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Clonal Hematopoiesis and the Heart: a Toxic Relationship

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Abstract

Purpose of Review Clonal hematopoiesis (CH) refers to the expansion of hematopoietic stem cell clones and their cellular progeny due to somatic mutations, mosaic chromosomal alterations (mCAs), or copy number variants which naturally accumulate with age. CH has been linked to increased risk of blood cancers, but CH has also been linked to adverse cardiovascular outcomes.

Recent Findings A combination of clinical outcome studies and mouse models have offered strong evidence that CH mutations either correlate with or cause atherosclerosis, diabetes mellitus, chronic kidney disease, heart failure, pulmonary hypertension, aortic aneurysm, myocardial infarction, stroke, aortic stenosis, poor outcomes following transcatheter aortic valve replacement (TAVR) or orthotopic heart transplant, death or need of renal replacement therapy secondary to cardiogenic shock, death from cardiovascular causes at large, and enhance anthracycline cardiac toxicity. Mechanistically, some adverse outcomes are caused by macrophage secretion of IL-1 β and IL-6, neutrophil invasion of injured myocardium, and T-cell skewing towards inflammatory phenotypes.

Summary CH mutations lead to harmful inflammation and arterial wall invasion by bone marrow-derived cells resulting in poor cardiovascular health and outcomes. Blockade of IL-1 β or JAK2 signaling are potential avenues for preventing CH-caused cardiovascular morbidity and mortality.

Keywords Clonal hematopoiesis · CHIP · Cardio-oncology · Therapy-related cardiac toxicity · TET2

Introduction

Somatic mutations and mosaic chromosomal alterations (mCAs) accumulate in hematopoietic stem cells (HSCs) and their cellular progeny as individuals age. When these

genetic lesions lead to clonal expansion of a population in the absence of a malignancy or cytopenia, it is referred to as CH. CH of indeterminate potential (CHIP) is a subset of CH and is generally restricted to somatic mutations in genes associated with hematologic malignancy (*DNMT3A*, *TET2*, *ASXL1*, *JAK2*, *TP53*, etc.) with a minimum variant allele frequency (VAF) of 2% [1]. CH has been primarily viewed as a precursor to myeloid malignancies such as acute myeloid leukemia or myelodysplastic syndrome, though it is recognized that some clonal expansions can predispose individuals to lymphoid malignancies as well, leading to the characterization of some mutations and mCAs as either myeloid or lymphoid CH [2].

Beyond increasing the risk of primary or secondary malignancies, clinical outcomes in other disease processes tend to be negatively affected by the presence of CH although there are some identified exceptions. Responses to chimeric antigen receptor T-cell efficacy are likely enhanced by the presence of CH, albeit with increased rates of cytokine release syndrome and neurotoxicity [3–6].

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Moreover, the presence of CH has been associated with improved overall survival (OS) in patients with metastatic colorectal cancer and with a reduction in the risk of developing Alzheimer's disease [7, 8]. Some CH mutations in the donor of allogeneic hematopoietic stem cell transplants are protective in the recipient and lead to reduced relapse risk and improved OS [9].

These benefits are firmly outweighed in quantity by the known negative health impacts of CH, likely mediated by excessive IL-6 and IL-1 β driven inflammation [1]. CH is associated with chronic obstructive pulmonary disease in multiple studies, and mouse models suggest CH mutations can be causative [10, 11]. CH is associated with excessive osteoclast activity and resulting osteoporosis [12]. CH correlates with post-transplant, non-relapse mortality in patients receiving stem cell transplants for multiple myeloma and lymphoma [3, 4]. In a cohort of myeloma patients that had undergone autologous stem cell transplants, the presence of CH was also associated with decreased progression free survival and decreased OS regardless of whether the patients were treated with immune modulating drugs [13]. The immune system's response to infections also appears impaired by the presence of CH as CH is associated with severe COVID-19 outcomes, as well as with *Clostridium Difficile* and *Enterococcal/Streptococcal* infections in solid tumor patients [14]. Diabetes is more common in patients with CH [15]. As will be reviewed here, the evidence implicating CH in poor cardiovascular outcomes is extensive, which is likely a primary driver for the association of CH with decreased OS in the general population [16]. The relationship between CH and coronary artery disease (CAD) was the first non-oncologic outcome to be recognized [15], with further cardiologic studies also linking CH to progression of heart failure [17–20], aortic aneurysm [21], pulmonary hypertension [22], deterioration from cardiogenic shock [23], aortic stenosis [24], poor outcomes after TAVR [25] or orthotopic heart transplantation [26], and increased sensitivity to cardiotoxic chemotherapy [27]. Here we will review the evidence connecting CH to cardiovascular outcomes, mechanistic explanations, potential practice changes, and future research directions.

