HHS Public Access

Author manuscript

Curr Heart Fail Rep. Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

Curr Heart Fail Rep. 2020 October ; 17(5): 271–276. doi:10.1007/s11897-020-00476-w.

Evidence of Clonal Hematopoiesis and Risk of Heart Failure

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Abstract

Purpose of Review: Clonal Hematopoiesis of Indeterminate Potential (CHIP) is characterized by persistent clonal expansion of adult hematopoietic stem cells, which has been increasingly found to be associated with cardiovascular disease and adverse outcomes in heart failure. Here we outline emerging studies on the prevalence of CHIP, and its association with cardiovascular and heart disease.

Recent Findings: Previous genomic studies have found CHIP mutations to be associated with increased risks of arterial disease, stroke, and mortality. Murine studies exploring *TET2, DNMT3A,* and *JAK2* mutations have shown changes in cellularity that decrease cardiac function after insult, as well as increase inflammasome activation.

Summary: Mutations in driver genes are associated with worse clinical outcomes in heart failure patients, as a potential result of the proinflammatory selection in clonal hematopoiesis. Advances in the field have yielded therapeutic targets tested in recent clinical studies and may provide a valuable diagnostic of risk in heart failure.

Keywords

CHIP; Clonal Hematopoiesis; Heart Failure; Ten-Eleven Translocation-2; Janus Kinase-2; Inflammasome

INTRODUCTION

Heart failure (HF) is a significant medical burden, comprising the leading cause of hospitalization in patients over 65 and exceeding $31B annually in care expenditures. [1] Thus, early diagnostic and prognostic tools are becoming increasingly emphasized in the clinical arena. Traditional risk factor assessments include HF risk scores, imaging modalities such as echocardiography and cardiac MRI, and electronic health record-based algorithmic approaches. [2–7] However, while these approaches are effective at risk assessment, additional strategies such as genomic measures may provide a complementary resource to other clinical modalities.

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Disclosure: Dr. Tang is a consultant for Sequana Medical A.G. and has received honorarium from Springer Nature for authorship/editorship, both unrelated to the contents of this paper. All other authors have no relationships to disclose.

Germline Variation

It is known that HF involves a complex interplay of environmental and genetic factors affecting risk, progression, and therapeutic response. [8] Much work identifying genetic HF risk has focused on germline variation, such as found in familial cardiomyopathies. [9] Familial cardiomyopathy accounts for 50% of total dilated cardiomyopathy cases, with 40% of these having known genetic causes. [10] Additionally, hypertrophic cardiomyopathy often presents as a monogenic disorder, associated with single mutations in up to 18 genes. [11] Therefore, genetic testing is recommended for patients with family members presenting with dilated, hypertrophic, and restrictive cardiomyopathies. [12]

To date, nearly 300 HF-associated variants have been identified, with a meta-analysis of more than 73,000 subjects revealing 52 loci of interest, correlating to QRS phenotypes and myocardial hypertrophy. [13, 14] Recently, a genome-wide association study (GWAS) meta-analysis of 47,309 HF cases and 930,014 controls identified 12 variants at 11 new genomic loci. [15] Nevertheless, a relatively small fraction of HF cases have been attributed to single-gene cardiomyopathies and GWAS investigations have provided limited insights, leaving the observed genetic contribution of HF largely unexplained. For example, a sequence analysis of 7,855 cardiomyopathy subjects compared to more than 60,000 control subjects highlighted wide variability in penetrance of known disease mutations – highlighting the challenges of clinical application. [16] While somatic mutations known to be associated with malignancies are often tested as part of routine care, this variation within non-malignant conditions such as HF is comparatively understudied, leaving additional opportunity for characterizing disease mechanisms.

