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Clonal Hematopoiesis: Connecting Aging and Inflammation in Atherosclerosis

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Abstract

Purpose of Review—Clonal hematopoiesis (CH) is a prevalent condition that results from the acquisition of somatic mutations in hematopoietic stem cells. When these mutations occur in "driver" genes, they can potentially confer fitness advantages to the cell, leading to a clonal expansion. While most clonal expansions of mutant cells are generally considered to be asymptomatic since they do not impact overall blood cell numbers, CH carriers display long-term risks of all-cause mortality and age-associated diseases including cardiovascular disease (CVD). This review summarizes recent findings in CH related to aging, atherosclerotic CVD, and inflammation, emphasizing epidemiological and mechanistic studies, and potential therapeutic options to treat CVDs that are promoted by CH.

Recent Findings—Epidemiological studies have revealed associations between CH and CVDs. Experimental studies with CH models employing the *Tet2*- and *Jak2*-mutant mouse lines display inflammasome activation and a chronic inflammatory state that leads to accelerated atherosclerotic lesion growth.

Summary—A body of evidence suggests that CH represents a new causal risk factor for CVD. Studies also indicate that understanding an individual's CH status could provide guidance for personalized approaches to treat atherosclerosis and other CVDs with anti-inflammatory drugs.

Keywords

Age-related clonal hematopoiesis; Clonal hematopoiesis of indeterminate potential; CANTOS; Inflammasome

Introduction

Multiple lineages of blood cells are produced by hematopoietic stem cells (HSCs) in the bone marrow. Over time, HSCs randomly acquire somatic mutations and thus become

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increasingly genetically distinct as the organism ages. While most of these mutations produce few if any biological effects, some can alter cell fate decisions toward self-renewal, decreased cell death or differentiation, or some combination of these fates, leading to their positive selection through a process referred to as clonal hematopoiesis (CH) (Fig. 1). These somatic mutations are also passed to progeny leukocytes, and can alter the inflammatory properties of immune cells and contribute to disease states [1].

Age-Related Clonal Hematopoiesis

The development of CH is best appreciated in the context of aging, and hence it can be referred to as age-related CH (ARCH). Alternatively, this phenomenon has been referred to as clonal hematopoiesis of indeterminate potential (CHIP). As individuals age, they will inevitably accumulate somatic mutations that include (1) single nucleotide variants (SNVs), including the spontaneous cytosine deamination that is a mutational signature of aging; (2) small insertions and deletions (indels); and (3) chromosomal alterations that include large chromosome insertions and deletions, inversions, loss of heterozygosity, and aneuploidy [2, 3]. While CH will increase the risk of hematological neoplasia, in most cases this condition does not progress to malignancy. CH is distinguished from hematological malignancies because it is believed that the clones are composed of fewer driver gene mutations, and the individual does not present with cytopenia, dysplasia, and abnormal blood cell counts [4]. CH is receiving increasing scientific interest because it has been recognized that this condition can produce physiological consequences beyond a neoplastic phenotype. In particular, the clonal expansions of blood cells can increase the risk of cardiovascular disease (CVD) and other non-neoplastic disorders.

Epidemiology: CH, Mortality, and CVD

Busque et al. [5••] reported the first association between CH and mutations in the driver gene ten-eleven translocation 2 (*TET2*). Later studies detected candidate driver gene clones by employing large-scale, next-generation sequencing (NGS) on peripheral blood cells from individuals with no hematological disorders [6••, 7••]. These studies reported common features including a strong association between age and the prevalence of CH. Both studies also reported clonal expansions predominantly associated with mutations in epigenetic regulator genes, specifically DNA methyltransferase three alpha (*DNMT3A*), *TET2*, and additional sex combs-like 1 (*ASXL1*). To a lesser extent, distinct clones also exhibited mutations in Janus kinase 2 (*JAK2*), tumor protein 53 (*TP53*), protein phosphatase, Mg2+/Mn2+-dependent 1D (*PPM1D*), Splicing Factor 3b Subunit 1 (*SF3B1*), and other genes. Based on low-coverage DNA sequence analysis, Jaiswal et al. [7••] reported that individuals under 40 years of age rarely exhibited CH, but showed an increase in CH frequency with age. A commonly quoted finding from this study is that clones arising from mutations in CH driver genes occurred in approximately 10% of individuals older than 70 years. However, studies employing different methodology for clone identification reveal that this underestimates the extent of CH, and this will be discussed below. As noted previously, Genovese et al. [6••] also reported the age-dependent prevalence of hematopoietic clones and similar frequencies of mutated driver genes. Notably, this study assessed the full exome

rather than candidate driver genes, and they reported that approximately half of the clonal events found in blood could be attributed to mutations in known driver genes.

