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Clonal Hematopoiesis of Indeterminate Potential and Cardiovascular Disease

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Abstract

Purpose of Review The purpose of this review article is to summarize the preclinical and clinical evidence supporting the notion of clonal hematopoiesis of indeterminate potential (CHIP), highlight current knowledge gap, and provide future directions.

Recent Findings Epidemiological studies show that advanced age is a major risk factor for the development of cardiovascular disease (CVD) and cancer, the two leading causes of morbidity and mortality worldwide. While the negative effect of aging on CVD is a reflection of cumulative exposure to various established traditional CVD risk factors, genetic sequencing of whole blood-derived DNA recently revealed that clonal mutations in myeloid stem cells are associated with higher risks of cardiovascular events and hematopoietic malignancies. The clinical repercussions of this biological state, termed CHIP, are increasingly appreciated. Historically, CHIP has been associated with an increased risk of hematological malignancies. However, new research is showing that CHIP is also associated with an increased risk of several cardiac-related conditions, including atherosclerosis, myocardial infarction, aortic valve stenosis, and congestive heart failure.

Summary CHIP is increasingly being appreciated worldwide as a CVD risk factor, and further studies are needed to better understand the complex relationship between these two disorders.

Keywords Aortic valve stenosis · Cardio-oncology · Cardiovascular disease · Clonal hematopoiesis of indeterminate potential · Congestive heart failure · Myocardial infarction

Introduction

Clonal hematopoiesis of indeterminate potential (CHIP) is a condition characterized by somatic mutations in genes implicated in myeloid neoplasms in the absence of an overt hematologic malignancy. The majority of CHIP cases are caused by mutations in the following genes: *DNMT3A*, *TET2*, *ASXL1*, *JAK2*, and *TP53*.

The current diagnostic criteria for CHIP include a normal peripheral blood count and a population of mutant cells that accounts for $\geq 2\%$ of the peripheral blood leukocytes. The focus of this paper will be to review the evidence underlying the relationship between CHIP and cardiovascular disease (CVD) using published preclinical and clinical studies.

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CHIP, Cardiovascular Disease, and Aging

As cells age, they acquire somatic mutations, and this has been shown in a variety of tissues, including the esophagus [1], skin [2], and blood [3] (Fig. 1). Hematopoietic stem cells (HSCs) within the bone marrow are also exposed to mutagenic events involving certain genes, which may give rise to clones of somatically mutated leukocytes [4]. By the age of 70 years, 10 to 20% of individuals have a leukocyte clone in peripheral blood with a variant allele fraction (VAF) $\geq 2\%$. The positive correlation between age and the development of CHIP is likely a direct consequence of the cumulative duration of exposure to environmental carcinogens, such as radiation, tobacco

Fig. 1 Clonal hematopoiesis and mechanisms that might accelerate atherothrombotic risk. Acquired mutations in bone marrow stem cells accumulate with age and can give rise to a clonal population of mutant leukocytes that circulate in peripheral blood, a condition called CHIP. This figure depicts how the clones arise. In peripheral blood, they account for a $\approx 20\%$ of leukocytes on the average (this diagram shows only this minority of mutant cells). Most individuals with CHIP will never develop a hematologic malignancy, but CHIP carriers have a marked increase in the risk of myocardial infarction, stroke, and perhaps venous thrombosis and pulmonary embolism. Only 4 mutations account for most

cases of CHIP. Some of them appear to cause increased cardiovascular risk because of changes in the methylation of DNA, epigenetic alterations that increase the transcription of proinflammatory genes that drive atherogenesis. Another common CHIP mutation in the kinase Jak2 associates with increased thrombotic risk attributable, at least in part, to a heightened propensity to develop neutrophil extracellular traps. CHIP indicates clonal hematopoiesis of indeterminate potential; CXCL, CXC chemokine ligand; IL-1 β , interleukin 1 β ; IL-6, interleukin 6; Pf4, platelet factor 4. Reproduced from [17], with permission from Wolters Kluwer Health, Inc. and the American Heart Association