Clonal Hematopoiesis

Adult humans have an estimated 10,000 to 200,000 hematopoietic progenitor and stem cells, where each cell may acquire approximately 170 DNA mutations with each decade of life. [17] While most are likely benign, the rare mutation providing a selective advantage may in turn facilitate expansion of a blood cell clone, known as “clonal hematopoiesis” (CH). CH refers to clonal persistence of hematopoietic adult stem cells. [18] Although most somatic mutations in adult stem cells are lost from cell turnover, a subset may persist and accumulate throughout life, which could lead to increased risk of hematologic malignancies and non-malignant conditions with age. [19, 20]

Clonal hematopoiesis was first observed in patients with chronic myelogenous leukemia using cytogenetic studies, establishing the clonal nature of hematologic cancers. [21] Later studies of healthy women looking at non-random X-inactivation in peripheral leukocytes suggested the association of CH and aging, particularly women over the age of 60, although specific mechanisms to account for this genetic skewing could not be determined at the time. [22] CH mutations are found in both early and late stages of hematopoietic differentiation. Progression of CH from early-state mutations have led to both myeloid and lymphocytic malignancies, with a potential to advance to a wide range of hematologic malignancies. [20]

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Despite this, CH mutations do not categorically lead to hematologic malignancy, evolving the term “Clonal Hematopoiesis of Indeterminate Potential” (CHIP) to indicate substantive clonal expansion in individuals without cytopenias or dysplastic hematopoiesis. [20] CHIP distinguishes CH on the basis of non-hematologic clinical significance. Specifically, CHIP is the presence of a cancer-associated mutation without hematologic malignancy, where the clone must have a variant allele frequency (VAF) of at least 2%. [23] VAF is calculated as the percentage of sequencing reads containing a mutant allele at a specific location divided by the total number of reads mapping to that location, with the current 2% threshold resulting from the resolution of whole-exome sequencing at ubiquitous 60–80x coverage. [24]

CH can be categorized based on its etiology, including therapy- and age-associated CH, and neutral drift. Therapy-associated CH is a result of prior radiation or chemotherapy, resulting in increased promotion of driver genes. [25] A study by Gibson et al. revealed a 30% CH incidence rate in patients treated with stem cell transplantation for non-Hodgkin lymphoma, associated with a higher risk for all-cause and CVD-related mortality. [26] Nonetheless, the prevalence of CHIP appears to be largely age-dependent. A study by Xie et al. examined patient data in The Cancer Genome Atlas, identifying CHIP mutations in >2% of the 2728 samples, rising to 5–6% in those older than 70 years. [27] A 2014 sequencing study of 12,380 patients with a 2- to 7-year follow-up found a 1% incidence in individuals less than 50 years old, increasing to 10% incidence for those greater than 65 years old. [28] Likewise, a study by Jaiswal et al. analyzed 17,182 samples from individuals without hematological malignancies, though at risk for diabetes, finding similar incidence rates. [29] While all three studies found a strong age association, CHIP was also found to be common after identifying specific somatic driver mutations in genes commonly mutated in myeloid cancers - including *DNMT3A*, *TET2*, *ASXL1*, *TP53*, *JAK2*, and *SF3B1*. [27–29] Collectively, most CHIP mutations have been found in the *DNMT3A* gene, followed by *TET2*, both epigenetic regulators of gene expression. [30] *DNMT3A* (DNA Methyltransferase 3A) is a DNA methyltransferase involved in de novo synthesis of 5-methylcytosine (5mC). [31] *TET2* (Ten-Eleven Translocation-2) is a methylcytosine dioxygenase responsible for converting 5mC to 5-hydroxymethylcytosine (5hmC), which is an early step in DNA demethylation. [32]

As the cost and availability of genomic sequencing continues to improve, larger cohorts with deeper sequencing coverage makes analysis of sub-clonal variants more accessible. Though low frequency variants are difficult to measure reliably, targeted sequencing with ultra-deep coverage provides an opportunity to capture evolving clonal mutations. Furthermore, in addition to single base mutations and small insertions/deletions, clonal expansion has been characterized as having large copy number alterations. [33] Though routine screening for CHIP mutations would offer an opportunity to assess hematologic malignancies and other comorbidities, there is currently no standardized recommendation due to present lack of targeted or palliative therapies. [18]

