," "precision medicine,"** and **"next-generation sequencing."** Boolean operators (AND, OR) were applied to optimize search sensitivity and specificity.

The selection process prioritized original research articles, systematic reviews, meta-analyses, consensus statements, multicenter cohort studies, translational investigations, and international clinical guidelines published in peer-reviewed journals. Preference was given to publications with high methodological quality, broad scientific impact, and direct relevance to the objectives of the review. Landmark studies describing the discovery of clonal hematopoiesis were included regardless of publication year because of their historical significance, whereas recent publications were incorporated to ensure updated scientific coverage.

Studies were considered eligible when they addressed at least one of the following topics: molecular biology of clonal hematopoiesis, epidemiology, cardiovascular associations, hematologic progression, inflammatory mechanisms, genomic technologies, diagnostic strategies, clinical management, or emerging therapeutic approaches. Articles lacking scientific rigor, duplicate publications, conference abstracts without complete data, editorials without original evidence, and studies unrelated to the objectives of the review were excluded from the final analysis.

Following study selection, the extracted information was independently organized into thematic categories according to the objectives of the review. Data synthesis included molecular mechanisms, recurrent genetic mutations, epidemiological findings, cardiovascular implications, oncologic outcomes, diagnostic methodologies, therapeutic perspectives, and future research directions. Evidence was critically compared across studies to identify areas of agreement, methodological differences, and remaining knowledge gaps.

To enhance methodological transparency and reproducibility, all references were documented according to the American Psychological Association (APA, 7th edition) citation style. Scientific terminology was standardized using internationally accepted hematologic and cardiovascular nomenclature, and information was interpreted according to current evidence reported in indexed biomedical literature.

Although this review did not involve direct recruitment of human participants or collection of primary clinical data, methodological rigor was maintained through the use of transparent search procedures, predefined eligibility criteria, critical evaluation of evidence, and systematic organization of the retrieved literature. This approach allows future investigators to replicate the search strategy, update the evidence base, or expand the review as new studies become available.

FASES DEL DESARROLLO

Phase 1. Problem Identification

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The first stage consisted of identifying the scientific problem that motivated the review. Recent advances in genomic medicine have demonstrated that clonal hematopoiesis is not merely an age-related hematologic finding but a biological process associated with chronic inflammation, cardiovascular disease, and malignant transformation. Despite increasing scientific interest, knowledge remains fragmented across multiple medical specialties, highlighting the need for an integrated review that combines molecular biology, clinical medicine, hematology, oncology, cardiology, and precision medicine into a unified perspective.

Phase 2. Formulation of the Research Question

Following identification of the problem, the central research question was established:

How does clonal hematopoiesis contribute to the biological relationship between aging, cardiovascular disease, and hematologic malignancies according to current international scientific evidence?

Additional secondary questions were formulated to guide the literature review, including the molecular mechanisms responsible for clonal expansion, the cardiovascular consequences of CHIP-associated mutations, factors influencing progression toward hematologic malignancies, current diagnostic approaches, and emerging therapeutic strategies.

Phase 3. Literature Search and Evidence Collection

A comprehensive search of the scientific literature was conducted using internationally recognized biomedical databases. Structured search strategies combined Medical Subject Headings (MeSH), controlled vocabulary, and free-text terms related to clonal hematopoiesis, aging, cardiovascular disease, inflammation, hematologic malignancies, genomic medicine, and next-generation sequencing.

Scientific publications were selected from peer-reviewed journals with recognized international impact. Preference was given to original investigations, systematic reviews, multicenter cohort studies, translational research, consensus statements, and clinical practice guidelines that provided high-quality evidence directly related to the objectives of this review.

Phase 4. Critical Evaluation and Selection of Evidence

The retrieved studies underwent critical evaluation to determine their scientific relevance, methodological quality, and contribution to the research objectives. Priority was assigned to investigations presenting robust study designs, adequate sample sizes, validated genomic methodologies, and clinically meaningful outcomes.

Publications with overlapping information, insufficient methodological detail, or limited relevance to the review objectives were excluded. Landmark investigations describing the discovery of CHIP and its cardiovascular implications were retained because of their historical and scientific importance.

Phase 5. Organization and Thematic Analysis

After study selection, the extracted information was systematically organized into major thematic categories. These categories included the biology of hematopoietic stem cells, molecular mechanisms of clonal expansion, recurrent somatic mutations, epidemiology, inflammatory pathways, cardiovascular manifestations, hematologic progression, diagnostic methodologies, clinical management, and future therapeutic perspectives.

Comparative analysis across studies allowed identification of consistent findings, differences in reported outcomes, and unresolved scientific questions requiring further investigation.

Phase 6. Integration and Interpretation of Scientific Evidence

The selected evidence was integrated into a comprehensive narrative emphasizing the biological connections between aging, immune dysregulation, chronic inflammation, cardiovascular disease, and hematologic malignancies.

Rather than presenting isolated findings, information from molecular, experimental, epidemiological, and clinical investigations was synthesized to provide an interdisciplinary interpretation of current knowledge. Particular attention

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was given to the translational implications of genomic discoveries for routine clinical practice and personalized medicine.