A Shot Through the Heart, CH Realized as a Risk Factor for Vascular Disease

Atherosclerosis is the result of inflammation in the blood vessel wall, and myeloid cells such as monocyte-derived macrophages are known to mediate this inflammation [28–30]. In CH, lineage restriction can occur leading to “myeloid bias” with mutated myeloid progeny cells that are more prone to causing atherosclerosis [31]. CH was first implicated in cardiovascular disease on a population

level by Jaiswal et al. after performing whole-exome sequencing of peripheral blood from 17,182 individuals. Mutations in genes associated with blood cancers were frequently found in *DNMT3A*, *TET2*, and *ASXL1*, and individuals with such mutations were found to be at an increased risk for all-cause mortality (HR 1.4; 1.1 to 1.8 95% CI), CAD (HR 2.0; 1.2 to 3.4 95% CI), and ischemic stroke (HR 2.6; 1.4 to 4.8 95% CI) [15]. A second landmark case–control study using whole-exome sequencing of 4,726 participants with CAD and 3,529 controls found that rates of CH were 1.9 \times greater in individuals with CAD [32]. Causality was also demonstrated by modeling CH with atherosclerosis-prone mice and a low-density lipoprotein receptor knockout mutation and engrafting them with bone marrow from *Tet2* control or heterozygous or homozygous knockout mice and then feeding them a high-fat, high-cholesterol diet. Loss of *Tet2* was associated with higher atherosclerotic burden in the aorta, as well as with macrophage expression of cytokines and chemokines associated with atherosclerosis, including *Cxcl1*, *Cxcl2*, *Cxcl3*, *Pf4*, *Il-1b*, and *Il-6* [32]. Together, these two studies provide strong evidence not only that CH is associated with atherosclerotic disease, but that CH mutations can cause atherosclerosis likely in part through macrophage recruitment of monocytes and other blood cells to the arterial intima. CH mutations may also contribute to the premature cardiovascular disease in people with HIV, as CH mutations are more common in individuals with HIV and in this patient population CH mutation carriers tend to have greater coronary atherosclerosis burden [33].

CH is also associated with the consequences of atherosclerosis. A prospective cohort study involving 78,752 individuals examined the association of CH with the risk of different types of stroke, and found CH to be associated more with hemorrhagic stroke (HR 1.24; 1.01 to 1.54 95% CI) than with ischemic stroke (HR 1.11; 0.98 to 1.25 95% CI) [34]. *TET2* mutations conferred the strongest association with stroke overall and with ischemic stroke among the 74 genes sequenced [34, 35]. CH is also prevalent in patients with ST-segment elevation myocardial infarction (STEMI) and correlates with poor outcomes following STEMI. *DNMT3A* or *TET2* CH mutations have been found in 12.4% of STEMI patients, and patients harboring these mutations have a much higher incidence of death (30.9% vs 15.5%, $p=0.001$) or major cardiac events (44.5% vs 21.8%, $p<0.001$) over a median 3-year follow-up after STEMI [36]. In patients with cardiogenic shock secondary to myocardial infarction, having a CH mutation is associated with an increased risk of death or requiring renal replacement therapy independent of age or renal function [23]. In summary, CH mutations appear to cause accelerated atherosclerosis and likely lead to the subsequent sequelae of atherosclerotic burden including stroke and myocardial infarction.