Since these initial reports, other methods of analysis have been applied to assess clonality in the blood. An early study by Zink et al. [8••] employed a non-biased, barcoded whole-genome DNA sequence analysis. They could detect clonal events in 50% of individuals by 85 years of age. These authors also noted that clonal hematopoiesis was probably inevitable with advanced age and that less than 15% of the clonal events could be attributed to the known clonal hematopoiesis driver genes identified previously [6••, 7••]. Others have reached similar conclusions [9-12]. In addition to these nonbiased analyses of clonal hematopoiesis, error-corrected ultra-deep DNA sequencing of a subset of driver gene candidates has revealed that small variant allele fraction (VAF) clones are essentially ubiquitous by middle age [13, 14].

Loh et al. [2] has examined clonal events in blood that are associated with age-related mosaic chromosomal alterations (mCAs). In a large cohort of individuals, mCAs occurred at a frequency of 5.6%, where most of the detected alterations are gains, deletions, or copy-number-neutral loss of heterozygosity. Similar to analyses of SNVs and small indels, the frequency of mCA-derived clones was found increased with age. Terao et al. [15] also found specific patterns of genomic mutations and clonal selection in hematopoietic cells in an analysis of autosomal mCAs in a Japanese cohort. In this study, mCAs were detected in more than 35% of individuals older than 90 years. Finally, mosaic loss of the Y chromosome (mLOY), another form of CH, represents the most prevalent human post-zygotic mutation. Like SNVs, indels, and other mCAs, the prevalence of mLOY is strongly associated with age, and mLOY can be detected in 40% of men who are 70 years of age [16].

Many studies have associated CH with mortality. In earlier studies, Genovese et al. [6••] and Jaiswal et al. [7••] found that CH carriers exhibited significantly reduced overall survival during a follow-up period. Zink et al. [8••] also reported that CH carriers had substantially higher rates of all-cause mortality. Notably, both Zink et al. and Genovese et al. reported increased mortality associated with CH regardless of whether the clone could be attributed to a known candidate driver gene or was the result of an unknown mechanism. The association between CH and mortality was further observed in carriers of large mCAs. Loh et al. [2] showed that those with an mCA had a 2-fold increased risk for all-cause mortality. Supporting these findings, analysis of the Japanese cohort also revealed that mCAs contribute to an increase in the risk of death [15]. Finally, mLOY has also been associated with an increased risk of all-cause mortality [17-19••].

What is driving the accelerated mortality in individuals with CH? An obvious explanation would be an increase in death from hematologic malignancies, as this would make sense from the standpoint that CH is an early step in the progression to blood cancer. While the incidence of blood cancer is elevated in individuals with CH [2, 6••, 7••], deaths from hematologic malignancies cannot explain these large increases in mortality associated with CH. Instead, it appears that increased CVD-associated death is a major factor in accounting for the increased mortality in CH carriers. This was first noted by a secondary analysis performed by Jaiswal et al. [7••] where it was found that CH carriers had a higher risk

of coronary heart disease and ischemic stroke. Following this initial study, the same group performed prospective and retrospective studies to illustrate the association between CH and CVD [20•]. It was found that CH carriers had 1.9-fold increased risk of coronary heart disease and a 4.0-fold increased risk of myocardial infarction. In a separate cohort, coronary-artery calcification was 3 times higher in CH carriers than in non-carriers [20•]. They also reported that the coronary-artery calcification score was 12 times higher in carriers of large CH clones (VAF ≥ 10%), whereas carriers of small CH clones showed no difference [20•]. A large cohort study of the UK Biobank has provided further evidence for the association between CH and the increased risk of CVD, and this study also reported that large clone size was associated with greater CVD risk [21]. Finally, it has been reported that there is an association between CH and incident coronary artery disease events in postmenopausal middle-aged women [22].

