The Impact of Clonal Hematopoiesis of Indeterminate Potential on Advanced Heart Failure

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Introduction

The many processes that contribute to age-related diseases include Harman’s free-radical1 telomere shortening, inflammaging,2 and Medewar’s mutation accumulation theory,1 especially in hematological malignancies.4,5 As we age, hematopoietic stem cells may acquire mutations that modulate their function, proliferation, or survival, thus expanding the pool of mutated cells in blood, a process termed clonal hematopoiesis (CH).6 With the addition of cooperating mutations, CH cells may progress to myelodysplastic syndrome and acute myeloid leukemia at rates ranging from 0.5 to 1% per year.7 There are dozens of known CH-driver genes, a subset of the known leukemia driver genes, the most frequent of which are DMNT3A, TET2, ASXL1, and JAK2, which account for approximately 80% of all CH mutations.8 CH increases with age: more than 2% of cells (Variant Allele Fraction [VAF]) will have these mutations in approximately 10% of individuals aged 70 years.9 Indeed, new and highly sensitive targeted sequencing techniques have shown nearly ubiquitous CH mutations in adults over 30 years of age.10

Although the risk of developing a hematologic malignancy is more than 10-fold in individuals with CH, most will have no overt manifestation, hence the term: Clonal Hematopoiesis of Indeterminate Potential (CHIP).7 Surprisingly, people with CHIP who carry leukocyte clones with mutated leukemia driver genes have a higher risk of developing and/or progressing to non-hematologic conditions of other age-related diseases, such as dementia,11 osteoporosis,12 stroke,13 and cardiovascular diseases.14 Various mechanisms linked with these diseases are associated with CHIP, including an excessive inflammatory response due to inflammasome activation and enhanced expression of inflammatory cytokines such as IL-1β and IL-6, increased thrombotic potential, and impaired DNA repair.15-18

Considering the increased risk of cardiovascular manifestation in carriers of CHIP mutations, independent of traditional risk factor (eg, high cholesterol), we discuss the implications of CHIP for heart diseases and progression to heart failure (HF). Assessment of such somatic mutations may provide a novel tool for personalized/precise cardiovascular medicine.

Cardiovascular impact of CHIP

Identifying cardiovascular risk factors, such as hypertension and diabetes, has enabled targeted treatments that have helped reduce cardiovascular mortality. In 2014, a landmark paper including more than 17,000 patients was the first to suggest an association between CHIP and increased adverse cardiovascular events.14 To further investigate the risk of CHIP, this team performed a case-control study of coronary artery disease (CAD) patients.15 They found that CHIP was associated with a 1.9-fold increase in CAD, a 4.0-fold increase in early-onset myocardial infarction (MI), and 3-fold increase in coronary artery calcification. CHIP was also associated with a 14% increase in ischemic stroke, as well as a 24% increase in hemorrhagic stroke in another study with more than 70,000 patients.13

Since age is a strong risk factor for CHIP and cardiovascular disease, CHIP could merely be indicative of older age rather than contribute causally to cardiovascular disease.14 Some data have also suggested “reverse causation”, ie, that atherosclerosis can increase CHIP. However, Mouse experiments have shown that loss of TET2 function in myeloid cells, the second most mutated gene in CHIP, accelerates atherosclerosis.19 These studies not only found larger atherosclerotic lesions in mice carrying CHIP mutations, but also the expression of several inflammatory cytokines and chemokines. On the clinical side, a small study including patients with severe degenerative aortic stenosis or chronic post-ischemic HF found higher expression of several inflammatory genes, such as IL-1β and IL-6, in individuals with CHIP mutations.20 TET2 mutation carriers with ischemic heart disease have shown higher levels of circulating IL-8.21 These markers of increased inflammation reveal a pathway by which CHIP can affect cardiovascular risk.16,19,20 A dose-response effect, crucial for determining causality, has also
been reported as a greater risk in those with larger clone size.\textsuperscript{15,21} In mice, mutations in \textit{TET2} and \textit{DNMT3A} can promote cardiac function remodeling, including lower ejection fraction, increased left ventricular diameter, and myocardial fibrosis.\textsuperscript{16,20}

In sum, abundant evidence supports CHIP as a newly recognized contributor to atherosclerosis and impaired ventricular function. Indeed, CHIP mutations are associated with a higher risk than hypertension, smoking status, and hypercholesterolemia, lower only than age and type 2 diabetes.\textsuperscript{22}