Molecular Mechanisms of CH-Mediated Cardiotoxicity

Myeloid CH gene mutations (such as *TET2* or *DNMT3A*) as a class have been strongly associated with all-cause mortality (HR = 1.6, $p < 0.001$) and an increased risk of CAD (HR = 1.35, $p = 0.005$) whereas lymphoid CH gene mutations as a class are not associated with either [2]. mCAs have been associated with all-cause mortality but are not associated with increased risk of CAD [2]. Thus, we will emphasize mutations in myeloid CH genes, like *TET2*. An abundance of literature has been developed around *TET2* and has delineated a mechanistic link with adverse cardiovascular outcomes. The *TET2* gene is one of three *TET* genes and resides at 4q24 where it encodes the Ten-eleven translocation 2 protein. TET proteins catalyze the production of cytosine derivatives and may be involved in the demethylation of CpG dinucleotides [37–39]. Murine *Tet2* knockouts demonstrate that loss or heterozygosity of *Tet2* leads to myeloid progenitor cell and multipotent progenitor cell expansion, and that hematopoietic stem cells harboring *Tet2* loss can outcompete wildtype hematopoietic stem cells in competitive engraftment experiments [40–44]. *TET2* mutations are frequently found in myeloid neoplasms but also in angioimmunoblastic T-cell lymphoma and in peripheral T-cell lymphoma not otherwise specified [39, 45–48].

TET2 has been firmly implicated in the development of atherosclerosis and subsequent myocardial infarction through the NLRP3 inflammasome-mediated secretion of IL-1 β . As mentioned previously, murine data demonstrates that *Tet2* loss enhances macrophage cytokine secretion of IL-1 β leading to plausible recruitment of monocytes, platelets, and other cell types to the arterial wall [32]. Similarly, *Tet2* deficiency in Ldl receptor null mice fed a high fat diet leads to markedly accelerated atherosclerosis that can be rescued by NLRP3 inhibition [49]. *Tet2* is also a master regulator of vascular smooth muscle cell plasticity and *Tet2* activation also promotes vascular smooth muscle proliferation and intimal hyperplasia, which may further contribute to accelerated atherosclerosis [50–54].

Murine models also suggest a role for myocardial *Tet2* in CH-associated heart failure. *Tet2* deficiency worsens cardiac remodeling and function after left anterior descending artery ligation or transverse aortic constriction, and increases IL-1 β expression in the remodeling heart tissue [55]. Moreover, blocking IL-1 β production by inhibiting the NLRP3 inflammasome has an enhanced protective effect following myocardial injury in *Tet2* deficient mice [55]. Infusion of *Tet2* mutant bone marrow cells induces clonal expansion of *Tet2* deficient Ccr2 + macrophages that infiltrate the mouse heart provoking age-related

cardiac hypertrophy and fibrosis [56]. Similar results have been found using CRISPR-mediated gene editing of stem cells [57]. Loss of *Tet2* also leads to cardiomyocyte hypertrophy through hyperactivation of ERK 1/2 suggesting that the hypertrophic phenotype of *Tet2* null mice may arise from both clonal populations of infiltrating cells and cardiomyocyte-autonomous effects [58]. *Asx1* CH mutations have also been shown to have similar negative effects on cardiac remodeling with similar enhancement of macrophage IL-1 β production [59].