smoke, and air pollutants [5]. Potential consequences of recurring somatic mutations include myelodysplastic syndrome and acute leukemia. However, hematologic malignancies generally require multiple successive mutations in leukemia-driver genes in the same leukocyte clone, which is a relatively rare occurrence with an incidence of $< 1\%$ per year in CHIP carriers [6]. Despite this low rate, individuals with CHIP have an associated 40% increase in all-cause mortality compared with the general population—which is not fully explained by the presence of a hematological malignancy [7•]. A series of large population-based analyses of whole-exome sequencing revealed that individuals with CHIP have a high prevalence of cardiovascular (CV) events and deaths due to myocardial infarction (MI) and stroke. Thus, an important consequence of CHIP is an increase in cardiovascular risk. Moreover, emerging preclinical evidence suggests a direct cause-and-effect relationship between CHIP and the development of CVD, possibly due to heightened inflammasome activity contributing to progression of atherosclerotic plaque and endothelial injury.

Preclinical Studies Linking CHIP and Cardiovascular Disease

Jaiswal et al. transplanted bone marrow from mice homozygous for loss-of-function mutations of *Tet2* and from control mice into irradiated atherosclerosis-prone, *Ldl-r* knockout mice, who were fed high-cholesterol diet. They then assessed atherosclerosis at various time points [7•]. The atherosclerosis-prone *Ldl-r*

knockout mice which received bone marrow from *Tet2* knockout mice had a twofold increase in atherosclerotic lesion size ($p = 0.02$). Fuster et al. conducted a similar study and demonstrated that *Tet2*-deficient mice, compared with control mice, had accelerated atherosclerosis [8]. Jaiswal et al. subsequently cultured bone marrow-derived macrophages from *Tet2* knockout mice and control mice and performed transcriptome analysis, showing that macrophages from *Tet2* knockout mice, compared with the control mice, expressed an increased amount of RNA encoding for inflammatory markers implicated in the pathogenesis of atherosclerosis, including the cytokines interleukin (IL)-1 β and IL-6. These findings imply that *Tet2* deficiency potentiates atherogenesis by stimulating inflammatory pathways. In a model of JAK-2 mutated mice, Wang et al. showed that *Jak2*^{V617F} erythrocytes undergo accelerated uptake by macrophages, leading to impaired clearance of senescent leukocytes and promoting necrotic core formation and plaque instability [9]. These observations indicate that CHIP due to *Tet2* deficiency or *JAK2* mutation promote CVD but via potentially disparate mechanisms.

CHIP is postulated to increase the risk of cardiovascular conditions beyond ASCVD, such as post-myocardial infarction heart failure and thrombus formation. Sano et al. evaluated the impact of *Tet2* deficiency in mice with heart failure, induced by aortic constriction or chronic ischemia. They discovered that *TET2*-deficient mice had poor cardiac remodeling secondary to increased IL-1 β levels [10]. At 4 weeks after induction of heart failure, the *Tet2* knockout mice, compared with the control mice, displayed greater increases in left ventricle systolic

Table 1 Overall and cardiovascular outcomes in chip carriers versus controls

Outcome	Name of study	# of CHIP carriers with outcome/# at risk (%)	# of non-CHIP carriers with outcome/# at risk	HR/OR	95% CI	p value
Development of CHD	Bioimage [7•]	19/44 (43%)	94/326 (30%)	HR = 1.8	1.1–2.9	0.03
	Malmo Diet and Cancer [7•]	21/33 (64%)	299/607 (49%)	HR = 2.0	1.2–3.1	0.003
History of early-onset MI	Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group [7•]	37/43 (86%)	1716/3293 (52%)	OR = 5.4	2.3–13.0	< 0.001
	Pakistan Risk of Myocardial Infarction Study [7•]	52/65 (80%)	2488/3844 (65%)	OR = 3.4	1.8–6.5	< 0.001
Mortality rate following TAVI for severe AS	Mas-Peiro et al. [12•]	35/91 (38%) ^a	62/178 (35%) ^b	HR = 3.1	1.2–8.1	0.022
Mortality rate in patients with CHF	Dorsheimer et al. [13•]	14/38 (37%)	39/162 (24%)	HR = 2.1	1.0–4.2	0.04