CHIP and Coronary Artery Disease (CAD)

The GWAS analysis by Xie et al. identified an association between increasing age and CHIP mutations, as well as an increase in all-cause mortality. [27] The work by Jaiswal et al. corroborated this, and further characterized CHIP-associated cardiovascular outcomes. CHIP was found to be associated with CAD (HR 2.0) and stroke (HR 2.6), even after adjusting for age, sex, diabetes, and BMI. [29] Interestingly, hematologic-related somatic mutations were found to be associated with a higher incidence of type 2 diabetes, after controlling for age, sex, and ancestry – substantiating previous observations of large somatic mutations in peripheral blood cells of type 2 diabetes patients. [34] A later study by Jaiswal compared CHIP between 4,726 CAD patients and 3,529 controls, and reported an increased risk of CAD (HR 1.8) when adjusting for these factors in addition to total cholesterol, HDL, smoking, and hypertension. [35] Interestingly, this cohort exhibited a significantly increased risk in premature myocardial infarction (OR 4.0), with higher indices of calcification in coronary arteries. Using a VAF of 10%, cardiac coronary events were found to be twice as likely in those with mutations compared to controls.

CHIP and Chronic Ischemic Heart Failure

Despite these associations, the cellularity of HSPCs in bone marrow due to CHIP mutations was yet unexplored. To this end, Dorsheimer et al. conducted exome sequencing of blood mononuclear cells and bone marrow from 268 HF patients and found that 19% of patients displayed CHIP mutations, with 62% of these harboring *TET2* and *DNMT3A* mutations. [36] CHIP patients were older and were observed to have more leukocytes compared to their non-CHIP counterparts. Given the high frequency of *TET2* and *DNMT3A,* patients' HSPCs were characterized in bone marrow to assess the potential effect of these driver mutations. Interestingly, *TET2* mutations enriched hematopoietic stem cells, suggesting the impact of CH from bone marrow expansion. Conversely, *DNMT3A* mutations did not impact the cellularity of bone marrow HSPCs. Subsequently, Dorsheimer et al. analyzed bone marrow from 200 chronic, post-ischemic HF patients for CHIP-associated prognostic differences. [30] The entire cohort had a median age of 65 years, a classification of NYHA II, and an LVEF of 31%. Utilizing a 2% VAF threshold, 38 patients were CHIP carriers. Of these, 9 patients had *TET2*-related mutations and 14 patients had *DNMT3A* mutations. These carriers had significantly worse clinical outcomes, including death and rehospitalization for HF across a 4.4-year follow-up, primarily due to progressive HF and emergent arrhythmia. Total CHIP carriers were older and had higher rates of hypertension, an effect that persisted even when examining *TET2* and *DNMT3A* mutations specifically. Altering the VAF threshold to 0.5% increased the detection of *TET2* carriers by 53 patients and *DNMT3A* carriers by 66 – suggesting high penetrance even with low clonal size. Of importance, clinical outcomes were independent of canonical signs and markers for prognostic risk, including LVEF, NT-proBNP, and traditional HF risk scores. Rather, there was a significant dose-response association between the VAF and outcome, suggesting a causal association between these mutations and adverse outcomes.

Ten-Eleven Translocation-2 (*TET2*)

