Clonal Hematopoiesis and Cardiovascular Risk: Atherosclerosis, Thrombosis, and beyond

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Abstract

Acquired mutations that lead to clonal hematopoiesis have emerged as a new and potent risk factor for atherosclerotic cardiovascular disease and other cardiovascular conditions. Human sequencing studies and experiments in mouse models provide compelling evidence supporting that this condition, particularly when driven by specific mutated genes, contributes to the development of atherosclerosis by exacerbating inflammatory responses. The insights gained from these studies are paving the way for the development of new personalized preventive care strategies against cardiovascular disease. Furthermore, available evidence also suggests a potential relevance of these mutation in the context of thrombosis, an area requiring thorough investigation. In this review, we provide an overview of our current understanding of this emerging cardiovascular risk factor, focusing on its relationship to atherosclerosis and thrombosis.

Keywords

- CHIP
- atherosclerosis
- thrombosis
- inflammation
- TET2

Introduction: Somatic Mutation-Driven Clonal Hematopoiesis

Human genetic research has significantly advanced our comprehension of the pathophysiology and clinical management of cardiovascular disease (CVD). In this context, genetic variants or mutations are categorized into two main groups: those originating in germ cells, which are passed on to offspring (known as germline mutations), and those acquired by non-germ cells during an individual's lifetime (referred to as somatic mutations). Over the past two decades, human genetic research has revealed the significant role played by inherited genetic variance in CVD.[1] However, more recently, somatic mutations are also emerging as noteworthy contributors to cardiovascular disorders.[2] The hematopoietic system has been especially investigated in this context, partly because of the ease of obtaining peripheral blood samples and the availability of extensive blood deoxyribonucleic acid (DNA) sequencing data from large cohorts. Hematopoietic stem cells (HSCs) have been shown to accumulate random mutations continuously as an individual grows older.[3–5] While the majority of these mutations are considered neutral "passenger" mutations, a select few impact a "driver" gene, conferring a competitive advantage to the mutant HSC. This advantage results in gradual expansion of the mutant cell over time, a phenomenon commonly termed somatic mutation-driven clonal hematopoiesis (CH).[6–8] Importantly, this clonal expansion initially occurs in the HSC population within the bone marrow, but it progressively has a reflection in its progeny. Therefore, an individual exhibiting CH harbors a varying percentage of mutant immune cells, red blood cells, and platelets. Given the important pathophysiological role of these cell types in a variety of settings, it is not surprising that CH is emerging as a major risk modifier for several age-related disorders, particularly CVD.

CH is commonly identified through the use of next-generation DNA sequencing on blood samples, which enables the detection of expanded somatic mutations by calculating variant allele fractions (VAF; i.e., the proportion of reads that support a mutant allele out of the total number of reads in a next-generation sequencing study). Recent sequencing efforts and reanalysis of existing datasets have unveiled a diverse array of mutations detectable in blood,

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encompassing base substitutions (known as single-nucleotide variants or SNVs), small insertions and deletions (indels), cytogenetic aneuploidies, and structural chromosomal variants. Accordingly, the definition of CH varies based on the type of mutations and various technical parameters. However, a definition that is gaining relevance, particularly in the cardiology and hematology fields, is that of CH of indeterminate potential, often referred to as CHIP. CHIP is defined as the presence in blood or bone marrow of an expanded SNV or indel in a known gene associated with hematological malignancies, with a VAF of at least 2%, and in the absence of overt hematological abnormalities.[9] CHIP is strongly linked to aging, as the likelihood of having randomly acquired a CH driver mutation increases as an individual ages, and the subsequent expansion of the mutant clone to detectable levels typically requires years or decades. Accordingly, CHIP can be estimated to be present in greater than 20% of cancer-free individuals over the age of 60,[10–15] although it is pertinent to acknowledge that reported CHIP prevalence rates depend on the sensitivity of the sequencing techniques employed. As increasingly sensitive sequencing methodologies are used to examine this phenomenon, it is anticipated that the documented prevalence of CHIP will rise accordingly.[16]

