



Troublemaking mutations: Clonal hematopoiesis for the prediction of prognosis in ST-segment elevation myocardial infarction

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In recent years, a new risk factor has emerged in cardiovascular disease (CVD): clonal hematopoiesis of indeterminate potential (CHIP). This condition occurs when acquired somatic mutations in cancer-related genes provide a selective advantage to hematopoietic stem and progenitor cells (HSPCs), leading to the expansion of mutant hematopoietic cells over the years.¹ The cellular progeny of HSPCs inherits these mutations and, therefore, CHIP can be detected in peripheral blood by DNA sequencing approaches. While CHIP confers an increased relative risk of developing hematological neoplasia, most CHIP mutation carriers will never transition to malignancy, as these conditions are relatively rare and typically require the acquisition of several mutations. However, CHIP is associated with higher all-cause mortality rates, mainly due to an increased risk of atherosclerotic CVD and related conditions.^{1,2} Experimental studies in mice suggest that this connection may be accounted for by an exacerbated inflammatory response driven by mutant immune cells.^{2–4} While research on CHIP has soared recently, there is still much to be learned about this new cardiovascular risk factor and its potential impact on the clinical management of CVD.

In this issue of EBioMedicine, Wang et al.⁵ shed light on the clinical implications of CHIP in patients affected by a myocardial infarction with ST-segment elevation (STEMI), a common acute clinical manifestation of coronary artery disease that is associated with increased risk of death and ischemic heart failure (HF) development. The authors performed deep targeted sequencing in a cohort of 485 patients with STEMI (median age of 62 years) to assess the prevalence and prognostic value of CHIP in this setting. While the sequencing panel

included 51 different genes, the study was primarily focused on mutations in the epigenetic regulatory genes *DNMT3A* and *TET2*, the two most common CHIP driver genes. Most analyses considered exclusively mutations with a variant allele fraction (VAF) > 2% (i.e. 4% mutant blood cells, assuming a monoallelic mutation), which is the threshold of mutant clone size most frequently used to define CHIP, although an exploratory analysis of the effect of smaller mutant clones was also executed. This undertaking yielded 3 major findings. First, the authors found that CHIP mutations were present in 16.5% of STEMI patients considering VAF ≥ 2%, with 70% of these mutations occurring in *DNMT3A* or *TET2*. Second, *DNMT3A* or *TET2* mutations with a VAF ≥ 2% were associated with >2-fold higher incidence of death or major adverse cardiac events (a composite of all-cause death, recurrent nonfatal MI, nonfatal stroke or HF-related hospitalization) during a median follow up of 3 years, independently of traditional CVD risk factors. Third, *DNMT3A* and *TET2* mutation carriers showed a modest, but statistically significant increase in circulating levels of the inflammatory cytokines IL-1β and IL-6, consistent with findings in previous CHIP studies in mice and humans.^{2–4,6} This increase in inflammatory cytokines was not accompanied by significant differences in high-sensitivity C-reactive levels, suggesting that this common indicator of systemic inflammation does not capture the exacerbated inflammation that accompanies CHIP.

The interesting findings reported by Wang and co-workers need to be interpreted in the context of the fast-evolving literature on CHIP. While some controversies have arisen about the intricacies of the connection between CHIP and CVD, a number of independent lines of evidence suggest that CHIP mutations, particularly in *DNMT3A* and *TET2*, are potent predictors of adverse outcomes in CVD patients.¹ Chronic HF patients who carry CHIP mutations display a substantially higher risk of adverse clinical progression, defined as higher risk of death or composites of all-cause or HF-specific death and HF-related hospitalizations.^{1,6–8} The current work extends the prognostic value of CHIP to STEMI patients and fuels the growing interest in using anti-inflammatory approaches to prevent recurrent

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CVD events.^{1,9} Based on the findings in the current study and prior work,^{2–4,10} it is logical to wonder whether the heightened IL-6/IL-1 β -driven inflammation associated with some CHIP mutations may be a precision target for the prevention of recurrent CVD events post-MI in CHIP mutation carriers. Testing this possibility will require the development of carefully- designed clinical trials.

A major strength of the work by Wang et al.⁵ is the use of a deep sequencing strategy, which allows for greater sensitivity in the detection of CHIP with relatively small mutant clones (e.g. VAF < 5%) than the whole exome/genome approaches used in previous larger studies.^{2,10} The findings reported herein suggest that CHIP with VAF as low as 1% may be clinically relevant in the context of STEMI, at least for *DNMT3A* and *TET2* mutations, similar to previous reports in the setting of ischemic HF.⁸ Although it is not currently recommended to screen unselected patients with STEMI or HF for CHIP, these findings indicate that sensitive sequencing technologies, such as the one used in this study, may be required in the future to capture clinically relevant CHIP clones in CVD patients. An important caveat that must be considered is the limited percentage of women in the study cohort (~27%), which does not allow to evaluate potential sex-differences in the clinical impact of CHIP. Similarly, the potential prognostic value of CHIP mutations beyond those affecting *DNMT3A* or *TET2* remains unexplored and requires further investigation.

In summary, the novel results reported by Wang et al.⁵ have important implications for our understanding of the prognostic value of CHIP mutations. This work expands the mounting body of evidence linking CHIP to CVD, and reinforces the notion that the detection of CHIP may in the future aid decision-making in the clinical management of the growing population of patients who survive a MI.

Declaration of interests

JJF is a consultant for FL86. MD-D has no relationships relevant to the contents of this article to disclose.

Contributors

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