The majority of studies mentioned herein have highlighted mutations in *TET2*, suggesting a causal, though unexplored, role in CHIP-related cardiovascular outcomes. Given the changes in cellularity in bone marrow, Fuster et al. developed a murine model to specifically examine the role of *TET2* deficiency in atherosclerosis development. [37] In this approach, irradiated lipoprotein receptor-deficient mice served as recipients of bone marrow containing 10% *TET2* knockout mutations, and were subsequently fed a diet high in fat and cholesterol. *TET2*-deficient mice experienced HSPC enrichment without increases in blood cell counts, indicating CH. Importantly, these mice fed with the supplemented diet exhibited larger plaques with an increase in total macrophage intimal counts, though without effect to lesion rupture, apoptosis, or macrophage proliferation. Partial inactivation of *TET2* specifically in myeloid cells caused an increase in aortic root plaque size, suggesting *TET2* mutation encourages atherogenesis by HSPC expansion of macrophages. Expanding on this, Sano et al. generated a *TET2*-disrupted murine model with angiotensin-induced HF, relying on transplant of CRISPR-edited bone marrow. [38] Clonal expansion was confirmed and after 8 weeks of angiotensin-II infusion, cardiac function was reduced as evidenced by decreased fractional shortening, and increases in cardiac mass and fibrosis. In a later study, Sano et al. transplanted *TET2*-deficient bone marrow into irradiated mice, in conjunction with chronic ischemic (left anterior descending artery ligation) or pressure overload (transverse aortic constriction) HF models. [39] Mice exhibited reductions in ejection fraction and increases to LV systolic and diastolic volume after 4 weeks, accompanied by increased fibrosis and adverse remodeling. Fully ablating *TET2* in the bone marrow along with arterial ligation showed similar results to *TET2*-deficient mice, though without any differences in mortality. Interestingly, selectively ablating *TET2* in myeloid cells with aortic constriction led to increased cardiac hypertrophy, fibrosis, and lung congestion – again reemphasizing the role of macrophages in the development of HF.

Janus Kinase 2 (*JAK2*)

Recently, the role of *JAK2* has been implicated as a CHIP-associated risk factor. *JAK2* is a signaling kinase, transducing intracellular signals for many various cytokine receptors. [40] Constitutive activation of *JAK2* (most commonly through V617F mutation) is a hallmark of myeloproliferative neoplasms, which can result in malignant proliferation of red blood cells and platelets. [41] However, *JAK2* mutations do have a potential to result in CH with the absence of these malignancies. [28] Mouse studies have shown *JAK2* activates β1 and β2 integrin in neutrophils, which promotes thrombus formation and a potential for ischemic events. [42, 43] This had been explored in a human cohort by Jaiswal et al. with *JAK2*-associated CH, showing increased incidence of coronary artery disease (HR 12.0). [35] However, Liu et al. performed a whole-exome analysis of more than 300,000 participants and found that while *JAK*2 may be associated with increased CAD risk, lower levels of triglycerides and LDLs were observed – hinting at a lipid-independent mechanism of CAD risk. [44] It has been suggested that *JAK2*-related CHIP may occur as a result of the heterogeneity of hematopoietic progenitor cells, resulting in variable penetrance in the patient population. [45] Meanwhile, while *TET2* and *DNMT3A* mutations tend to cause an indiscriminate proliferative capacity in all leukocytes, *JAK2* mutation favors neutrophil and monocyte expansion. [46] In fact, one of the limitations of animal studies is that *JAK2*

mutation often results in either hematopoietic proliferation or myeloid amplification, potentially obfuscating CHIP-related outcomes. However, Sano et al. attempted a selective activation approach, using a lentivirus in transplanted bone marrow to express a V617F mutation in monocytes and neutrophils exclusively. [46] With chronic ischemic and pressure overload surgical injury, these mice favored myeloid expansion of *JAK2* mutants, as well as developed larger infarctions, increased fibrosis, and deterioration of echocardiographic measurements. *JAK2* mutation also exacerbated inflammation, with ischemia resulting in increased IL-1β and IL-6, and pressure overload resulting in increased IL-6 and macrophage infiltration. [46] Taken together, CHIP-associated *JAK2* mutations may increase susceptibility to cardiovascular events by fostering clonal subpopulations that increase inflammation by cytokine production.