^a Patients with DNMT3A- or TET2-CHIP-driver mutations with a variant allele frequency of $\geq 2\%$

^b Patients without DNMT3A or TET2 mutations

AS aortic stenosis, CHD coronary heart disease, CHF congestive heart failure, CHIP clonal hematopoiesis of indeterminate potential, CI confidence interval, HR hazard ratio, OR odds ratio, MI myocardial infarction, TAVI transcatheter aortic valve implantation

and diastolic volumes, suggesting systolic dysfunction. Staining of the fibrotic myocardial tissue revealed that myocytes of the *Tet2* knockout mice had greater hypertrophy relative to control mice. Edelmann et al. evaluated the role of *JAK2*^{V617F} mutation in promoting thrombus formation and found that this mutation upregulates β_1 integrin expression in monocytes, T cells, and B cells and β_2 integrin expression in granulocytes, monocytes, and T cells [11].

Clinical Studies Linking CHIP and Cardiovascular Disease

CHIP and Coronary Heart Disease, Early-Onset Myocardial Infarction, and Coronary Artery Calcification

Individuals with CHIP are at an increased risk for coronary heart disease (CHD) [3], independent of established traditional CVD risk factors (e.g., diabetes mellitus type 2, hypercholesterolemia, hypertension, and smoking). Jaiswal et al. assessed whether CHIP contributes to the development of CHD by using blood samples from 2 different prospective case-control studies—BioImage and Malmo Diet and Cancer (MDC) [7•]. CHD was defined as a history of

myocardial infarction (MI) or coronary revascularization after time of DNA collection. In BioImage, 43% (19/44) of CHIP carriers and 30% (94/326) of non-CHIP carriers developed CHD over a median follow-up time of 2.6 years. In MDC, 64% (21/33) of CHIP carriers and 49% (299/607) of non-CHIP carriers developed CHD over a median follow-up time of 17.7 years. Combining these two studies showed that CHIP carriers, compared with non-carriers, were 1.9 times more likely to develop CHD ($p < 0.001$) (Table 1).

The investigators also assessed whether CHIP contributed to early-onset MI (age < 50 years) by using blood samples from 2 different retrospective case-control studies—the Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group (ATVB) and Pakistan Risk of Myocardial Infarction Study (PROMIS). In ATVB, 86% of CHIP carriers and 52% of non-CHIP carriers had a history of early-onset MI. In PROMIS, 80% of CHIP carriers and 65% of non-CHIP carriers had a history of early-onset MI. Combining these two studies revealed that CHIP carriers, compared with non-CHIP carriers, were 4 times more likely to develop early-onset MI ($p < 0.001$) (Table 1). In addition, Jaiswal et al. assessed if an increased atherosclerosis burden was the pathophysiological mechanism linking CHIP and CHD by reviewing coronary artery calcification (CAC) scores as detected by cardiac computed tomography from participants in the BioImage study. Among patients with CHD, CAC scores were approximately 2-fold higher in CHIP

Fig. 2 Clonal hematopoiesis of indeterminate potential: preclinical associations with cardiovascular conditions. CAC, coronary artery calcium; CI, confidence interval; HR, hazard ratio; IL-1 β , interleukin 1 β ; IL-6, interleukin 6; IL-8, interleukin 8; OR, odds ratio; TNF- α , tumor necrosis factor alpha