In addition to the studies mentioned above, it has been reported that carriers of *DNMT3A* and *TET2* who undergo aortic valve implantation demonstrate an increase in mortality during follow-up [23]. Yu et al. [24] examined whether CH predisposes to hospitalized HF incidence in a large population. They found that mutations in *TET2*, *JAK2*, and *ASXL1* were strongly associated with an increased risk of HF, whereas *DNMT3A* sequence variants were not. They also found a strong association between *ASXL1*-mediated CH and reduced left ventricular ejection fraction. In HF patients, CH was found to be associated with morbidity and mortality combined with rehospitalization [25•-27]. Dorsheimer et al. [27] analyzed bone marrow and peripheral blood mononuclear cells of 419 patients with chronic ischemic HF using deep error-corrected sequencing. A total of 223 mutations were found in 154 of the 419 patients with a 0.5% VAF detection threshold. As expected, most mutations occurred in the *DNMT3A* and *TET2* genes, and the carriers of these mutant clones had worse prognosis than the non-carriers. In a subsequent study, this group analyzed the VAF threshold for prognostic significance of CH in HF [25•]. They determined a VAF cut-off value of 0.73% for *TET2* and 1.15% for *DNMT3A* CH mutations. Pascual-Figal et al. [28] have extended these studies and reported that *DNMT3A*- and *TET2*-mediated CH contributes to HF progression, independently of its ischemic or nonischemic etiology.

In view of findings discussed above, it should be emphasized that multiple approaches are employed to assess CH in patient populations. On one hand, some investigations have employed relatively shallow, whole-exome sequence analysis to assess clonal expansions in blood. The advantage of this approach is that it is relatively unbiased and it can employ existing DNA sequencing data from large biobanks (such as the UK Biobank). A disadvantage of this approach is the low sensitivity of variant detection such that only very large clonal events can be detected. On the other hand, some investigations have employed ultra-deep, error-corrected sequencing on relatively small, but more highly phenotyped, cohorts [29]. The advantage of this approach is that it can detect associations between smaller clones and disease conditions. The disadvantage with this approach is that the analysis is biased because it only focuses on a panel of pre-selected, candidate driver genes to contain costs.

Mechanistic Studies on CH and Atherosclerosis

Epidemiological studies have identified associations between CH and multiple disease processes [30]. However, these studies are generally descriptive in nature and they do not provide information about cause-and-effect relationships or the directionality of the association. Thus, to understand the causal and mechanistic relationships between CH and CVD in more detail, we and others have developed several mouse models of CH that recapitulate human CH [31-36]. Details on these mouse models have been presented elsewhere [37-39].

Tet2 and Atherosclerosis

To study *TET2*-mediated CH in a CVD model, our group used a competitive bone marrow transplantation (BMT) to mimic the hematopoietic clone expansion event in humans. Atherosclerosis-prone low-density lipoprotein receptor-deficient mice were engrafted with 10% $Tet2^{+/+}$ or $Tet2^{-/-}$ bone marrow cells and treated with a high-cholesterol, Western diet. Over time, the $Tet2^{-/-}$ cells underwent expansion, with a slight myeloid bias, in bone marrow, spleen, peripheral blood, and the infiltrating pool of immune cells of the aorta [32••]. These conditions promoted atherosclerosis progression and increased plaque size. Mechanistically, it was found that *Tet2*-deficient macrophages display upregulated expression of IL-1β, its precursor pro-IL-1β, and components of NLRP3 inflammasome [32••]. Furthermore, treatment with an NLRP3 inhibitor reduced plaque size, suggesting that an inflammasome product, such as IL-1β, plays a crucial role in the Tet2-mediated acceleration of atherogenesis (Fig. 1). Subsequently, it was reported that a conventional BMT method, i.e., the transplantation of 100% $Tet2^{+/+}$ or $Tet2^{-/-}$ mouse bone marrow cells, also led to an increase in atherosclerotic plaque size [20•]. While this model was confounded by the systemic effects of a complete BMT of $Tet2^{-/-}$ cells, this study provided further support for the notion that TET2-mediated CH accelerates atherosclerosis.