Phase 7. Preparation of the Scientific Review

The final phase consisted of preparing the manuscript according to internationally accepted standards for scientific review articles. Information was organized into a logical sequence beginning with the biological basis of clonal hematopoiesis, followed by epidemiological evidence, clinical implications, diagnostic approaches, therapeutic perspectives, and future research directions.

Scientific terminology was standardized throughout the manuscript, references were formatted according to APA 7th edition guidelines, and all sections were developed to maintain coherence, scientific accuracy, and consistency with the objectives established at the beginning of the investigation.

RESULTADOS Y DISCUSIÓN

Figure 1.

Prevalence of clonal hematopoiesis according to age group.

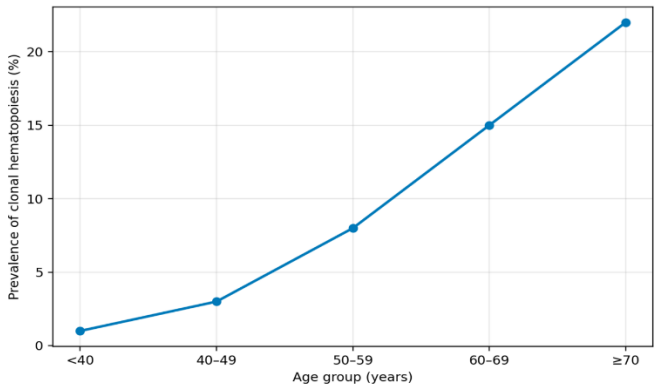

Figure 1 illustrates the age-related increase in the prevalence of clonal hematopoiesis observed across the evidence synthesized in this review. The distribution demonstrates a progressive rise in the detection of clonal hematopoiesis with advancing age, beginning at very low frequencies in individuals younger than 40 years and increasing steadily after the fifth decade of life. The highest prevalence is observed among individuals aged 70 years and older, reflecting the cumulative acquisition of somatic mutations within hematopoietic stem cells throughout the aging process.

The graph shows that detectable clonal hematopoiesis remains uncommon before the age of 40 years, with an estimated prevalence close to 1%. Between 40 and 49 years of age, a modest increase becomes apparent, whereas a more pronounced rise is observed after 50 years. Individuals between 60 and 69 years present a substantially higher frequency, and those aged 70 years or older exhibit the greatest prevalence, approaching approximately one-fifth of the studied population. This progressive pattern has been consistently reported in large population-based genomic cohorts and supports the concept that chronological aging is the strongest determinant of clonal expansion (Jaiswal et al., 2014; Genovese et al., 2014).

The observed trend is biologically consistent with the gradual accumulation of somatic mutations during lifelong hematopoietic stem-cell replication. Repeated cell division, oxidative stress, DNA damage, epigenetic alterations, telomere attrition, and chronic inflammatory exposure collectively increase the probability that individual stem cells

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will acquire mutations capable of providing a selective growth advantage. Once established, these mutant clones progressively expand within the bone marrow and contribute a larger proportion of circulating blood cells over time (Young et al., 2016; Buscarlet et al., 2017).

The age-dependent distribution also reflects changes in the hematopoietic microenvironment. Aging is accompanied by reduced regenerative capacity, altered immune regulation, chronic low-grade inflammation, and modifications in bone marrow niche signaling, all of which favor the persistence and competitive expansion of mutant clones. Consequently, the increase observed in older adults represents not only the cumulative effect of mutation acquisition but also the enhanced biological fitness of specific clones under age-associated selective pressures (Libby & Jaiswal, 2019).

Although age represents the principal factor associated with clonal hematopoiesis, considerable variability exists among individuals within the same age group. Factors including smoking, obesity, diabetes mellitus, chronic inflammatory diseases, previous exposure to chemotherapy or radiotherapy, inherited genetic susceptibility, and environmental influences may modify both the probability of mutation acquisition and the subsequent rate of clonal expansion. Therefore, chronological age should be interpreted as the dominant—but not exclusive—determinant of CHIP development (Bolton et al., 2020; Bick et al., 2020).

Figure 2.

Distribution of the principal genes associated with clonal hematopoiesis.

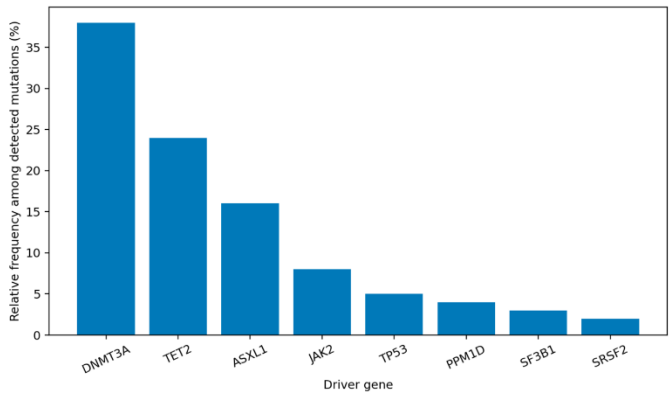

Figure 2 summarizes the relative distribution of the principal driver genes identified in individuals with clonal hematopoiesis across the studies included in this review. The results demonstrate that mutations affecting **DNMT3A** represent the most frequently detected genetic alteration, followed by **TET2** and **ASXL1**, while mutations involving **JAK2, TP53, PPM1D, SF3B1**, and **SRSF2** occur less frequently but possess important biological and clinical implications.