The majority of known CHIP mutations are concentrated in a select group of genes, particularly those encoding epigenetic regulators like *DNMT3A*, *TET2*, and *ASXL1*. Other frequently mutated genes associated with CHIP are related to DNA damage responses (e.g., *TP53*, *PPM1D*), messenger ribonucleic acid (mRNA) splicing (e.g., *SF3B1*, *SRSF2*), and intracellular signaling (e.g., *JAK2*). Considering that these genes are known oncogenes and tumor suppressor genes, it is not surprising that CHIP mutation carriers exhibit a significantly heightened relative risk of developing hematological diseases.[10,11] Nonetheless, the absolute risk of developing hematological malignancies in CHIP mutation carriers remains relatively low, which reflects the frequent requirement for multiple cooperative oncogenic mutations to drive the malignant transformation of the mutant clone. Most CHIP mutation carriers display just one detectable mutation and, accordingly, do not develop hematologic malignancies and maintain normal blood cell counts. However, beyond cancer, CHIP is closely associated with increased all-cause mortality due to its strong connection with CVD, which is the primary focus of this review article.

Clonal Hematopoiesis and Atherosclerosis: Unveiling A New Cardiovascular Risk Factor

Atherosclerotic CVD is the condition most robustly linked to CHIP, both in human sequencing studies and in experimental studies in animal models. Atherosclerosis develops as a result of the accumulation of cholesterol-rich low-density lipoproteins in the artery wall, which triggers an unresolved inflammatory response that results in the remodeling of the artery walls and the formation and growth of atherosclerotic plaques. Ultimately, rupture or erosion of these plaques, and the resulting blockage of arteries by a thrombus, represents the main cause of most ischemic cardiovascular events.[17] As an inflammatory condition, it is not surprising that mutations present in immune cells impact the development of atherosclerosis.

The first report of an association between CHIP and atherosclerotic CVD emerged from a secondary analysis of whole exome sequencing (WES) datasets from several human cohorts.[11] While originally intended to identify preleukemic mutations, closer examination of these data revealed a notable association between CHIP and elevated all-cause mortality, primarily attributed to CVD. Subsequent analyses unveiled an unexpected revelation: individuals with CHIP displayed a more than twofold increased risk of developing coronary heart disease, even after adjusting for age, sex, and other established CVD risk factors.[11] This association between CHIP and atherosclerotic CVD was subsequently corroborated in case-control cohorts focusing on coronary heart disease and early-onset myocardial infarction,[18] as well as in various other population cohorts, most recently including greater than 400,000 participants in the UK Biobank.[19,20] Beyond primary coronary heart disease, CHIP has also been associated with heightened incidence of peripheral artery disease[19] and a higher risk of adverse clinical outcomes in patients with established atherosclerotic CVD[21,22] or heart failure.[23–25] Overall, these studies provide strong human evidence of the relevance of CHIP as a new risk factor for CVD, with comparable impact to traditional risk factors such as smoking or hypercholesterolemia. They also represent an excellent example of the power of large genetic datasets and biobanks to unveil nonconventional contributors to CVD. However, it must be noted that many of these studies are limited by the sequencing depth typical of WES, which leads to a marked underestimation of the prevalence of CHIP mutations with VAF of between 2 and 10% (i.e., 4–20% mutant blood cells if mutations are monoallelic). This limitation is relevant, as most individuals with CHIP are likely to carry mutant hematopoietic clones within this size range. Additionally, small differences in the processing, filtering, or interpretation of somatic mutations can significantly affect results when using WES data to study CHIP. Such differences in technical variables may account for the discrepant findings regarding the magnitude of the association between CHIP and coronary heart disease that has been reported in analyses of WES data from the UK Biobank conducted by different groups.[20,26,27] High-sensitivity sequencing endeavors in large cohorts will be essential for an accurate determination of the extent of the association between CHIP and atherosclerotic CVD, and for the identification of the VAF threshold that identifies clinically relevant CHIP. Nonetheless, an important emerging observation is that the effects of mutations in different genes are heterogeneous, so the clinical significance of CHIP most likely depends on the specific mutated gene. A particularly intriguing and relevant case is that of mutations in the epigenetic regulatory gene *DNMT3A*, which have been linked to atherosclerotic events in some populations[18,22] but not in others.[19,20] Given that *DNMT3A* mutations are the most prevalent in CHIP, elucidating their role in CVD will be essential for understanding the clinical significance of this phenomenon.