$JAK2^{V617F}$ and atherosclerosis

The $JAK2^{V617F}$ variant is a gain-of-function mutation that constitutively activates the STAT family of transcription factors. $JAK2^{V617F}$ was originally identified as a myeloproliferative neoplasm (MPN)–associated mutation, but it is increasingly recognized that hematopoietic cell clones with this mutation are also detected in non-symptomatic individuals with few if any indications of MPN [6••, 7••, 40]. Fidler et al. [31] utilized Cre/LoxP-mediated recombination and a BM transplantation strategy to achieve $Jak2^{V617F}$ expression specifically in myeloid cells to avoid the MPN phenotype. They found that hyperlipidemic recipient mice reconstituted with macrophage specific-$Jak2^{V617F}$ donor cells exhibited increased necrotic core sizes, despite lower levels of circulating LDL cholesterol. They attributed the enhanced atherogenesis to greater DNA oxidative damage, replication stress, AIM2 inflammasome activation, and IL-1β production [31].

Mechanistic Studies on CH and Other Types of CVD

The mechanistic relationships between CH and other CVD entities have also been examined by experimental studies in mice. Models of *TET2*, *DNMT3A*, *PPM1D*, and $JAK2^{V617F}$ CH

have been found to promote pathological remodeling in models of HF that are induced by LAD ligation, angiotensin II infusion, and/or transverse aortic constriction [33-35, 39, 41•, 42•]. Furthermore, the adoptive transfer model of TET2-mediated CH in non-conditioned mice has been shown to accelerate age-associated cardiomyopathy [36], and the adoptive transfer model of TP53-mediated CH has been shown to promote anthracycline-induced cardiomyopathy [34]. In a model of TET2-mediated CH, increased insulin resistance was observed in aging mice and in young mice fed a high calorie diet [43]. In contrast to these findings with traditional driver gene-mediated clonal hematopoiesis, it has been reported that mLOY promotes profibrotic signaling and diminishes IL-1β-signaling [19••], indicating the complex actions of somatic mutations on immune cell function.

CH and Inflammation

Experimental work on several different CH driver genes in multiple murine models of CVD have led to the general conclusion that CH promotes CVD risk through mechanisms involving inflammation. Notably, a number of these mechanistic studies have implicated the NLRP3 inflammasome in many of these processes [32••, 41•-43]. For example, in multiple CVD models in mice, we have shown that treatment with an inflammasome inhibitor MCC950 counteracted the effect of CH on atherosclerosis, HF, and insulin resistance [32••, 41•-43]. Consistent with the experimental work, studies have reported that CH carriers also exhibit elevated inflammatory markers [21, 44, 45]. For example, single-cell RNA sequencing analyses of circulating peripheral monocytes revealed that individuals with aortic valve stenosis who carried sequence variations in the *DNMT3A* driver gene displayed increased expression of IL-6, CXCL2, IL-1β, TNF, NLRP3, and genes involved in T-cell stimulation [44].

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial tested the hypothesis that blockade of IL-1β using a specific monoclonal antibody reduces the rate of major adverse cardiovascular events (MACEs) in patients with a previous myocardial infarction and evidenced for elevated systemic inflammation (Fig. 1) [46]. This large trial found that the middle dose of canakinumab led to a statistically significant 15% reduction in MACE. A subsequent exploratory analysis assessed the association of clinical outcome with CH in a subset of this cohort [47••]. Whereas individuals that harbored no detectable CH exhibited a 7% relative risk reduction of MACE in response to any dose of canakinumab, those with *TET2*-mediated CH displayed a 62% relative risk reduction in MACE. These findings are consistent with experimental studies of CVD showing that mice are superior responders to an inflammasome inhibitor if they also harbor an expansion of Tet2-deficient cells in the hematopoietic system [32••, 42•]. The beneficial effects among the population with a specific form of CH suggest an opportunity to implement personalized medicine based on the identity of mutations that have been acquired in the somatic cells of an individual.

Mosaic Loss of the Y Chromosome

Recent studies have provided evidence that hematopoietic mLOY in men can be causally linked to CVD. This condition is remarkably prevalent, affecting a larger portion of the

population than CH mediated by any individual ARCH/CHIP driver gene or the combined prevalence of all known driver genes associated with ARCH/CHIP [30]. Sano et al. [19••] have reported that mLOY is associated with cardiovascular disease and heart failure-associated mortality in the UK Biobank and that mice reconstituted with bone marrow lacking the Y chromosome display accelerated cardiac dysfunction and other pathologies. In contrast to the pro-inflammation paradigm that has been developed from studies of ARCH/CHIP [48], mLOY leads to an over-activation of pro-fibrotic signaling in the immune system and a reduction in pro-inflammatory signaling. These data suggest that the age-associated somatic mosaicism that develops in the immune system can give rise to a complex interplay of pro- and anti-inflammatory processes. Collectively, these data indicate new avenues for experimental and clinical CH research.