There is some evidence in humans implicating *TET2*-regulated IL-1 β secretion as pathogenic as well. In the Canakinumab Anti-inflammatory Thrombosis Outcomes Trial (CANTOS), participants with a prior myocardial infarction and an elevated hs-CRP level were randomized to placebo or escalating doses of canakinumab: an anti-IL-1 β monoclonal antibody [60•]. Higher doses of canakinumab led to a 15% relative risk reduction in the combined end points of myocardial infarction, stroke, and cardiovascular-related death (major adverse cardiac events, MACE). A follow-up study identified patients as having CH or not having CH mutations using a 74 gene panel, and found that 8.6% of participants in CANTOS had CH mutations, with *TET2* gene mutations being the most common variant [60•]. Patients that harbored a *TET2* mutation had higher rates of major cardiac events than those that did not, as well as a statically significant response to canakinumab, whereas patients without a *TET2* mutation had no significant effect in major myocardial events after treatment with canakinumab [60•]. Together with the data from mouse models, these results strongly implicate *TET2* dysfunction as driving the production of IL-1 β and causing vascular disease as manifested by higher rates of myocardial infarction, stroke, and cardiovascular-related death.

DNMT3A is another CH gene, which like *TET2* regulates the methylation of CpG dinucleotides. In fact, mendelian randomization studies have identified subsets of DNA methylation sites that likely cause the increased risk of CAD associated with these two mutations [61]. In a study of 485 patients with STEMI, those that harbored either a *DNMT3A* or *TET2* mutation had an increased risk of death or MACE and had higher levels of plasma IL-1 β and IL-6, but not higher levels of TNF β or IFN γ [36]. Extensive evidence supports a pathogenic role for IL-6 in numerous forms of cardiovascular disease and the IL-6 antagonist ziltivekimab was associated with favorable atherothrombotic outcomes in a recent phase 2 clinical trial [62, 63]. Patients with CH defined by *DNMT3A* or *TET2* mutations have higher rates of cardiovascular disease and this effect is greater in patients with high VAF (> 10%), but this effect is abrogated in patients with congenital deficiency in IL-6 signaling that carry the *IL6R* p.Asp358Ala germline mutation [64]. In a

macaque model of *TET2* CH, macrophages with a *TET2* loss-of-function mutation expressed higher levels of IL-6 and IL-1 β , and treating the macaques with tocilizumab slowed *TET2*-mutated clone expansion, suggesting that IL-6 may enable the selective advantage of *TET2*-mutated clones [65•].

Another commonly mutated CH gene is *JAK2*, which has now been implicated in the development of pulmonary hypertension: a cause of right heart failure [22]. In a prospective clinical cohort, *JAK2V617F*-positive CH was more common in patients with pulmonary hypertension than in healthy controls [22]. Extending this finding into mice for mechanistic insight, transgenic mice harboring *Jak2V617F* had exacerbated pulmonary hypertension and pulmonary arterial remodeling after being exposed to chronic hypoxia. This was accompanied by increased neutrophil invasion of the pulmonary arterial regions and increases in neutrophil-derived elastase activity [22]. Inhibiting Alk1/2, which is upregulated by *Jak2V617F*, completely stopped the development of pulmonary hypertension in *Jak2V617F* mice [22]. *JAK2V617F* may also cause venous thromboembolism and pulmonary embolism further contributing to pulmonary hypertension [66–69]. One demonstrated mechanism for thromboembolism caused by *JAK2* mutations is through enhanced production of neutrophil extracellular traps: large structures that are web-like, pro-thrombotic and made of cytosolic and granule proteins stuck together on a scaffold of decondensed chromatin [69, 70]. Interestingly, because *JAK2* can be inhibited by ruxolitinib, this may be a therapy for pulmonary hypertension in the future. *TET2* has also been implicated in pulmonary hypertension as germline mutations are disproportionately found in patients with pulmonary hypertension, as circulating *TET2* expression is reduced in this disease, and as *TET2* knockout mice spontaneously develop pulmonary hypertension which can be reversed by IL-1 β blockade [71].