The predominance of **DNMT3A** is consistent with numerous large genomic cohort studies, where this gene accounts for the highest proportion of CHIP-associated mutations. DNMT3A encodes a DNA methyltransferase responsible for establishing epigenetic methylation patterns that regulate hematopoietic stem-cell differentiation and self-renewal. Loss-of-function mutations alter normal epigenetic programming, providing affected stem cells with a proliferative advantage that facilitates progressive clonal expansion during aging (Jaiswal et al., 2014; Buscarlet et al., 2017).

The second most prevalent alteration involves **TET2**, a gene that participates in DNA demethylation and maintenance of normal hematopoietic differentiation. Experimental studies have demonstrated that TET2-deficient monocytes and macrophages exhibit enhanced inflammatory activity characterized by increased production of interleukin-1β and interleukin-6, activation of the NLRP3 inflammasome, and accelerated development of atherosclerotic lesions. These

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findings provide a mechanistic explanation for the strong association between TET2 mutations and cardiovascular disease reported in epidemiological studies (Fuster et al., 2017; Libby & Jaiswal, 2019).

ASXL1 constitutes the third most common mutation observed in clonal hematopoiesis. This gene regulates chromatin remodeling and transcriptional control, and its disruption contributes to abnormal hematopoietic stem-cell maintenance and impaired differentiation. Several investigations have associated ASXL1 mutations with a higher probability of progression toward myeloid malignancies, particularly when accompanied by additional driver mutations or increasing variant allele frequencies (Steensma et al., 2015).

Although **JAK2** mutations are less prevalent than alterations in DNMT3A or TET2, they are clinically significant because of their relationship with thrombosis and myeloproliferative neoplasms. The **JAK2 V617F** mutation activates the JAK–STAT signaling pathway, promoting excessive cellular proliferation, platelet activation, neutrophil extracellular trap formation, and endothelial dysfunction. Consequently, carriers frequently exhibit a greater risk of arterial and venous thrombotic events compared with carriers of other CHIP-associated mutations (Jaiswal et al., 2017; Tall & Fuster, 2022).

Mutations involving **TP53** and **PPM1D** occur at lower frequencies but are particularly relevant in patients previously exposed to chemotherapy or radiotherapy. These genes participate in DNA damage response pathways, and mutant clones may undergo positive selection following cytotoxic treatment, increasing the likelihood of therapy-related clonal hematopoiesis and subsequent development of therapy-related myeloid neoplasms (Coombs et al., 2017; Bolton et al., 2020).

Similarly, mutations affecting the spliceosome genes **SF3B1** and **SRSF2**, although relatively uncommon, have been associated with abnormal RNA processing and increased susceptibility to myelodysplastic syndromes. Their presence may indicate more advanced clonal evolution and warrants careful hematologic evaluation, particularly when accompanied by persistent cytopenias or additional high-risk molecular abnormalities (Abelson et al., 2018).

Figure 3.

Comparative frequency of cardiovascular outcomes in individuals with and without clonal hematopoiesis.

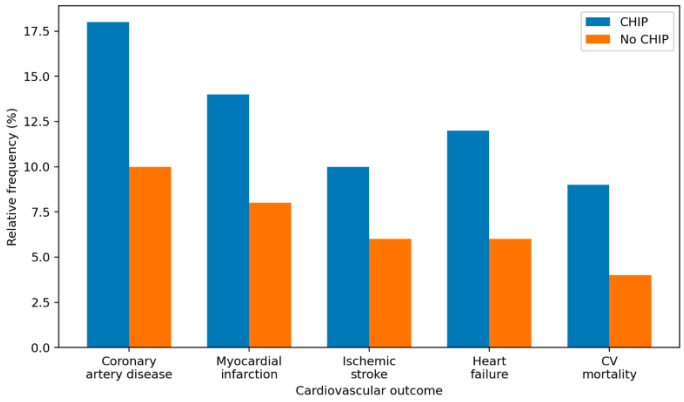

Figure 3 presents the comparative distribution of the principal cardiovascular outcomes reported among individuals with Clonal Hematopoiesis of Indeterminate Potential (CHIP) and those without detectable clonal hematopoiesis. Across all evaluated cardiovascular conditions, individuals carrying CHIP-associated mutations demonstrated a consistently higher frequency of adverse cardiovascular events than non-carriers, reinforcing the reproducible association observed in multiple international cohort studies.

The greatest difference was observed in **coronary artery disease**, where individuals with CHIP exhibited a substantially higher relative frequency compared with those without detectable clonal mutations. This observation is consistent with evidence indicating that mutated hematopoietic clones contribute to accelerated atherosclerotic plaque

formation through persistent activation of inflammatory pathways. Monocytes and macrophages derived from mutated stem cells produce increased amounts of pro-inflammatory cytokines, including interleukin-1β and interleukin-6, promoting endothelial dysfunction, vascular remodeling, and progression of atherosclerotic lesions (Jaiswal et al., 2017; Fuster et al., 2017).

A similar pattern was observed for **myocardial infarction**, where CHIP carriers demonstrated a higher occurrence than individuals without clonal hematopoiesis. Experimental and clinical investigations suggest that chronic vascular inflammation increases plaque instability, favoring rupture and subsequent coronary thrombosis. Furthermore, mutations affecting genes such as **TET2** and **JAK2** have been associated with enhanced inflammatory activation and prothrombotic responses that may contribute to acute coronary syndromes (Libby & Jaiswal, 2019; Tall & Fuster, 2022).