Limitations of CH Research

It should be noted that studies of CH currently suffer from numerous limitations. First, it should be recognized that there is a high degree of observational bias in the epidemiological analyses. This bias largely results from an incomplete knowledge of the driver gene repertoire that give rise to these clonal events. Second, there is an overfocus on the large clones and insufficient appreciation of the potential cumulative effect of many smaller clones that are difficult to accurately detect [11, 26, 49]. Related to this point, there are technical limitations due to the high degree of error associated with base calling with current NGS procedures, masking the ability to detect small clones [13, 14]. Finally, most clinical analyses treat CH as a binary readout. Treating CH as a simple binary readout does not account for the distinct mechanistic features of the different driver genes. For example, some clones could be derived from driver genes that are highly pathological, whereas other driver gene clones might be benign, or even protective, as has been reported in other systems [50-52]. Thus, current conclusions about the association of CH with CVD are likely based on analyses of data that are rife with false-positive as well as false-negative signals, suggesting that there is great need for improving these analyses through a deeper understanding of the biology of CH.

Concluding Remarks

CH is increasingly recognized as a causal risk factor for CVD. CH results from the age-dependent acquisition of mutations in somatic cells, and it represents a new mechanism of CVD that occurs at the interface of aging and cancer (Fig. 1). Assessing CH in patient populations will likely provide opportunities for improving prognosis and guiding interventions. While CH can be determined by the analysis of a blood sample, currently this assessment is technically difficult and expensive. However, a better understanding of the pathophysiology of CH and technical improvements in DNA sequence analysis could make the analysis of CH a routine procedure by a clinical laboratory.

Regardless of the limitations discussed in the section above, considerable progress has been made in documenting the utility of CH measurements in assessing CVD risk and patient prognosis. Notably, the exploratory analysis of CH in the CANTOS trial provides a compelling indication that the analysis of CH could offer a new avenue in

the development of personalized medicine approaches where therapies target the effects of specific somatic mutations [47••]. Thus, it is reasonable to expect that the associations between CH and disease prognosis will strengthen considerably with advances in DNA sequence methodology and a better understanding of how this condition mechanistically contributes to CVD.

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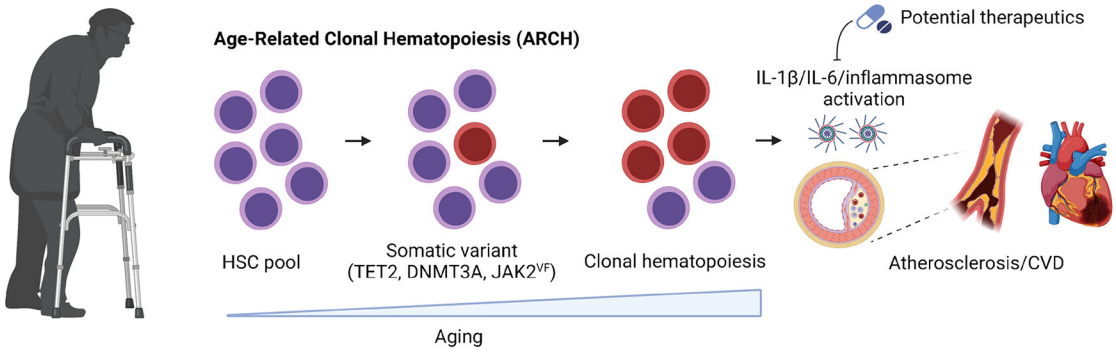

Fig. 1.

Scheme of age-related clonal hematopoiesis. As individuals age, their hematopoietic stem cells can acquire somatic mutations in their hematopoietic stem cells that confer a fitness advantage in the bone marrow niche. As a result of this process, clones harboring mutations in *TET2*, *DNMT3A*, *JAK2*, or other driver genes increasingly expand, promoting the risk of all-cause mortality, cardiovascular disease, and less often hematological malignancies. Created with BioRender.com