Returning to *JAK2*, *JAK2* mutations have been associated with cardiovascular outcomes other than pulmonary hypertension. *Jak2V617F* mice are predisposed to developing aortic aneurysms, suggesting vascular effects beyond the pulmonary arterial bed [21]. *Jak2V617F* bone marrow transplanted into wildtype mice show increased bone marrow-derived hematopoietic cells invading the aorta, and this translocation can be blocked by ruxolitinib [21]. *JAK2V617F* also accelerates atherosclerosis in part through activation of the AIM2 inflammasome, by promoting neutrophil invasion into early atherosclerotic lesions, and by causing defective macrophage erythrophagocytosis [72•, 73].

Adaptive immune mechanisms have been implicated in poor cardiac outcomes due to CH as well. Patients with *TET2* or *DNMT3A* mutations had significantly reduced OS after undergoing TAVR [25]. No differences in cytokine serum levels were found between patients with and without CH

mutations, but patients with *TET2* or *DNMT3A* mutations did have elevated Th17 / Treg ratios on flow cytometry, suggestive of increased systemic T-cell driven inflammation [25].

Patients with CH mutations have higher rates of diabetes mellitus at baseline (21.2% vs 33.3%, $p=0.035$) [36]. This observation corresponds with evidence from mice showing that *Tet2* deficiency modeled through bone marrow transplants enhances insulin resistance in aged mice as well as obese mice while increasing IL-1 β production from bone marrow-derived macrophages in adipose tissue [74]. Like in the murine models of heart failure and atherosclerosis, these effects could be rescued through NLRP3 inflammasome inhibition [74]. Large population studies have also found higher rates of diabetes mellitus type 2 in patients with CH [15]. Investigation into the incidence or progression of diabetic kidney disease have not found an association with CH but there is evidence that CH promotes the development of chronic kidney disease at large, especially in the context of myeloid CH mutations and myeloid mCAs [75, 76]. Thus, aggravation of cardiac risk factors like diabetes and chronic kidney disease is an additional mechanism through which CH mutations are able to impact cardiovascular outcomes. Moreover, other established cardiovascular risk factors may cause CH. Smoking may mediate some of its negative cardiovascular effects through promoting the development of CH. Some studies have shown an association between smoke exposure and somatic CH mutations and others have shown an association with mCAs [10, 77, 78]. Unhealthy diets, defined as being low in fruits and vegetables and high in red meat, processed food, and added salt, have also been associated with a higher prevalence of CH [79]. The cardiovascular effects of CH with the corresponding mechanisms are summarized in Fig. 1.

Saving the Heart or the Blood Within It, CH Enhances Therapy-Related Cardiac Toxicity

Human studies have demonstrated clear evidence that cancer therapy can influence the development of CH and hence influence cardiovascular risk longitudinally [80]. Anthracyclines are chemotherapeutic agents employed against a wide variety of solid and liquid malignancies. Anthracyclines inhibit topoisomerase 2 β and in doing so kill tumor cells but also cause cardiomyocyte injury, leading to left ventricular dysfunction [81]. In a mouse model of therapy-related CH in which *TP53* heterozygous deficient hematopoietic stem and progenitor cells (HSPCs) were transferred to mice treated with doxorubicin, doxorubicin treatment promoted the expansion of *TP53* deficient HSPCs [27]. Furthermore, mice harboring the *TP53* heterozygous HSPCs had accelerated doxorubicin cardiac toxicity as measured by decreased capillary density, decreased fractional shortening, decreased