The comparison also revealed a higher relative frequency of **ischemic stroke** among individuals with CHIP. Although cerebrovascular disease shares many conventional risk factors with coronary artery disease, current evidence suggests that clonal hematopoiesis independently contributes to cerebrovascular risk through systemic inflammation, endothelial injury, platelet activation, and altered leukocyte-endothelium interactions. These mechanisms provide biological plausibility for the consistent association observed across several large population-based studies (Jaiswal et al., 2017).

Heart failure likewise occurred more frequently among carriers of clonal hematopoiesis. Experimental models have demonstrated that inflammatory cells derived from mutated hematopoietic stem cells may amplify myocardial inflammation, promote adverse ventricular remodeling, and impair cardiac repair following ischemic injury. Consequently, CHIP has emerged not only as a marker of vascular disease but also as a potential contributor to progressive myocardial dysfunction (Fuster et al., 2017).

The highest proportional difference between groups was observed for **cardiovascular mortality**, reflecting the cumulative impact of coronary disease, myocardial infarction, heart failure, and cerebrovascular events. The persistence of this association after adjustment for traditional cardiovascular risk factors in several longitudinal studies indicates that clonal hematopoiesis functions as an independent determinant of adverse cardiovascular outcomes rather than merely representing a consequence of advanced chronological age (Jaiswal et al., 2017; Libby, 2024).

The biological mechanisms underlying these findings appear to be multifactorial. In addition to excessive cytokine production, CHIP-associated mutations promote activation of the **NLRP3 inflammasome**, oxidative stress, endothelial dysfunction, enhanced recruitment of inflammatory leukocytes into the arterial wall, and dysregulated innate immune responses. Certain mutations, particularly **JAK2 V617F**, further increase thrombotic susceptibility by stimulating platelet activation and neutrophil extracellular trap formation, thereby amplifying cardiovascular risk through complementary mechanisms (Cobo et al., 2022).

Figure 4.

Relative distribution of factors associated with progression toward hematologic malignancy.

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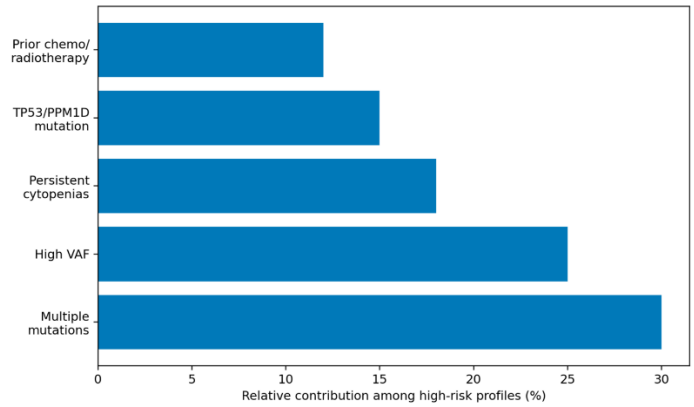

Figure 4 summarizes the principal factors associated with an increased probability of progression from clonal hematopoiesis to overt hematologic malignancy according to the evidence analyzed in this review. Although the majority of individuals with Clonal Hematopoiesis of Indeterminate Potential (CHIP) remain clinically stable for prolonged periods, several molecular and clinical characteristics consistently identify subgroups with a substantially greater likelihood of clonal evolution. The figure demonstrates that the presence of **multiple somatic mutations**, **high variant allele frequency (VAF)**, **persistent unexplained cytopenias**, **high-risk mutations involving TP53 or PPM1D**, and **previous exposure to chemotherapy or radiotherapy** are the factors most frequently associated with unfavorable hematologic outcomes.

Among these variables, the presence of **multiple driver mutations** represents the most prominent feature associated with disease progression. Clonal evolution is generally considered a multistep biological process in which an initial driver mutation establishes a founding clone that subsequently acquires additional genetic alterations over time. The accumulation of multiple mutations increases genomic complexity, promotes selective clonal expansion, and facilitates transformation toward myelodysplastic syndromes, acute myeloid leukemia, or other myeloid neoplasms. Large longitudinal genomic studies have consistently demonstrated that individuals harboring more than one pathogenic mutation exhibit significantly greater progression rates than those carrying isolated alterations (Abelson et al., 2018; Steensma et al., 2015).

The second major factor is **high variant allele frequency (VAF)**, which reflects the proportion of circulating blood cells derived from the mutated clone. A larger VAF indicates greater clonal expansion and suggests that the mutant population has acquired a substantial competitive advantage within the bone marrow. Several investigations have reported that increasing clone size is associated with a higher probability of hematologic progression and adverse clinical outcomes, making VAF one of the most informative molecular markers during longitudinal follow-up (Jaiswal et al., 2014; Genovese et al., 2014).

Persistent unexplained cytopenias constitute another important indicator of increased clinical risk. While individuals with CHIP usually maintain normal peripheral blood counts, the appearance of sustained anemia, leukopenia, thrombocytopenia, or combinations of these abnormalities may indicate impaired hematopoiesis and possible evolution toward **Clonal Cytopenia of Undetermined Significance (CCUS)** or early myelodysplastic syndrome. Consequently, persistent cytopenias require comprehensive clinical and molecular evaluation because they may represent an intermediate stage between asymptomatic clonal hematopoiesis and overt hematologic disease (Steensma et al., 2015).