Table 1 Summary of experimental studies in mouse models of clonal hematopoiesis and experimental atherosclerosis or thrombosis, and proposed mechanisms underlying the effects of mutations in these genes

Gene	Phenotype in mouse models	Main proposed mechanisms
DNMT3A	Accelerated atherosclerosis in *Ldlr* −/− mice after competitive BMT with 10% *Dnmt3a* −/− bone marrow cells[30] Accelerated atherosclerosis in *Ldlr* −/− with full inactivation of *Dnmt3a* restricted to myeloid cells[30]	Elevated expression of several proinflammatory chemokines and cytokines in mutant macrophages[30]
TET2	Accelerated atherosclerosis in *Ldlr* −/− mice after competitive BMT with 10% *Tet2* −/− or *Tet2* +/− bone marrow cells[31] Accelerated atherosclerosis in *Ldlr* −/− mice with pan-hematopoietic ablation of *Tet2*[18] Accelerated atherosclerosis in *Ldlr* −/− with myeloid-restricted ablation of *Tet2*[18,31]	Increased expression and secretion of IL-1β[18,31] Increased NLRP3 inflammasome activity[31,44] Increased expression and secretion of IL-6[31,45] Elevated expression of several proinflammatory chemokines and cytokines in mutant macrophages[18,30,31]
JAK2	Accelerated atherosclerosis in *Ldlr* −/− mice with pan-hematopoietic expression of *Jak2*-V617F[34] Accelerated atherosclerosis in *Ldlr* −/− mice with macrophage-specific expression of *Jak2*-V617F[29] Increased propensity to thrombosis[35,61,62]	Erythrocytosis, thrombocytosis, and neutrophilia[34] Increased mutant macrophage proliferation within atherosclerotic plaques[29] Increased AIM2 inflammasome activation in mutant macrophages[29] Increased adhesion and recruitment of mutant cells to the vascular wall[29,34,62] Elevated formation of neutrophil extracellular traps (NETs) within thrombi[35]
TP53	Accelerated atherosclerosis in *Ldlr* −/− mice after competitive BMT with 20% *Trp53* −/− BM cells[19]	Increased plaque macrophage proliferation and accelerated cell cycle kinetics[19]

Abbreviation: BMT, bone marrow transplantation.

Despite the compelling human genetic evidence supporting the relevance of CHIP as a new cardiovascular risk factor, one must approach these findings with caution when trying to establish cause–effect relationships. The association between CHIP and atherosclerotic CVD could simply reflect shared consequences of the normal aging process or result from confounding factors. In this context, experimental studies using hyperlipidemic mouse models provide strong support for the causal role of CHIP mutations in *DNMT3A*, *TET2*, *JAK2*, and *TP53* in the development of atherosclerosis.[19,28–31] These investigations have also unveiled that this accelerated atherosclerosis results primarily from an exacerbation of inflammatory responses within the atherosclerotic plaque. However, while there may be shared inflammatory mechanisms connecting CHIP to CVD, the main mechanisms underlying CHIP's impact on atherosclerosis are often mutation specific (►**Table 1**). Mutations in the epigenetic regulatory genes *DNMT3A* and *TET2* appear to accelerate atherosclerosis development predominantly through qualitative changes in macrophage phenotypes.[30–33] Mouse models of *DNMT3A*- or *TET2*-mutant CHIP display accelerated atherosclerosis development in the absence of differences in blood cell counts, which stems primarily from the heightened production of proinflammatory cytokines and chemokines by mutant macrophages.[30,31] In contrast, macrophages with CHIP mutations in *TP53* and *JAK2* accelerate atherosclerosis development through quantitative alterations in plaque macrophage numbers.[19,29] These mutant macrophages expand within atherosclerotic plaques through increased proliferation, albeit through distinct molecular mechanisms, as reviewed elsewhere.[28] In addition, the *JAK2*^{V617F} hotspot variant linked to CHIP may accelerate atherosclerosis development through a variety of mechanisms beyond its direct effects on macrophage biology. Hematopoietic expression of this *JAK2* gain-of-function mutation leads to a complex hematological phenotype, including expansion of hematopoietic stem and progenitor cells (HSPCs) and increased numbers of multiple blood cell types, which promotes accelerated atherosclerosis development in mouse models.[34] Furthermore, the *JAK2*^{V617F} mutation enhances the formation of neutrophil extracellular traps (NETs),[35] an important contributor to atherosclerotic plaque vulnerability[36] and superficial erosion.[37,38]