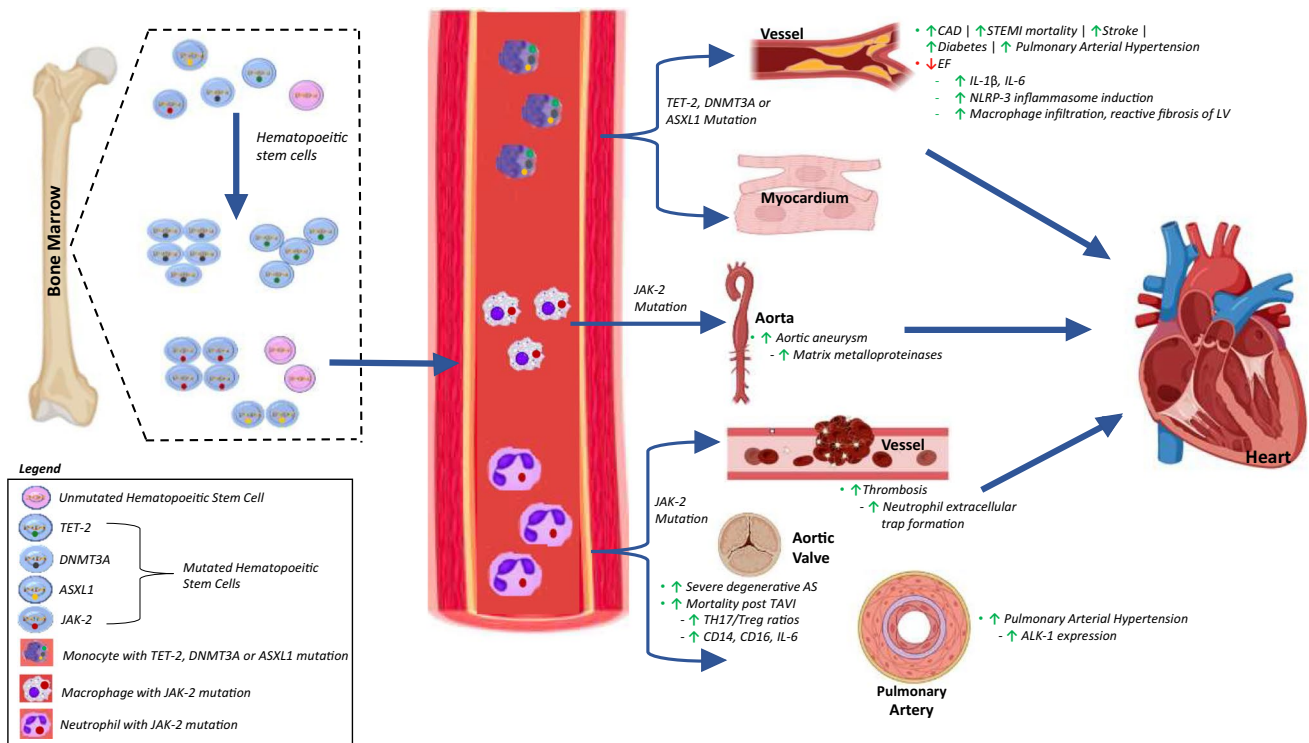


Fig. 1 Schematic of clonal hematopoiesis, its cardiovascular effects, and the underlying molecular mechanisms

left ventricular posterior wall thickness diameter, increased left ventricular end-systolic diameter, and decreased left ventricular mass. While cardiac monocyte and macrophage population sizes were not affected by *TP53* deficiency, cardiac neutrophil counts were increased and depleting neutrophils with α -Ly6G antibody rescued the cardiotoxic effects of doxorubicin. These murine results demonstrate that *TP53*-mediated CH enhances neutrophil invasion and damage of cardiac tissue after treatment with doxorubicin.

While CH is classically driven by the age-related accumulation of somatic mutations, CH can also be caused by the selection of HSPCs and genotoxic stress produced by cancer directed therapy and will be referred to as therapy-related CH (t-CH). Mutations in DNA-damage response pathways are common following chemotherapy or radiotherapy, specifically in *PPM1D* and in *TP53* [82, 83]. *PPM1D* is another myeloid CHIP gene [2], and mutations in *PPM1D* are seen in up to 20% of patients with therapy-related myeloid neoplasms [84]. In mice with *Ppm1d* HSPC mutations introduced by CRISPR-Cas9, *Ppm1d* mutations caused adverse ventricular remodeling and contractile dysfunction in mice challenged with an angiotensin II infusion [82]. Similar to the studies on *Tet2*, *Ppm1d* mutations caused higher levels of IL-1 β and the cardiac remodeling effects noted were prevented by NLRP3 inflammasome inhibition suggesting that *Ppm1d* mutations mediate cardiac toxicity at least in part through