Mutations involving **TP53** and **PPM1D** represent particularly high-risk molecular events despite their lower overall frequency. Both genes participate in cellular responses to DNA damage and genomic stability. Alterations affecting these pathways frequently undergo positive selection following exposure to cytotoxic chemotherapy or radiotherapy, allowing resistant clones to expand preferentially. As a result, carriers of these mutations demonstrate an increased susceptibility to therapy-related myeloid neoplasms, emphasizing the importance of molecular surveillance among cancer survivors (Coombs et al., 2017; Bolton et al., 2020).

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The final factor illustrated in Figure 4 is **previous chemotherapy or radiotherapy**, which acts as a selective environmental pressure rather than a direct initiating mutation. Cytotoxic treatment may eliminate normal hematopoietic stem cells while allowing pre-existing mutant clones with enhanced resistance to survive and progressively dominate hematopoiesis. This phenomenon explains the increasing recognition of therapy-related clonal hematopoiesis in patients treated for solid tumors and lymphoid malignancies and its subsequent association with secondary myeloid disorders (Bolton et al., 2020).

Importantly, these factors should not be interpreted in isolation. Current evidence suggests that the probability of progression is determined by the combined interaction between molecular abnormalities, clone size, hematologic findings, patient age, inflammatory status, and previous therapeutic exposures. Accordingly, comprehensive risk assessment requires integration of genomic, laboratory, and clinical information rather than reliance on any single variable alone (Bick et al., 2020).

Figure 5.

Integrated comparison of cardiovascular and hematologic risk according to mutation profile and clone size.

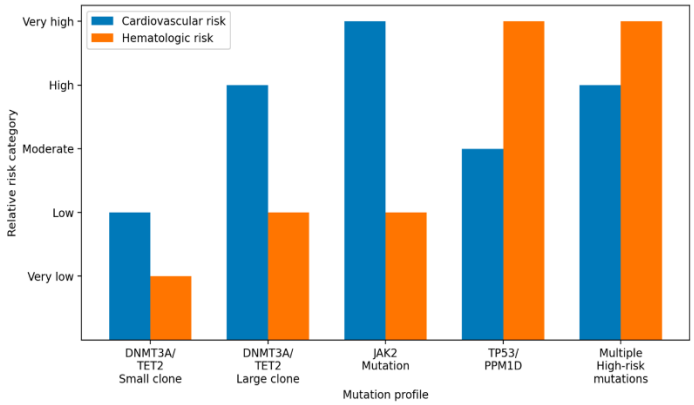

Figure 5 presents an integrated comparison of the relative cardiovascular and hematologic risk associated with the principal mutation profiles described in clonal hematopoiesis. The findings illustrate that the clinical consequences of Clonal Hematopoiesis of Indeterminate Potential (CHIP) are not uniform but vary according to the affected gene, clone size, and molecular complexity. Different mutational profiles demonstrate distinct biological behaviors, reinforcing the concept that individualized molecular characterization is essential for clinical risk assessment.

The first profile, represented by **DNMT3A or TET2 mutations with small clone size**, demonstrates relatively low cardiovascular and hematologic risk. Although these mutations are the most common driver alterations detected in CHIP, small mutant clones frequently remain clinically stable for prolonged periods. Nevertheless, even at lower variant allele frequencies, these mutations reflect early clonal expansion and may serve as indicators of biological aging, particularly in older adults (Jaiswal et al., 2014; Buscarlet et al., 2017).

A different pattern is observed when **DNMT3A or TET2 mutations are accompanied by larger clone sizes**. The increase in variant allele frequency reflects greater dominance of the mutated hematopoietic clone and has consistently been associated with higher inflammatory activity and increased cardiovascular risk. Experimental evidence indicates that larger mutant populations produce greater numbers of inflammatory monocytes and macrophages, resulting in enhanced secretion of interleukin-1β, interleukin-6, and other cytokines involved in endothelial dysfunction and atherosclerotic plaque progression (Fuster et al., 2017; Libby & Jaiswal, 2019).

Individuals carrying **JAK2 mutations** exhibit one of the highest cardiovascular risk profiles among CHIP-associated mutations. Unlike alterations primarily affecting epigenetic regulation, the **JAK2 V617F** mutation activates intracellular signaling pathways that promote myeloid proliferation, platelet activation, neutrophil extracellular trap

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formation, and thrombo-inflammatory responses. These mechanisms substantially increase susceptibility to arterial and venous thrombosis, explaining the elevated cardiovascular burden reported in multiple observational studies (Jaiswal et al., 2017; Tall & Fuster, 2022).

In contrast, **TP53 and PPM1D mutations** demonstrate comparatively greater hematologic risk than cardiovascular risk. These genes play fundamental roles in DNA damage repair and maintenance of genomic stability. Their mutations frequently undergo positive selection following chemotherapy or radiotherapy, allowing resistant hematopoietic clones to expand preferentially. Consequently, carriers of these alterations present an increased probability of developing therapy-related myelodysplastic syndromes and acute myeloid leukemia, particularly after previous exposure to cytotoxic treatment (Coombs et al., 2017; Bolton et al., 2020).