**Heart Failure and CHIP**

Although CHIP was initially associated with increased risk of atherosclerotic diseases, including CAD and MI, recent sequencing studies have also revealed a connection between CHIP and HF.\textsuperscript{15,21,23,24} Dorsheimer et al. studied the incidence and prognostic significance of CHIP in a cohort of 200 patients with chronic HF who underwent autologous bone marrow treatment for acute MI.\textsuperscript{21} DNA from bone marrow–derived mononuclear cells was isolated and analyzed for the presence of CHIP, and 18.5% of participants were carriers of CHIP with VAF ≥ 2%. Over a median follow-up of 4.4 years, the survival analyses showed that CHIP carriers, particularly those with \textit{DNMT3A} and \textit{TET2} mutations, had worse clinical outcomes for death and death-plus-HF hospitalization than non-carriers. Remarkably, most deaths arose from worsening HF and emergent arrhythmia, with only one death due to subsequent MI. These results support the association of CHIP not only with the pathogenesis of atherosclerotic cardiovascular diseases but also with HF. There was also a significant dose-response association between %VAF and clinical outcomes, with VAF > 2% leading to worse outcomes.\textsuperscript{21} Notably, the authors also found that halving the threshold to 1% VAF was still associated with poor outcomes, albeit to a lesser extent, further implying that CHIP has a “dose effect”.\textsuperscript{25} Moreover, CHIP mutation was associated with higher %VAF independently of other risk factors in a larger cohort of patients with previous MI and stable chronic HF.\textsuperscript{26} Pascual-Figal et al. corroborated these findings, showing that clonal hematopoiesis due to \textit{TET2} or \textit{DNMT3A} mutations predicted worse outcomes in patients with HF, regardless of etiology.\textsuperscript{23}

Subsequently, Yu et al. performed a meta-analysis of archived sequencing data to identify CHIP mutations among 56,597 individuals from 5 population-based cohorts in up to 20 years of follow-up to investigate the association between CHIP and incident HF.\textsuperscript{24} CHIP was prospectively associated with a 25% increased risk of HF, which was comparable in individuals with and without CAD, regardless of traditional cardiovascular risk factors. These findings suggest a direct link between CHIP and HF, arguing against the possibility that this association only reflects a connection between CHIP and atherosclerosis. Interestingly, in single gene-specific analysis, \textit{ASXL1}, \textit{TET2}, and \textit{JAK2} sequence variations were each associated with an increased risk of HF, whereas \textit{DNMT3A} sequence variations were not associated with HF. This result may have biological significance since \textit{ASXL1} and \textit{JAK2} may provoke cardiovascular events through mechanisms that are distinct from \textit{DNMT3A} or from \textit{TET2}.\textsuperscript{25}

CHIP may also contribute to the development and progression of HF with preserved ejection fraction; however, this hypothesis remains untested. Identifying CHIP in individuals with HF could provide diagnostic information and guide the development of therapeutic strategies that target the downstream consequences of specific mutations.

**Future perspectives**

CHIP is a newly recognized risk factor for cardiovascular disease that can help clarify the relationship between aging and CAD, MI, stroke, and HF.\textsuperscript{15,21,23} According to clinical and experimental data, some CHIP mutations are associated with dysregulation of several inflammatory cytokines, indicating a new potential targeting strategy for cardiovascular disease treatments.\textsuperscript{15,16,26} For example, in the Canakinumab Anti-Thrombotic Outcomes Study, individuals with \textit{TET2} mutations benefited more from administration of an anti-interleukin-1 beta antibody. Moreover, probing the mechanistic links between specific CHIP mutations and cardiovascular diseases may help elucidate the pathophysiology of HF. Finally, such explorations may lead to new targeted treatments for HF orthogonal to current approaches focused on neurohormonal blockade or SGLT2 inhibition.

**Author Contributions**

Conception and design of the research; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Leitão SAT, Scolari FL, Vieira JL, Libby P.

**Potential Conflict of Interest**

Dr. Vieira reports fees for serving on an adjudication committee from the Academic Research Organization of Hospital Israelita Albert Einstein and speaker’s fees from Boehringer Ingelheim-Lilly and Novartis.

Dr. Libby is an unpaid consultant to, or involved in clinical trials for Amgen, AstraZeneca, the Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Norvo Nordisk, Novartis, Pfizer, and Sanofi-Regeneron.

He is a member of the scientific advisory board for Amgen, Caristo Diagnostics, Cartesian Therapeutics, CSL Behring, DaiCor Pharmaceuticals, Dewpoint Therapeutics, Kancera, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, PlaqueTec, TenSixteen Bio, and XBiotech, Inc. Dr. Libby is on the Board of Directors of XBiotech, Inc. and has a financial interest in XBiotech, a company developing therapeutic human antibodies.

His interests were reviewed and are managed by Brigham and Women’s Hospital and Partners HealthCare in accordance with their conflict-of-interest policies.

Dr. Libby’s laboratory has received research funding in the last 2 years from Novartis and receives funding from ABC Heart Fail Cardiomyop. 2022; 2(2):218-221
support from the National Heart, Lung, and Blood Institute (1R01HL134892), the American Heart Association (18CSA34080399), the RRM Charitable Fund, and the Simard Fund.

**Sources of Funding**

There were no external funding sources for this study.

**References**


Research Letter

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