Implications of Clonal Hematopoiesis in Personalized Medicine: The Case of *TET2* Mutations

The connection between CHIP and atherosclerotic CVD has opened up exciting discussions regarding the development of personalized CVD prevention strategies tailored to CHIP mutation carriers. In this context, although we still lack evidence-based interventions to prevent the heightened cardiovascular risk associated with CHIP, targeting the inflammatory pathways overactivated in mouse models of CHIP is an attractive possibility. The mutated gene that has seen greater progress in this context is *TET2*.

TET2 was the first gene reported to exhibit somatic mutations in blood cells in individuals with CH without blood cancer.[39] Inactivating mutation in this gene represent

the second most common driver of CHIP[10,11,13–15] and have been found to be associated with elevated risk of developing coronary heart disease and peripheral artery disease.[18–20] *TET2* encodes for a epigenetic regulator of gene transcription that catalyzes the oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) in the DNA, a process that facilitates subsequent DNA demethylation and transcriptional activation.[40–42] TET2 can also mediate transcriptional repression through noncatalytic actions, for instance by recruiting histone deacetylases to gene promoters.[43] Initial experimental evidence linking somatic TET2 mutations to atherosclerosis came from our research group, which demonstrated accelerated atherosclerosis in a mouse model of *TET2*-mutant CHIP.[31] In brief, atherosclerosis-prone *Ldlr* −/− mice received BM cell transplants containing 10% TET2-deficient hematopoietic cells, followed by a high-cholesterol diet to induce hypercholesterolemia and atherosclerosis. TET2-deficient cells expanded significantly in the bone marrow, spleen, and blood cell populations, and this expansion led to accelerated atherosclerosis, with an approximately 60% increase in plaque size.[31] Subsequent studies by multiple independent groups have confirmed these initial results in a variety of experimental settings.[18,30,44,45] Although these transplantation experiments were often conducted using hematopoietic cells with complete TET2 inactivation (i.e., homozygous TET2-knockout cells), similar, albeit less pronounced, effects have been observed with heterozygous TET2-knockout cells.[18,31] Using heterozygous cells mirrors the human scenario of CH better given that somatic *TET2* mutations are likely to be monoallelic in most individuals. These experimental studies in mouse models of *TET2*-mutant CH typically do not show significant differences in peripheral white blood cell counts, arguing against the possibility that leukocytosis is a significant contributor to accelerated atherosclerosis in carriers of somatic *TET2* mutations. Instead, multiple mechanistic studies suggest that this accelerated atherosclerosis is primarily due to the proinflammatory properties of TET2-deficient macrophages, predominantly, but not exclusively, to the overproduction of the proinflammatory cytokine interleukin-1 beta (IL-1β).[18,31,44,46,47] TET2 inactivation significantly elevates the IL-1β transcript levels in macrophages exposed to various proinflammatory stimuli,[18,31,46,47] which are, in part, mediated by increased histone acetylation at the *Il1b* promoter.[31] Additionally, TET2-deficient macrophages demonstrate heightened activity of the NLRP3 inflammasome,[31,44,46] the main regulator of IL-1β maturation and secretion in atherosclerosis.[48] Consequently, TET2-deficient macrophages exhibit a notable increase in IL-1β secretion.[31,44,46] Consistent with these observations in mice, human individuals carrying somatic *TET2* mutations exhibit elevated circulating levels of IL-1β.[15] Such elevation is not observed in carriers of other CHIP mutations, supporting the notion of a specific effect of somatic *TET2* mutations on the production of this proinflammatory and proatherogenic cytokine. Overall, these findings strongly suggest that targeting IL-1β-driven inflammation may be particularly effective for the prevention of atherosclerotic CVD in individuals carrying somatic mutations in *TET2*. Supporting this possibility, pharmacological NLRP3 inhibition suppresses the effects of *Tet2*-mutant cells on experimental atherosclerosis,[31] and similar results have been obtained in mouse models of other cardiometabolic conditions.[46,47]