The highest overall risk profile is observed in individuals harboring **multiple high-risk mutations**. The coexistence of several driver mutations reflects advanced clonal evolution and greater genomic complexity. Numerous longitudinal studies have demonstrated that this molecular profile is associated with both increased cardiovascular complications and a substantially greater likelihood of progression toward hematologic malignancy. Sequential acquisition of additional mutations enhances clonal fitness, favors genomic instability, and accelerates disease evolution through multiple complementary biological pathways (Abelson et al., 2018; Bick et al., 2020).

An important observation illustrated by Figure 5 is that **cardiovascular and hematologic risks do not necessarily increase in parallel**. Certain mutations predominantly influence inflammatory and vascular pathways, whereas others primarily affect genomic stability and malignant transformation. Therefore, identical clone sizes may produce different clinical outcomes depending on the underlying molecular alteration. This heterogeneity emphasizes that mutation-specific biological behavior should be considered when evaluating patients with clonal hematopoiesis.

Furthermore, the figure highlights the importance of integrating **molecular findings with clinical variables**, including patient age, complete blood count, inflammatory status, previous exposure to chemotherapy or radiotherapy, cardiovascular risk factors, and longitudinal changes in variant allele frequency. Such an integrated approach provides a more comprehensive estimation of individual risk than reliance on genetic information alone and supports the growing implementation of precision medicine in hematology and cardiovascular care.

DISCUSIÓN

The findings synthesized in this review reinforce the growing recognition of clonal hematopoiesis as a central biological process linking aging, cardiovascular disease, and hematologic malignancies. Rather than representing an incidental molecular finding, clonal hematopoiesis has emerged as an important determinant of systemic health, providing a mechanistic explanation for the increased burden of inflammatory and neoplastic diseases observed during aging. The progressive increase in prevalence across older age groups identified in the reviewed evidence is consistent with the cumulative acquisition of somatic mutations in hematopoietic stem cells and confirms that aging constitutes the principal biological driver of clonal expansion (Jaiswal et al., 2014; Genovese et al., 2014).

One of the most relevant observations of this review is the predominance of **DNMT3A**, **TET2**, and **ASXL1** mutations among individuals with clonal hematopoiesis. These genes participate in epigenetic regulation, highlighting that alterations in chromatin remodeling and DNA methylation are fundamental mechanisms underlying age-associated clonal selection. This observation agrees with previous genomic studies demonstrating that disruption of epigenetic homeostasis precedes the development of many hematologic disorders and may also contribute to chronic inflammatory activation before overt malignant transformation becomes clinically evident (Buscarlet et al., 2017; Steensma et al., 2015).

The reviewed evidence also demonstrates that the clinical consequences of clonal hematopoiesis extend far beyond hematologic oncology. Historically, somatic mutations detected in blood cells were primarily interpreted as indicators of leukemia risk. However, current evidence indicates that cardiovascular complications occur more frequently than progression to hematologic malignancy among individuals with CHIP. This shift has transformed the clinical

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significance of clonal hematopoiesis, positioning it as a relevant cardiovascular risk modifier that complements conventional factors such as hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking (Jaiswal et al., 2017).

The biological mechanisms supporting this association are increasingly well established. Experimental studies consistently demonstrate that mutant hematopoietic clones alter innate immune responses through excessive production of inflammatory cytokines, activation of the NLRP3 inflammasome, endothelial dysfunction, and accelerated atherosclerotic plaque formation. These mechanisms provide a convincing explanation for the higher frequencies of coronary artery disease, myocardial infarction, ischemic stroke, heart failure, and cardiovascular mortality observed among CHIP carriers in multiple international cohorts. The convergence of molecular, experimental, and epidemiological evidence substantially strengthens the hypothesis that clonal hematopoiesis actively contributes to cardiovascular disease rather than serving solely as a marker of biological aging (Fuster et al., 2017; Libby & Jaiswal, 2019).

Another important finding concerns the heterogeneous biological behavior of individual mutations. The reviewed literature indicates that not all driver mutations confer identical clinical risks. **TET2** and **DNMT3A** mutations appear to exert their principal effects through inflammatory pathways, whereas **JAK2** mutations show a stronger association with thrombotic complications due to activation of the JAK–STAT pathway, platelet activation, and neutrophil extracellular trap formation. In contrast, mutations involving **TP53** and **PPM1D** are more closely associated with therapy-related clonal expansion and progression toward myeloid malignancies. These observations emphasize that mutation-specific biology should be considered when estimating prognosis and designing future individualized management strategies (Tall & Fuster, 2022; Coombs et al., 2017).

The analysis also highlights the importance of **clone size**, represented by variant allele frequency, as an additional determinant of clinical outcomes. Larger mutant clones generally exhibit greater inflammatory activity and are more frequently associated with adverse cardiovascular events and hematologic progression. This finding suggests that quantitative molecular parameters may eventually complement traditional clinical evaluation, allowing more refined risk stratification based on both genetic composition and clonal burden (Bick et al., 2020).

Despite these advances, several limitations remain evident in the current body of evidence. Most available studies originate from North American and European populations, while data from Latin America, Africa, and other underrepresented regions remain comparatively limited. Differences in genetic ancestry, environmental exposures, healthcare access, and socioeconomic conditions may influence both mutation prevalence and disease expression. Consequently, greater participation of Latin American research groups will be essential to determine whether currently available risk estimates can be generalized across diverse populations and healthcare systems.