Abbreviations: CAC – coronary artery calcium, CI – confidence interval, HR – hazard ratio, IL-1 β – interleukin 1 β , IL-6 – interleukin 6, IL-8 – interleukin 8, OR – odds ratio, TNF α – tumor necrosis factor α

carriers compared with those in non-CHIP carriers ($p = 0.03$). In patients without CHD, CAC scores were 3.3 times higher in CHIP carriers compared with those in non-CHIP carriers. Since CHIP is associated with a higher risk of developing hematologic cancer, the investigators assessed if there was any correlation between CHIP clone size and atherosclerosis burden. CHIP carriers with a VAF of $\geq 10\%$, compared with non-CHIP carriers, were 12 times more likely to have CAC scores ≥ 615 Agatston units ($p = 0.002$). These findings imply that CHIP increases the risk of developing CHD and early-onset MI by promoting atherosclerosis.

Since preclinical studies suggested that CHIP-induced accelerated atherogenesis occurred secondary to an increase in IL-1 β /IL-6 signaling and that this heightened risk can be ameliorated by disrupting the signaling pathway, Bick et al. hypothesized that inhibition of the IL-1 β /IL-6 pathway in humans with CHIP would reduce CVD risk [14]. The investigators tested this hypothesis by comparing the cumulative CVD event rate in patients with large CHIP and the *Asp358Ala* variant in the IL-6 receptor gene, a mutation known to disrupt IL-6 signaling, to those with large CHIP but without this variant mutation. CVD event was defined as MI, coronary revascularization, stroke, or death. Large CHIP was defined as an allele fraction $> 10\%$. Patients with large CHIP and the variant mutation in the IL-6 receptor gene had a CVD event rate that was less than half of that compared with those with large CHIP and without the variant mutation. This study suggests that an array of genetic factors modulate the association between CHIP and CV disease.

CHIP and Aortic Valve Stenosis

Since the incidence of calcified degenerative aortic valve (AV) stenosis increases with age, Mas-Peiro et al. assessed the incidence of 2 mutations commonly associated with CHIP,

DNMT3A and *TET2*, in patients with severe calcified AV stenosis and their impact on mortality following transcatheter aortic valve implantation (TAVI) [12•]. Among the 279 patients with severe calcified AV stenosis undergoing TAVI, 93 were carriers of a *DNMT3A* ($n = 53$) or *TET2* ($n = 40$) mutation with a VAF $\geq 2\%$ and 10 had mutations in both genes. The prevalence of *DNMT3A/TET2* mutations and severe AV stenosis increased with age: from 25% (2/8) in the age group 55–69 years, to 25.4% (17/67) in the age group 70–79 years, to 34.7% (65/187) in the age group 80–89 years, and finally to 52.9% (9/17) in the age group 90–99 years. Although the CHIP cohort, compared with the non-CHIP cohort, had a slightly higher frequency of female patients, the remaining baseline characteristics, echocardiographic findings, and laboratory values did not significantly differ between the two cohorts. Patients in the CHIP cohort ($n = 91$), compared with those in the non-CHIP cohort ($n = 178$), experienced a significantly higher mortality during the first 8 months after TAVI ($p = 0.012$). Multivariable Cox proportional regression analyses revealed that the presence of a CHIP mutation increased mortality by approximately 3-fold (Table 1). Consequently, in patients with severe AV stenosis undergoing TAVI, harboring a *DNMT3A/TET2* mutation portends a worse clinical outcome. Since calcific aortic stenosis occurs due to fibrosis secondary to chronic inflammation [15] and loss-of-function mutations in *DNMT3A* and *TET2* in murine models of heart disease have shown to promote fibrosis [7•], one hypothesis is that these mutations contribute to the biology of AV stenosis. Exploratory analyses revealed that patients with a *DNMT3A* mutation demonstrate a significantly higher ratio of the pro-inflammatory Th17 cells to the anti-inflammatory regulatory T cells, and patients with a *TET2* mutation showed increased levels of CD14^{dim}CD16⁺⁺, monocytes known to secrete high levels of proinflammatory cytokines, including tumor necrosis factor alpha, IL-1 β , and IL-8. Thus, *DNMT3A/TET2* mutations yield heightened inflammatory states and do so differently.