Implications of CHIP: Targeting Inflammasome in Heart Failure

Heart failure is associated with chronic low-grade inflammation, leading to maladaptive cardiac remodeling. [47] This persistent inflammation is due largely to the *NLRP3* inflammasome - a complex of intracellular proteins that trigger maturation of proinflammatory cytokines including IL-1β, a proinflammatory cytokine associated with cardiomyocyte apoptosis and tissue remodeling. [48, 49] *NLRP3* inflammasome activity first requires an initiation signal (such as danger-associated molecular patterns from sterile infection) which increases pro-IL-1β expression, and then an activation signal which promotes total inflammasome assembly. [37] In an acute setting of myocarditis, more inflammasome-containing leukocytes were found in myocardial tissue corresponding to <40% EF and NYHA classes III and IV. [50] Indeed, strategies concentrating on inhibition of the inflammasome have gained traction in the field. Bracey et al. examined genetic ablation of *NLRP3* in a proinflammatory mouse model of cardiac hypertrophy, which reduced local caspase-1 and systemic IL-1β, and resulted in decreased apoptosis and improved systolic function. [51] In human atrial tissue, in vitro studies revealed that inhibition of the proinflammatory cytokine IL-18 resulted in improved contractile function after I/R injury. Furthermore, decreasing the cleavage of IL-1β to IL-18 through the inhibition of caspase 1 also minimized decreases to contractile function - suggesting the importance of the conversion in IL-1β to IL-18 in cytokine-mediated cardiac depression, following ischemia. [48] In humans, the 2012 Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) examined the effect of IL-1β inhibition by canakinumab on the incidence of myocardial infarction, stroke, and cardiovascular death in patients with coronary artery disease and elevated CRP. [52] Subsequent analysis found significant decreases in CRP with administration and modest reduction in MACE incidence at higher doses. [53] Indeed, IL-1β blockade has been promising – the use of the IL-1 receptor agonist, anakinra, in patients after myocardial infarction reduced cardiac remodeling evidenced through echocardiographic indices. [54, 55] In the face of these efforts, CH represents another avenue in which therapies for inflammation may prove fruitful. The link between leukemic transformation and the incidence of cardiovascular disease is underscored by chronic inflammation and its ability to initiate clonal evolution and CH. [56] This common denominator has not been ignored in the aforementioned studies. The study by Fuster et al. also observed the effect of *TET2* deficiency on the inflammasome, showing that

increased IL-1β production in macrophages could be rescued by the *NLRP3* inhibitor, MCC950, without changes to cellularity. [37] Additionally, CRISPR disruption of *TET2* and *DNMT3A* by Sano et al. led to increases in inflammatory cytokines, including IL-6, Ccl5, IL-1β, Cxc11, and Cxcl2. [38] Subsequent examination in mice with the chronic ischemic and pressure overload surgical models mirrored these findings, as well as corroborated MCC950 treatment with the rescue of echocardiographic measures and diminished fibrosis. [39]

Conclusions

With origins in hematological cancers and common incidence in older populations, CHIP is developing increasing pertinence in the cardiovascular arena. Studies thus far have demonstrated the roles of common mutations - such as in *TET2*, *DNMT3A*, and *JAK2* – in CH, as well as cytokine changes that increase inflammation. A large portion of these studies mentioned explore the relationship between CHIP and ischemic heart pathologies, and our understanding may be improved with longitudinal studies to characterize the evolution of CAD with CHIP mutations. However, the association with non-ischemic HF is less clear. Undoubtedly, increases to inflammation, like those found with CHIP mutations, may adversely affect cardiovascular outcomes. Additionally, while most genomic studies have focused on exome sequencing, the role of non-coding variation in transcription and translation is still unknown and could confer additional metrics for HF risk. While the etiology between CHIP and HF is yet incomplete, recent work has highlighted a novel and promising angle for identifying and disseminating clinical risk. As the role of CHIP in HF becomes clearer, so do the opportunities for reducing these risks and ameliorating adverse outcomes.

Funding Support:

Dr. Tang is partially supported by grants from the National Institutes of Health and the Office of Dietary Supplements (R01DK106000, R01HL126827).

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