Clonal Hematopoiesis of Indeterminate Potential (CHIP) A Novel Cardiovascular Risk Factor with Potential Relevance to Chronic Kidney Disease

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tly recently, clonal hematopoiesis of indeterminate potential (CHIP) has been proposed as a novel cardiovascular risk factor linking the innate immune system with aging and vascular inflammation (1, 2).

Somatic gene mutations can spontaneously occur in different cell types and are thought to accumulate throughout a lifetime (3). Certain acquired mutations in hematologic stem cells provide proliferative stimuli and survival advantages and lead to a disproportionate expansion of myeloid leukocyte progenies in peripheral blood. This mechanism has been described for mutations in a set of genes often referred to as leukemia-associated genes or leukemia driver genes (4). The term CHIP was first introduced in 2015 and defines an acquired mutation of a leukemia-associated gene without evidence of a hematologic malignancy or an abnormal blood count (5).

Although different genes are associated with CHIP, mutations are most commonly found in DNMT3A, TET2, ASXL1, and JAK2 (4–8). The diagnosis may be obtained by DNA sequencing of peripheral blood, and the current cutoff value to meet the criteria for CHIP is a variant allele frequency (VAF) of at least 2% (9). In the absence of gene deletions or duplications, the VAF is proportional to the size of the leukocyte clone: When assuming heterozygosity, a VAF of 5%, for instance, indicates that approximately 10% of all peripheral blood leukocytes are mutation carriers. CHIP is rare in individuals under the age of 40, but prevalence increases with every decade thereafter and may be as high as 20% in 70-year-olds (1, 2).

Although genes mutated in CHIP are also frequently mutated in hematologic malignancies such as acute myeloid leukemia and myelodysplastic syndrome, the progression rate from CHIP to acute myeloid leukemia or myelodysplastic syndrome is low (0.5% to 1% per year) and resembles the progression rate from monoclonal gammopathy of undetermined significance to multiple myeloma (5, 6). Nonetheless, the overall mortality in individuals with CHIP is significantly higher than in the age-matched general population, primarily as a result of increased cardiovascular events.

The association between CHIP and worse cardiovascular outcome was first described by Jaiswal et al. (6) in late 2014. In that study, the authors noted an increased risk of coronary heart disease (hazard ratio, 2.0; 95% CI, 1.2–3.4) and stroke (hazard ratio, 2.6; 95% CI, 1.4–4.8) became apparent. In 2017, the association between CHIP and cardiovascular risk was confirmed in a second study that included data from four independent case-control cohorts (7). The risk of myocardial infarction was found to be two to four times higher among CHIP carriers, and CHIP was strongly associated with early-onset myocardial infarction. In 2018 and 2019, the presence or absence of CHIP was assessed in two populations with chronic ischemic heart failure and degenerative calcified aortic valve stenosis, respectively (8, 9). In both studies, individuals with detectable CHIP-associated mutations had a worse prognosis in terms of hospitalization and death. Among CHIP carriers, prognosis was further aggravated with increasing size of the mutated leukocyte clone (VAF) (7, 8).

Age appears to be the main predictor of CHIP. However, evidence suggests that CHIP is enriched in populations with type 2 diabetes, ischemic heart failure, or degenerative aortic valve stenosis (6, 8, 9).

Although causality between CHIP and poor cardiovascular outcome has not yet been unequivocally demonstrated, experimental data hint at endothelial inflammation as a possible mechanism (1, 2). It appears that clonally derived macrophages and monocytes promote atherosclerosis, vessel wall sclerosis, and tissue fibrosis by way of inflammatory stimuli. A simulation of a TET2 loss-of-function mutation in mice transplanted with TET2 knockout bone marrow revealed increased atherogenesis and also marked glomerulosclerosis in the kidney. TET2 knockout macrophages had increased RNA expression of inflammatory mediators such as IL-6 and IL-1β (7). Sano et al. (10) showed that mice with an inactivating mutation in TET2 or DNMT3a experienced more evident cardiac dysfunction along with cardiac and renal fibrosis after experimental challenge with angiotensin II. They further showed that mice with myeloid-restricted JAK2V617F expression had increased cardiac inflammation and dysfunction (11).

Chronic low-grade inflammation contributes to the development and progression of chronic kidney disease, especially in diabetes (12), and experimental data from animal models suggest kidney involvement with loss of TET2 and DNMT3 function (7, 10). Thus, it seems reasonable to assume that CHIP not only influences cardiovascular disease but also may have a negative impact on renal outcome. This hypothesis, however, has not yet been investigated and awaits future studies. CHIP is not yet routinely tested because knowledge is still emerging and no specific therapies are currently available.

CHIP will become more prevalent as the population ages, and a better understanding of this condition is an important step toward individualized patient treatment.

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References