CHIP and Congestive Heart Failure

Dorsheimer et al. assessed the incidence and prognostic significance of CHIP in 200 patients with chronic heart failure (CHF) of ischemic origin [13•]. Eligible patients had stable CHF symptoms consistent with New York Heart Association class II or greater, a history of MI status post successful revascularization ≥ 3 months before bone marrow aspiration, and echocardiographic evidence of a well-demarcated region of left ventricular dysfunction. DNA from bone marrow–derived mononuclear cells was isolated and analyzed for the presence of CHIP, and 18.5% (38/200) of CHF patients were CHIP carriers with a VAF of $\geq 0.02\%$. Baseline clinical characteristics, except for age, did not significantly differ between the CHIP and non-CHIP cohorts. Over a median follow-up of 4.4 years, 37% (14/38) of CHF patients with CHIP, compared with 24% (39/162) CHF patients without CHIP, died. Kaplan-Meier event-free survival analyses revealed that CHF patients with the two most common CHIP mutations, *DNMT3A* and *TET2*, compared with CHF patients without CHIP, had worse long-term clinical outcomes with respect to death and death plus rehospitalization for heart failure. Since aging is associated with and increases the risk of developing CHIP, multivariate Cox proportional regression analyses accounting for this variable showed that the presence of somatic mutations within *DNMT3A* and *TET2* increased mortality by approximately 2-fold (Table 1). These findings demonstrate that CHF patients have a high prevalence of CHIP and that the most commonly CHIP-associated mutations, *DNMT3A* and *TET2*, are associated with poor clinical outcomes.

Conclusions

This review article briefly discussed the preclinical and clinical studies linking CHIP to various forms of CVD, including CHD, early-onset MI, CAC, AVS, and CHF. Based on the novelty and complexity of this relationship, a multidisciplinary approach involving cardiologists, oncologists, and geneticists familiar with the field is essential for positive outcomes [16].

Future Directions

The link between CHIP and CVD is new, and many unanswered questions regarding the biology, mechanisms, and clinical significance of this novel association remain. In terms of biology, only a handful of key somatic mutations leading to CHIP have been identified and therefore discovery of additional mechanisms underlying CHIP generation and progression is paramount (Fig. 2). Specifically, prospective studies looking at the impact of CAC score changes and aortic valve stenosis severity overtime on the rate of cardiac events for each known CHIP mutation can aid in understanding potential predictors of adverse cardiac events, and this novel knowledge can then be used

to update the 10-year ASCVD risk calculator. An increased atherosclerotic burden has been hypothesized to predispose CHIP carriers to developing overt CVD, but it remains unclear if other mechanisms are at play. Accordingly, prospective cohort studies comparing the impact of baby aspirin and statins on the primary and secondary prevention of cardiac events in patients with CHIP versus controls is merited. A similarly designed study looking at whether these preventive measures can also alter cancer-related outcomes by looking into patients with CHIP and hematologic malignancies should likewise be pursued. Since CHIP is associated with poor clinical outcomes, the value of routine screening or screening in high-risk individuals, such as those older than 65 years of age or those with unexplained cardiovascular disease, warrants further research. The association between CHIP and cardiovascular risk enhancers, such as chronic kidney disease and family history of premature atherosclerosis, should be investigated further. In addition, an understanding of the unique relationship between specific CHIP phenotypes and CV- and cancer-specific outcomes will be very important to develop. In terms of treatment, since CHIP increases the expression of proinflammatory genes, therapies targeting inflammatory mediators might be useful for alleviating the risk of CVD and cancer.

Compliance with Ethical Standards

Conflict of Interest Preetham Kumar declares that he has no conflict of interest.

Stephen L. Kopecky has received research support from True Health and compensation from Prime Therapeutics (consulting), Amgen (workshop), and Applied Clinical Intelligence (Data Safety Monitoring Board) and is a member of the Board of Directors of Mayo Clinic Support Services, TX.

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Dr. Oren reports no disclosures.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
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