the same cytokine pathway as *Tet2* mutations [82]. Additionally, *Ppm1d*-mutated macrophages exhibited impaired DNA damage repair pathways, higher reactive oxygen species levels, and increased IL-18 secretion [82]. Thus, chemotherapy and radiotherapy can cause t-CH via mutations in *Ppm1d*, which subsequently shifts macrophage polarization towards a pro-inflammatory phenotype (M1), contributing to cardiomyocyte injury that synergizes with the direct cardiotoxicity of prior chemotherapy or radiotherapy. These preclinical findings, that CH mutations enhance anthracycline cardiac toxicity, are corroborated in human studies: within adult lymphoma patients treated with anthracyclines, *TET2* mutations markedly increased the risk of developing anthracycline-induced cardiotoxicity (odds ratio: 5.15, 1.10–24.05 95% CI) [85].

Conclusions

- Available data extensively implicate CH as a cardiovascular risk factor in the settings of atherosclerosis, heart failure, aortic stenosis/TAVR, orthotopic heart transplantation, pulmonary hypertension, aortic aneurysm, and stroke. CH may potentiate cardiac risk via associations with smoking, diabetes mellitus, and chronic kidney disease.

- CH due to mutations in myeloid genes but not lymphoid genes or mCAs is associated with CAD. Evidence that *TET2* mutations are causative is especially strong.
- *TET2*, *DNMT3A*, and *ASXL1* mutations cause macrophages to secrete higher levels of cytokines and chemokines, including IL-1 β and IL-6, which contribute to accelerated atherosclerosis, heart failure, and diabetes mellitus type 2. Canakinumab, a monoclonal antibody that neutralizes IL-1 β as secondary myocardial infarction prophylaxis, has enhanced efficacy in patients that carry a *TET2* mutation.
- CH mutations, specifically in *TP53* and *TET2*, can increase myocardial toxicity from anthracycline chemotherapy in part through enhanced trafficking of neutrophils to the injured myocardium.
- *PPM1D* t-CH is common in both patients with solid tumors and myeloid malignancies. Similar to *TET2*, *PPM1D* CH promotes non-ischemic heart failure in mice through IL-1 β inflammation.

Future Research Directions

- Generate prospective evidence that canakinumab can lead to improved cardiovascular outcomes in patients harboring myeloid CH mutations. Similarly, evaluate whether inhibiting JAK2V617F with ruxolitinib can treat pulmonary hypertension patients harboring the V617F mutation.
- More rigorously assess mechanisms alternative to IL-1 β production, such as IL-6 or IL-18 production or T-cell driven inflammation for contributions to cardiovascular toxicity of CH mutations.
- Expand research into uncharacterized CH mutations and mCAs, and into their effects on the cardiovascular system. mCAs as a class have not been implicated in cardiac outcomes, and understanding the effects of individual mCAs remains unknown.

Acknowledgements Figure 1 is created with BioRender.com.

Declarations

Conflict of Interest Jeffrey L. Jensen is an AbbVie and Pfizer shareholder. Saumya Easaw declares no conflicts of interest. Travis Anderson declares no conflicts of interest. Yash Varma declares no conflicts of interest. Jiandong Zhang declares no conflicts of interest. Brian C Jensen has served as a consultant for AstraZeneca. Catherine C. Coombs has served as a consultant for AbbVie, has served on steering committees for AbbVie and Loxo Oncology, has served on independent review committees for AbbVie and Octapharma, has served on Speaker's Bureau for AbbVie, has received honoraria from AbbVie, AstraZeneca, Beigene, Genentech, Loxo Oncology, MEI Pharma, Novartis, TG Therapeutics, is a CTI Biopharma and Bluebird bio shareholder, and has received research funding (paid to the institution) from AbbVie and Loxo Oncology.

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