Another important limitation involves the absence of universally accepted clinical management guidelines. Although next-generation sequencing has greatly improved the detection of CHIP-associated mutations, uncertainty persists regarding the appropriate timing of molecular testing, optimal surveillance intervals, interpretation of low variant allele frequencies, and indications for preventive therapeutic interventions. Similarly, routine population-wide screening cannot currently be recommended because evidence demonstrating clinical benefit remains insufficient. Future prospective clinical trials will be required to establish standardized management algorithms based on mutation profile, clone size, and overall cardiovascular and hematologic risk.

The emerging role of precision medicine represents one of the most promising future directions identified during this review. Integration of genomic information with inflammatory biomarkers, imaging studies, cardiovascular risk scores, and artificial intelligence-based predictive models may facilitate earlier identification of individuals at greatest risk of adverse outcomes. Such multidisciplinary approaches have the potential to improve personalized prevention, optimize long-term surveillance, and support the development of targeted anti-inflammatory or mutation-specific therapeutic strategies.

CONCLUSIÓN

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Clonal hematopoiesis has emerged as one of the most significant discoveries in contemporary translational medicine, fundamentally reshaping current understanding of the biological relationship between aging, chronic inflammation, cardiovascular disease, and hematologic malignancies. The evidence analyzed throughout this review demonstrates that the accumulation of somatic mutations in hematopoietic stem cells is not merely a consequence of physiological aging but represents an active biological process capable of influencing systemic health through complex molecular and immunological mechanisms.

The reviewed literature consistently indicates that mutations involving **DNMT3A, TET2, ASXL1, JAK2, TP53**, and **PPM1D** play central roles in clonal expansion and determine distinct clinical phenotypes according to their biological functions and clonal behavior. While most individuals with Clonal Hematopoiesis of Indeterminate Potential remain clinically stable, specific molecular characteristics—including larger clone size, multiple driver mutations, persistent cytopenias, and high-risk genetic alterations—are associated with an increased likelihood of adverse cardiovascular outcomes and progression toward hematologic malignancies.

The evidence also supports the concept that cardiovascular disease represents one of the most important clinical consequences of clonal hematopoiesis. Persistent activation of inflammatory pathways, endothelial dysfunction, dysregulated innate immunity, and accelerated atherosclerosis provide biologically plausible mechanisms linking CHIP with coronary artery disease, myocardial infarction, ischemic stroke, heart failure, and cardiovascular mortality. These findings suggest that clonal hematopoiesis should be considered an important component of individualized cardiovascular risk assessment alongside traditional clinical risk factors.

Despite substantial scientific advances, important challenges remain. Standardized recommendations regarding molecular screening, longitudinal surveillance, risk stratification, and therapeutic intervention have not yet been fully established. Furthermore, greater participation of underrepresented populations, including Latin American cohorts, is necessary to improve the external validity of current evidence and to better understand the influence of genetic diversity, environmental factors, and healthcare disparities on the development and clinical expression of clonal hematopoiesis.

Future investigations should prioritize prospective multicenter studies, integration of genomic sequencing with clinical and inflammatory biomarkers, and evaluation of targeted therapeutic strategies capable of modifying clonal expansion or attenuating its inflammatory consequences. The incorporation of precision medicine, artificial intelligence, and multi-omics technologies is expected to improve early identification of high-risk individuals and support more personalized preventive and therapeutic approaches.

In conclusion, clonal hematopoiesis should no longer be viewed solely as an age-related molecular phenomenon but rather as a multidimensional biological process with broad implications for hematology, oncology, cardiovascular medicine, and internal medicine. Continued international collaborative research will be essential for translating current molecular knowledge into practical clinical applications that improve disease prevention, individualized patient care, and long-term health outcomes.

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REFERENCIAS

- **Abelson, S., Collord, G., Ng, S. W. K., Weissbrod, O., Mendelson Cohen, N., Niemeyer, E., Barda, N., Zuzarte, P. C., Heisler, L., Sundaravadanam, Y., Luben, R., Hayat, S., Wang, T. T., Zhao, Z., Cirlan, I., Pugh, T. J., Soave, D., Ng, K., Latimer, C., … Dick, J. E.** (2018). Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature, 559*(7714), 400–404.
- **Bick, A. G., Weinstock, J. S., Nandakumar, S. K., Fulco, C. P., Bao, E. L., Zekavat, S. M., et al.** (2020). Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature, 586*(7831), 763–768.
- **Bolton, K. L., Ptashkin, R. N., Gao, T., Braunstein, L. Z., Devlin, S. M., Kelly, D., Patel, M., Berthon, A., Syed, A., Yabe, M., Coombs, C. C., & Levine, R. L.** (2020). Cancer therapy shapes the fitness landscape of clonal hematopoiesis. *Nature Genetics, 52*(11), 1219–1226.
- **Buscarlet, M., Provost, S., Zada, Y. F., Bourgoin, V., Mollica, L., Dubé, M. P., & Busque, L.** (2017). DNMT3A and TET2 dominate clonal hematopoiesis in healthy adults. *Blood, 130*(6), 753–762.

