

Expanding approaches to detect clonal hematopoiesis

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Clonal hematopoiesis (CH) occurs when a single hematopoietic stem cell acquires a mutation that gives it a competitive advantage over other stem cells. CH is often driven by somatic mutations in genes that are recurrently mutated in myeloid malignancies such as *DNMT3A*, *ASXL1*, or *TET2*. CH is present at an appreciable fraction of the blood in more than 10% of people older than 70 years and is a precursor to hematologic cancers. The rate of development of neoplasia in patients with CH is estimated to be approximately 0.5% to 1% per year.¹ The contributing factors to clonal progression other than the selective pressure conferred by the driver mutation² are incompletely understood but proposed mechanisms include inflammation,³ short telomeres leading to chromosomal instability,⁴ an aging bone marrow microenvironment that favors expansion of clonal stem cells⁵ and germline genetic predisposition.⁶ Unexpectedly, CH was also found to increase the risk of diverse forms of cardiovascular disease.⁷ Accumulating evidence supports a mechanism of accelerated atherogenesis because of vascular inflammation driven by clonally derived monocytes and macrophages.

Many ongoing studies seek to profile the diverse disease consequences of CH and how CH evolution is associated with both malignant and non-malignant disease consequences. Existing collections of samples frequently comprise serial plasma samples to measure changes in biomarkers over time. However, blood for genotyping is usually only collected at a single time point (Figure 1).

Prior studies have observed that plasma cell-free DNA (cfDNA) may contain CH mutations. For example, CH is a frequently observed “contaminant” in the context of liquid biopsies when using peripheral blood to detect solid tumor mutations.⁸

In this issue of *Haematologica*, Gutierrez-Rodriguez *et al.*⁹ highlight both the potential and shortcomings of utilizing cfDNA to identify individuals with CH. In their study, cfDNA samples from patients with aplastic anemia, myelodysplastic syndrome, and healthy individuals from the Baltimore Longitudinal Study of Aging were screened for somatic variants in CH driver genes using a chemiluminescent immunoassay commercial targeted sequencing panel. Results were compared to those of DNA derived from paired samples of blood cells from the same individuals. The authors found excellent concordance between cfDNA and paired blood samples among individuals with a hematologic malignancy, particularly with large CH clones. However, they observed poor concordance between cfDNA and paired blood samples among the general healthy aging cohort. It was found that 85% of healthy subjects, 36% of patients with aplastic anemia and 74% of those with myelodysplastic syndrome had somatic cfDNA variants, most frequently in *DNMT3A*, *TET2*, *ASXL1* and *SF3B1*. Importantly, there was relatively low agreement between clonal fraction of blood as measured by cfDNA and matched blood cells. The cfDNA CH assay used in this study can be applied to detect CH from historical collections of serial plasma samples. In doing so, this study paves the way for future expanded studies of clonal evolution. However, this study leaves several questions unresolved. In particular, the methodological details of cfDNA isolation and targeted sequencing assays vary considerably from laboratory to laboratory, so it is unclear whether the observations are generally true of other CLIA cfDNA assays. Second, it is unclear whether the clonal fraction estimates from blood and cfDNA are a more reliable estimate of the underlying hematopoietic stem cell clonality that exists in the bone mar-

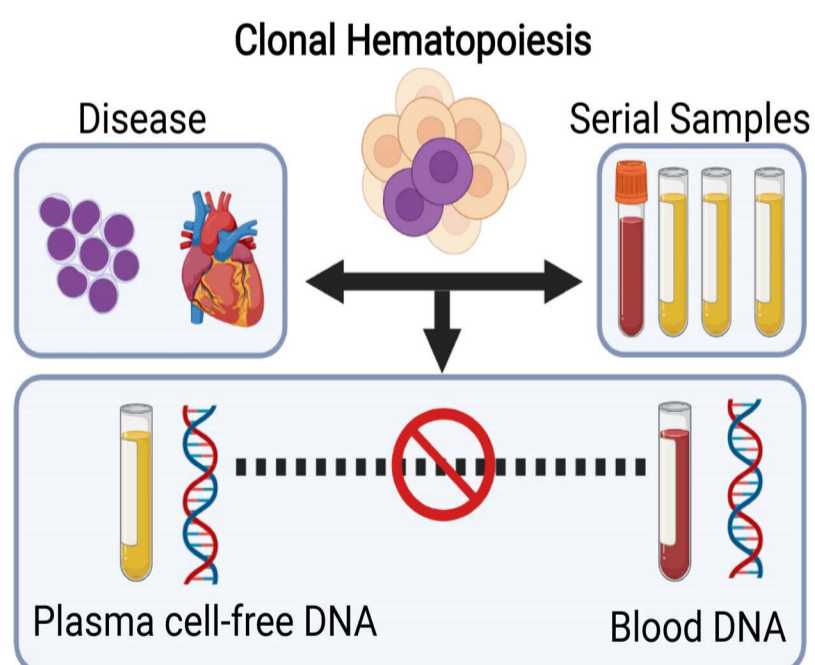


Figure 1. Clonal hematopoiesis is a risk factor for multiple hematologic malignancies and other diseases of aging.

Serial plasma samples are often available from large epidemiological cohorts; however, blood is frequently collected at only a single time-point. Gutierrez-Rodriguez *et al.* demonstrated that it is possible to detect clonal hematopoiesis from plasma cell-free DNA, but the clonal fraction from cell-free DNA is not always consistent with measurements of clonal hematopoiesis from blood-derived DNA.

row or whether these two estimates have different prognostic relevance.

Taken together, the results from this study show both the promise and the limitations of using cfDNA for studying CH in research and clinical settings. From a research perspective, the data presented here suggest that it is possible to detect CH in cfDNA, but rigorous assay validation is required. From a clinical perspective, a physician making a diagnosis of CH based on a cfDNA test would be wise to

perform confirmatory testing in peripheral blood to quantify the clonal fraction accurately, given the discordance between the clonal fraction in cfDNA and blood.

Disclosures

AGB is a consultant to Foresite Labs.

Contributions

MAWK and AGB co-wrote the manuscript.

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