In humans, preliminary support for the potential value of targeting IL-1β as a personalized preventive care strategy in *TET2* mutation carriers comes from a retrospective analysis of the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) clinical trial.[49] This trial explored the effects of canakinumab, an IL-1β-neutralizing antibody, on the risk of recurrent ischemic cardiovascular events in post-myocardial infarction patients with elevated C-reactive protein levels.[50] A subsequent exploratory sequencing analysis within a subgroup of CANTOS participants revealed that canakinumab reduced the risk of ischemic events by 62% in carriers of *TET2* mutations, which represents approximately a ninefold increase in benefit compared with that in individuals without CHIP.[49] While these findings are promising, this *post hoc* analysis needs to be interpreted cautiously due to several limitations. These limitations include the modest number of CANTOS participants who were sequenced (3,923 individuals, 103 with *TET2* mutations) and the inherent constraints associated with retrospectively evaluating a clinical trial not originally designed for this specific purpose. New prospective clinical trials will be needed to confirm the efficacy of canakinumab in individuals carrying mutations in blood cells in *TET2* or other CHIP genes. Moreover, implementing canakinumab as a precision strategy for preventing CVD in *TET2* mutation carriers presents substantial challenges, primarily related to its high cost[51] and prior regulatory decisions regarding its use for the prevention of atherosclerotic CVD.[52,53] Hence, ongoing experimental and sequencing studies are underway with the aim of identifying novel therapeutic approaches that may form the basis for personalized CVD risk management in *TET2* mutation carriers.[20,30,44,45,54]

An unresolved clinically relevant question is whether the elevated inflammatory risk linked to carrying a mutation in *TET2* or other CHIP genes can be detected simply by measuring circulating inflammatory biomarkers, specifically high-sensitivity C-reactive protein (hsCRP), known for its association with increased atherosclerotic CVD risk and IL1β-/IL-6-driven inflammation.[55] Should this approach prove effective, DNA sequencing to detect CHIP mutations might offer limited additional value for predicting CVD risk or implementing specific anti-inflammatory approaches. However, while further research is needed, available evidence suggests that hsCRP does not fully capture CHIP-related CVD risk and may provide limited value in identifying carriers of CHIP mutation. In populations free of clinically overt CVD, conflicting results have been reported when exploring the relationship between CHIP and hsCRP. Some studies report no clear association,[15] while others indicate a modest, but significant elevation of hsCRP in CHIP mutation carriers.[56,57] Among the latter, one study found moderately higher hsCRP levels in unadjusted analyses, which were mitigated upon adjusting for relevant covariates,[56] suggesting a potential confounding influence of other variables in driving these heightened hsCRP levels in CHIP mutation carriers. In populations with

established atherosclerotic CVD, available evidence supports a more robust link between CHIP and increased hsCRP levels, yet this elevation remains moderate.[21] Furthermore, the association between CHIP and atherosclerotic CVD or related clinical outcomes does not change materially after statistical adjustments for hsCRP,[15,21] indicating that the augmented CVD risk in CHIP is independent of this widely used biomarker of systemic inflammation.