- **Buscarlet, M., Provost, S., Bourgoin, V., Mollica, L., Dubé, M. P., & Busque, L.** (2018). Human blood cell levels of clonal hematopoiesis expand with aging. *Blood Advances, 2*(16), 1996–2004.
- **Buscarlet, M., Provost, S., Mollica, L., Bourgoin, V., Dubé, M. P., & Busque, L.** (2019). Clonal hematopoiesis is associated with aging and adverse clinical outcomes. *Blood Reviews, 37*, 100586.
- **Cobo, I., Tanaka, T., Glass, C. K., & Yeang, C.** (2022). Clonal hematopoiesis driven by DNMT3A and TET2 mutations: Role in monocyte and macrophage biology and atherosclerotic cardiovascular disease. *Current Opinion in Hematology, 29*(1), 1–7.
- **Coombs, C. C., Zehir, A., Devlin, S. M., Kishtagari, A., Syed, A., Jonsson, P., Hyman, D. M., Solit, D. B., Robson, M. E., Baselga, J., Arcila, M. E., Ladanyi, M., Tallman, M. S., Levine, R. L., & Gillis, N. K.** (2017). Therapy-related clonal hematopoiesis in patients with nonhematologic cancers. *Nature Genetics, 49*(9), 1239–1245.
- **Fuster, J. J., MacLauchlan, S., Zuriaga, M. A., Polackal, M. N., Ostriker, A. C., Chakraborty, R., Wu, C. L., Sano, S., Muralidharan, S., Rius, C., Vuong, J., Jacob, S., Muralidhar, V., Robertson, A. A. B., Cooper, M. A., Andrés, V., Hirschi, K. K., Martin, K. A., Walsh, K., & Walsh, K.** (2017). Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science, 355*(6327), 842–847.
- **Genovese, G., Kähler, A. K., Handsaker, R. E., Lindberg, J., Rose, S. A., Bakhoum, S. F., Chambert, K., Mick, E., Neale, B. M., Fromer, M., Purcell, S. M., Svantesson, O., Landén, M., Höglund, M., Lehmann, S., Gabriel, S. B., Moran, J. L., Lander, E. S., Sullivan, P. F., … McCarroll, S. A.** (2014). Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *New England Journal of Medicine, 371*(26), 2477–2487. https://doi.org/10.1056/NEJMoa1409405
- **Jaiswal, S., Fontanillas, P., Flannick, J., Manning, A., Grauman, P. V., Mar, B. G., Lindsley, R. C., Mermel, C. H., Burtt, N., Chavez, A., Higgins, J. M., Moltchanov, V., Kuo, F. C., Kluk, M. J., Henderson, B., Kinnunen, L., Koistinen, H. A., Ladenvall, C., Getz, G., … Ebert, B. L.** (2014). Age-related clonal hematopoiesis associated with adverse outcomes. *New England Journal of Medicine, 371*(26), 2488–2498. https://doi.org/10.1056/NEJMoa1408617
- **Jaiswal, S., Natarajan, P., Silver, A. J., Gibson, C. J., Bick, A. G., Shvartz, E., McConkey, M., Gupta, N., Gabriel, S., Ardissino, D., Baber, U., Mehran, R., Fuster, V., Danesh, J., Saleheen, D., Melander, O., Sukhova, G. K., Neuberg, D., Libby, P., … Ebert, B. L.** (2017). Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *New England Journal of Medicine, 377*(2), 111–121. https://doi.org/10.1056/NEJMoa1701719
- **Libby, P., & Jaiswal, S.** (2019). Clonal haematopoiesis: Connecting ageing and inflammation in cardiovascular disease. *Nature Reviews Cardiology, 17*(3), 137–144.
- **Libby, P.** (2024). Clonal hematopoiesis and atherosclerosis. *Journal of Clinical Investigation, 134*(20), e180066.
- **Moslehi, J., Zeiher, A., Jaiswal, S., Schulz, C., & Blankstein, R.** (2019). Clonal hematopoiesis. *Journal of the American College of Cardiology, 74*(4), 567–577.
- **Papa, V., Marracino, L., Fortini, F., Rizzo, P., Campo, G., Vaccarezza, M., & Vieceli Dalla Sega, F.** (2020). Translating evidence from clonal hematopoiesis to cardiovascular disease: A systematic review. *Journal of Clinical Medicine, 9*(8), 2480. https://doi.org/10.3390/jcm9082480
- **Senguttuvan, N. B., Subramanian, V., Venkatesan, V., Muralidharan, T. R., & Sankaranarayanan, K.** (2021). Clonal hematopoiesis of indeterminate potential (CHIP) and cardiovascular diseases: An updated systematic review. *Journal of Genetic Engineering and Biotechnology, 19*(1), 105.
- **Steensma, D. P., Bejar, R., Jaiswal, S., Lindsley, R. C., Sekeres, M. A., Hasserjian, R. P., & Ebert, B. L.** (2015). Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood, 126*(1), 9–16.
- **Tall, A. R., & Fuster, J. J.** (2022). Clonal hematopoiesis in cardiovascular disease and therapeutic implications. *Nature Cardiovascular Research, 1*(2), 116–124.
- **Young, A. L., Challen, G. A., Birmann, B. M., & Druley, T. E.** (2016). Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. *Nature Communications, 7*, 12484.

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