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EDITORIAL COMMENT

A New Murine Model of Clonal Hematopoiesis Investigates *JAK2*^{V617F} in Heart Failure*

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Aging is often the strongest risk factor for diverse cardiovascular diseases. The mechanisms by which aging influences these conditions are poorly understood. A common feature of aging hematopoietic stem cells, whose progeny interface with and influence diverse organ systems, is the acquisition and selection of acquired mutations. When such mutations are clonally selective, they are linked to future risk of hematologic malignancy. Given the general infrequency of hematologic malignancy in the population and, thus, overall low absolute risk conferred, this phenomenon has been termed "clonal hematopoiesis of indeterminate potential" (CHIP; a.k.a., age-related clonal hematopoiesis [ARCH]).

Recent work indicates that CHIP is independently associated with other age-related phenotypes outside of cancer, most notably in atherosclerotic cardiovascular disease. Mutations in genes leading to CHIP commonly occur in methylation and transcriptional regulators such as *DNMT3A*, *TET2*, and *ASXL1*, as well as in genes promoting cellular growth and division such as *JAK2*. When individuals are sequenced very deeply, most individuals harbor deleterious mutations in these genes among very small populations of blood cells. By definition, CHIP is the presence of such mutations with a variant allele frequency (VAF) of at least 2%, indicating a degree of clonal expansion. Using this definition, 1% of individuals younger than 50 years of age are carriers, and 10% of individuals older than 65 years are carriers. In addition to increased risk for hematologic malignancy, there is a 1.4-fold all-cause mortality risk. Carriers are at increased risk for coronary artery disease and early onset myocardial infarction, independent of age. Atherogenic murine models of bone marrow *Tet2* and *Dnmt3a* deficiency are linked to heightened development of atherosclerosis (1).

Recent studies have begun to shed light on the associations and mechanistic underpinnings of CHIP and the development of congestive heart failure (CHF) under pathophysiologic stressors. Previous studies by Sano et al. (2,3) have demonstrated a role for *Tet2* deficiency in the incidence of greater cardiac dysfunction in pressure overload and chronic ischemia-induced CHF by using murine models of hematopoietic and myeloid-only *Tet2* deficiency. Furthermore, those studies implicated interleukin-1 beta (IL-1β) as the key mediator of *Tet2* deficiency and CHF development (2,3). By using a lentivirus vector and clustered regularly interspaced short palindromic repeats (CRISPR)-mediated gene editing, the authors demonstrated heightened cardiac hypertrophy, dysfunction, and fibrosis in response to angiotensin II infusion in the setting of murine

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models with *Tet2*-deficient bone marrow versus wild-type bone marrow (3). Investigation in humans has further implicated the role of CHIP in CHF. In a study of 200 patients with prevalent CHF, individuals found to have mutations in *DNMT3A* and *TET2* had a 2.1-fold increased incidence of death or CHF hospitalization compared to those without these mutations (4).

The *JAK2* mutation V617F (*JAK2*^{V617F}) particularly is associated with an increased risk for atherosclerotic cardiovascular disease, potentially with distinct mechanisms. Prior studies linked *JAK2*^{V617F} with increased formation of neutrophil extracellular traps, extracellular strands of DNA and histone proteins expelled by neutrophils to trap microorganisms as part of innate immunity, thereby increasing the risk of thrombosis (5). However, the mechanistic relationship between the *JAK2*^{V617F} mutant and CHF remains unclear.

SEE PAGE 684

In this issue of *JACC: Basic to Translational Science*, Sano et al. (6) present transgenic mouse models of *JAK2*^{V617F} in clonal hematopoiesis and shed light on the mutant's role in response to models of CHF. The authors performed competitive *JAK2*^{V617F} transgenic mouse bone marrow transplantations into irradiated wild-type mice and demonstrate phenotypes similar to myeloproliferative neoplasms. These mice were shown to have increased de novo cardiac hypertrophy believed to be a response to myeloproliferative neoplasia, as previously observed. To more closely approximate CHIP (i.e., without notable blood cell count changes or neoplastic features), the authors also performed myeloid-specific *JAK2*^{V617F} transduction by using a lentivirus, limiting *JAK2*^{V617F} expression to neutrophils, monocytes, and macrophages (6). Importantly, these mice did not develop cardiac hypertrophy. In their model, the authors demonstrated that myeloid cells harboring the *JAK2*^{V617F} mutation displayed enhanced inflammatory properties dependent on downstream STAT signaling. After exposing these mice to stressors of coronary artery ligation-induced myocardial infarction and aortic constriction-induced pressure overload, the authors demonstrated that the expression of myeloid *JAK2*^{V617F} in mice led to accelerated cardiac remodeling, larger infarct size, and more cardiac dysfunction.

These studies continue to advance our understanding of CHIP, with prior models interrogating *Tet2* and *Dnmt3a*, and now new models for *JAK2* which help highlight its role in CHIP-related cardiovascular disease (3). The authors' myeloid-specific *JAK2*^{V617F} transgene expression model resulted in clonal hematopoiesis without affecting hematopoietic cell line counts, similar to CHIP (6).

This study provides additional evidence supporting CHIP as a risk factor of CHF development in murine heart failure models. Although this finding remains consistent with observations in humans that CHIP may exacerbate complications when CHF is manifest (4), data implicating CHIP for the onset of CHF in humans are currently lacking. Furthermore, because CHF is characterized by diverse causes and manifestations, it is unclear how homogenously CHIP may contribute to the risk of diverse CHF types. The study by Sano et al. (6) indicates that CHIP may exacerbate CHF risk across diverse genes under 2 distinct stressors, ischemia (i.e., coronary artery ligation) and pressure overload (i.e., transaortic clamp). Nevertheless, human validation of these types for heart failure are required to better understand clinical scope.

The authors demonstrated that human monocyte cells transduced by *JAK2*^{V617F} have greater expression of the inflammatory cytokines IL-1β, IL-6, tumor necrosis factor-alpha, and C-C chemokine ligand 2 when stimulated with lipopolysaccharide. Similarly, the authors show that myeloid-restricted *JAK2*^{V617F} transgenic mice undergoing coronary artery ligation express greater levels of IL-1β and IL-6 in the infarct zone. Recently, the authors implicated these interleukins in similar heart failure models for *Dnmt3a* and *Tet2* bone marrow deficiency (2). In prior studies, they mitigated cardiac maladaptation through inhibition of the pathway through an NLRP3 inflammasome inhibitor. The present study does not show similar rescue experiments, and it remains unclear whether consequential inflammatory changes from *JAK2*^{V617F} causally promote heart failure.

A general challenge of current CHIP murine models is the relatively rapid bone marrow reconstitution of hematopoietic cells with mutations of CHIP genes when altered bone marrow is transplanted. Limited longitudinal human analyses indicate relatively stable VAF over years. Nevertheless, our understanding of the kinetics and consequences of changing CHIP VAF is limited. Larger longitudinal analyses of CHIP in humans may help better inform the interpretation of murine models.

CHIP represents a new putative risk factor for CHF requiring human validation. The present

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paper by Sano et al. (6) shows consistent cardiac effects across multiple CHIP genes and murine models of heart failure. These exciting studies implicate a distinct pathophysiology not presently detected by current CHF risk prediction approaches nor addressed by current risk reduction strategies.

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