Is Clonal Hematopoiesis a Shared Driver of Atherosclerosis and Thrombosis?

The integrity of the vessel wall and normal blood function depend on a balanced interplay among endothelial cells, leukocytes, and platelets, and their proper interaction with circulating cytokines, coagulation factors, and plasma proteins.[58] Given the known effects of CHIP mutations mentioned earlier, there is a growing interest in the potential effects of CHIP on this intricate interplay and its relationship with the risk of thrombotic events. While much work still needs to be done to determine whether CHIP is a shared contributor to both atherosclerosis and thrombosis (►Fig. 1), available evidence suggests that this area of investigation deserves particular attention.

Although the connection between most CHIP mutations and thrombosis remains largely unexplored, there is one gene, *JAK2*, for which somatic mutations in blood cells are unequivocally linked to thrombotic events. The *JAK2*^{V617F} gain-of-function mutation has long been recognized as a risk factor for thrombosis in patients with myeloproliferative neoplasms (MPN),[59] and recent evidence has expanded this association to individuals without an MPN diagnosis.[60] Experimental studies in mouse models also provide strong support for the close relationship between this mutation and the development of thrombosis.[35,61,62] Notably, in one of these studies, hematopoietic *JAK2*^{V617F} expression led to an increase in venous thrombosis alongside an elevated formation of NETs within thrombi.[35] An important role of NETs in this context is further supported by the observation that neutrophils from human individuals with myeloproliferative disorders displayed increased NETosis.[35] Additionally, increased venous thrombosis in mice with hematopoietic *JAK2*^{V617F} expression has also been suggested to result from enhanced adhesion of mutant granulocytes to endothelial cells through the activation of β1/β2 integrins.[62]

Beyond *JAK2*, emerging evidence support the adverse impact of mutations in other CHIP genes on endothelial cells and platelets, which could contribute to an elevated risk of thrombotic events. For instance, increased IL-1β-driven inflammation in mouse models of *TET2*-mutant CHIP leads to an elevated expression of endothelial adhesion molecules.[31] Additionally, peripheral blood mononuclear cells from carriers of *DNMT3A* or *TET2* mutations exhibit increased expression of IL-1β and several other endothelium-activating cytokines, such as tumor necrosis factor (TNF).[63] CHIP mutations may also affect blood platelet count and volume, which could have significant implications in atherothrombotic disease, as both low and high platelet counts are associated with increased all-cause mortality and CVD-related mortality.[64] A possible link between CHIP and platelet counts first emerged from the evidence that some types of thrombocythemia, thrombocytosis, and associated blood cancers are caused by CHIP gene mutations. For instance, a case/control analysis of the Lifelines cohort demonstrated that CHIP mutations in spliceosome-related genes are enriched in thrombocytopenia, whereas mutations in MPN-related genes are enriched in cases with thrombocytosis.[65] Several additional CHIP genes, such as *ASXL1* or *DNMT3A*, have also been reported to influence to some extent circulating platelet counts and consequently thrombotic risk, as reviewed in detail elsewhere.[66] While some gene-specific effects exist, the emerging picture is that CHIP is positively associated with platelet counts, as shown in several cohort studies including the Framingham Heart Study, the Atherosclerosis Risk in Communities Study, the TOPMed study, the UK Biobank, and the Mass General Brigham Biobank.[15,19,26,67–69] Although much less studied, CHIP mutations may also be linked to changes in platelet phenotype or function. An emerging platelet-related trait that is worth mentioning in this context is platelet distribution width (PDW), a marker of platelet heterogeneity that has been shown to be a direct readout of platelet activation[70] and to predict all-cause mortality and CVD-related mortality in a large general

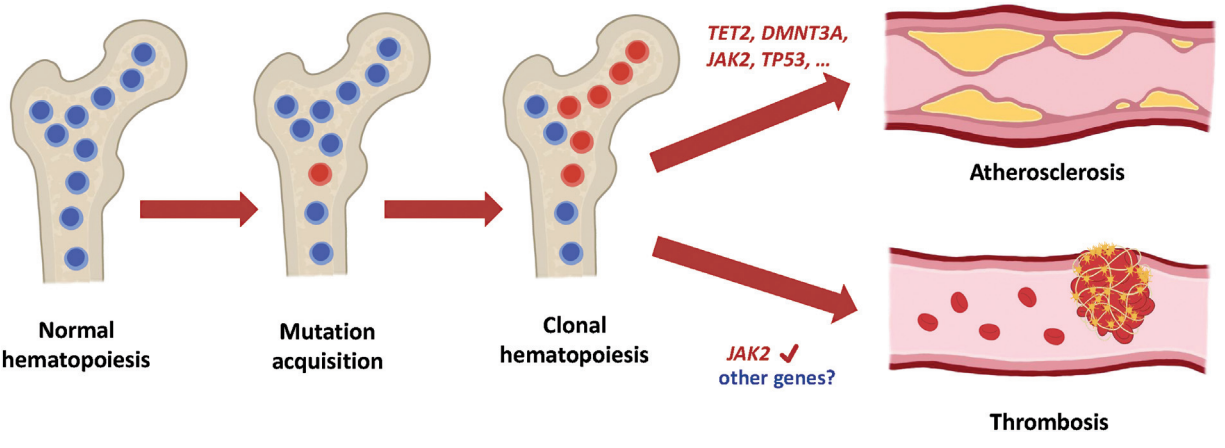

Fig. 1 Somatic mutations and clonal hematopoiesis: a new risk factor for atherosclerotic cardiovascular disease and, potentially, thrombosis.

population.[71] CHIP mutations are typically found to be associated with PDW in asymptomatic individuals.[26,69] Mechanistically, in addition to the plausible direct effects of CHIP mutations on megakaryopoiesis (which remain largely unexplored), CHIP mutations may also impact platelet number and function indirectly due to an exacerbated inflammatory environment resulting from the proinflammatory effects of mutant immune cells. For instance, increased IL-1β-driven inflammation in *TET2*-mutant CHIP can be speculated to create a prothrombotic environment, as IL-1β has been shown to promote megakaryocyte maturation and platelet activation.[72] Future experimental and clinical studies are needed to investigate this possibility and its potential contribution to atherothrombotic disease.

Concluding Remarks

Sequencing studies in humans and experimental investigations in mice collectively offer robust evidence supporting CHIP mutations as a prominent risk factor for atherosclerotic CVD and potentially other age-related conditions. Despite this, several crucial questions regarding the impact of these mutations on atherosclerosis remain unanswered, driving intensive research efforts. Existing evidence suggests that the increased CVD risk in individuals with these mutated clones often relates to heightened inflammation, which accelerates atherosclerosis. Nevertheless, there is a pressing need for further research into the specific effects of various mutated genes. Some CHIP genes, such as *TET2*, have been thoroughly investigated both in humans and in mouse models of atherosclerosis. The knowledge derived from these studies has laid the foundation for the development of personalized preventive care strategies tailored to carriers of mutations in this gene, which await testing in prospective clinical trials. Additional research is necessary to understand the effects of other common drivers of CHIP in atherosclerosis and other cardiovascular disorders. In the context of thrombosis, aside from the established role of the *JAK2*^{V617F} mutations, there is much work to be done in determining the relevance of CHIP. Large DNA sequencing studies with high sensitivity will be required to determine whether CHIP mutations are associated with an elevated risk of thrombosis. Furthermore, experimental studies with mutant mouse strains will be essential to examine causality and gain mechanistic insight. Such investigations may lay the groundwork for the development of innovative strategies to manage the risk of atherothrombotic disease in individuals with CHIP mutations.

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Conflict of Interest

The authors declare that they hve no conflict of interest.

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