Introduction to the Review Series. Clonal hematopoiesis review series – from biology to clinical management

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Clonal hematopoiesis (CH) can be considered a disease of 21st century medicine with its focus on the genetic basis of disease.[1] Although CH was first recognized as a biological entity in the 1960s, clinical genetic sequencing of cancers in the 2010s and beyond brought this condition to the forefront of scientific research and clinical medicine.[1-3] A series of articles in this issue of *Haematologica* reviews CH from biological discovery, to translational research, and the clinical diagnosis and management of affected patients.

CH is characterized by the clonal expansion of otherwise phenotypically normal hematopoietic cells from a somatically mutated hematopoietic stem cell (HSC).[4,5] The defining feature of CH is the fitness advantage conferred by somatic mutations in leukemia-associated genes, resulting in the skewed outgrowth of hematopoietic cells derived from a single HSC clone.[4-6] CH is an age-associated condition,[5] with approximately one protein-coding mutation expected to occur in a single HSC per decade of life. As such, individuals are estimated to accumulate 350,000 to 1.4 million protein-coding mutations in their HSC pool over their lifespan.[5] While the majority of these somatic mutations are inconsequential, some confer a selective fitness advantage to the clonal populations of hematopoietic cells arising from these mutated HSC.[5] For this reason, CH is considered a condition of aging.[5] However, in addition to age, CH is also influenced by heritable and environmental risks such as germline predisposition, smoking, exposure to environmental mutagens, and malignancies and/or exposure to cytotoxic chemotherapy.[5-7] CH is more prevalent in cancer patients than in the healthy aging population as a result of the formers' increased predisposition to malignancy and treatment with cytotoxic therapies that can select for pre-existing treatment-resistant CH clones often enriched for mutations in the DNA damage repair genes *PPM1D* and *TP53*.[8,9] Consequently, cancer cohorts with CH have a greater risk of developing therapy-related hematologic malignancies and an inferior cancer-related survival compared to cancer patients without CH.[8]

In order to better distinguish the origins of CH in individuals, a more narrowly defined condition called clonal hematopoiesis of indeterminate potential (CHIP) was defined in 2015 by Steensma *et al*.[10] CHIP refers to the presence of CH in individuals without a history of prior malignancies or clonal disorders and is characterized by a candidate driver gene mutation at a variant allele frequency (VAF) ≥2% in the peripheral blood.[10] The VAF threshold of 2% was proposed to ensure clinical relevance as studies such as that of Young *et al*. have demonstrated higher resolution sequencing can detect CHIP mutations below a 2% VAF in the majority of healthy individuals aged 50-70 years old.[5,7,10,11] Thus, the prevalence and associated clinical significance of CHIP depend on the sensitivity of the sequencing method used to detect mutant clones.[4]

In CH, both individual gene mutations and larger structural variants such as deletions, duplications, and neutral loss of heterozygosity, collectively referred to as mosaic chromosomal alterations, can promote the clonal expansion of hematopoietic cells.[5,7] The most common driver mutations in CH occur in the epigenetic regulator genes *DNMT3A*, *TET2, ASXL1*, the DNA damage repair genes *PPM1D, TP53,* the tyrosine kinase *JAK2* responsible for signal transduction, or the spliceosome components *SF3B1* and *SRSF2*.[7,12] Mutations in the epigenetic regulators *DNMT3A, TET2*, and *ASXL1* are the most frequent and account for approximately 80% of all CH mutations.[7] *DNMT3A*, the most frequent CH mutation, catalyzes the *de novo* DNA methylation of the C5 position of cytosines whereas *TET2*, the second most frequently mutated CH gene, catalyzes DNA demethylation by the oxidation of 5-methylcytosine to 5-hydroxycytosine.[5] CH-associated *DNMT3A* mutations are loss-of-function missense or truncating mutations and are classified as being either arginine 882 (R882) or non-R882 mutations.[13] R882 is a missense mutation hotspot in the *DNMT3A* catalytic domain that confers a higher risk of progression to acute myeloid leukemia (AML) compared to non-R882 mutations.[13,14] *TET2* mutations in CH are similarly loss-of-

function truncating mutations.[15] Despite *DNMT3A* and *TET2* having opposite functions, mutations in both genes lead to convergent HSC phenotypes of enhanced self-renewal and impaired differentiation, conferring a competitive advantage to HSC and their resulting progeny.[5,7] *ASXL*, the third most commonly mutated gene in CH, is a chromatin remodeling protein that recruits histone-modifying complexes such as PRC2 and BAP1 to regulate gene expession.[7,13] *ASXL1* mutations are gain-of-function frameshift or nonsense mutations that stabilize the interaction of ASXL1 with BAP1 and activate myeloid and stem cell gene expression programs.[13,16] CH can also be identified without driver mutations, suggestive of limitations in detection methods, mutations in non-coding sequences, mosaic chromosomal alterations, epigenetic modifications, or the neutral drift of small HSC populations.[7,17,18] Most CH cases do not contain obvious driver mutations.[17]

HSC carrying somatic mutations give rise to mutated myeloid and lymphoid cells, establishing a reservoir for future disease development which includes both malignant and non-malignant inflammatory diseases such as cardiovascular disease (CVD).[1,5] The overall risk however depends on the individual driver mutations, the mutational complexity, and the size of the mutant clone.[4,5]

CH can progress to hematologic neoplasms similarly to other clonal disorders such as monoclonal gammopathy of unknown significance and monoclonal B-cell lymphocytosis which are clonal precursors of multiple myeloma and chronic lymphocytic leukemia, respectively.[10] While CH is not a malignant condition, it confers an approximate 10-fold increase in the relative risk of a hematologic malignancy compared to individuals without detectable CH mutations.[5,19,20] This is because CH mutations are commonly the 'first hit' required for malignant transformation and many of the mutations in CH are shared with AML, myelodysplastic syndromes, myeloproliferative neoplasms and certain lymphomas.[5] However, the overall increase in absolute risk is low, with many CH mutations shown to be stable longitudinally and the odds of progression to a hematologic malignancy being exceptionally rare at approximately 0.5-1% per year.[11,19] This progression requires additional cooperating gene mutations to drive malignant transformation.[5,7,21] Cooperating gene mutations promote activated signal transduction and proliferation pathways with examples of mutations specific to AML, myelodysplastic syndromes, and myeloproliferative neoplasms including mutations in the Neuroblastoma RAS viral oncogene homolog (*NRAS*), Runt-related transcription factor 1 (*RUNX1*), Nucleophosmin 1 (*NPM1*), and FMS-like tyrosine kinase-3 (*FLT3*).[21,22]

Mutations in CH are associated with an increased risk of all-cause mortality - a risk that cannot be fully attributed to hematologic malignancies alone but is largely driven by the associated increased risk of CVD.[19] In fact, CH is associated with an approximately 2-fold increase in CVD risk independently of traditional risk factors such as smoking, cholesterol levels, and hypertension.[4,19] CVD studied in relation to CH include coronary artery disease, ischemic stroke, myocardial infarction, and the related blood vessel conditions atherosclerosis and arterial and venous thrombosis.[5,7,19] Aging and inflammation drive the risk of CVD and it is the pro-inflammatory environment in CH that has been demonstrated to be causally linked to CVD.[4,5,23] Many frequently mutated CH genes such as *DNMT3A, TET2, JAK2,* and *ASXL1* have been individually associated with a pro-inflammatory state and hence CVD.[4,23,24] For example, both *DNMT3A* and *TET2* mutations in CH patients demonstrate increased activation of the NLRP3 inflammasome complex and elevated expression of pro-inflammatory cytokines in monocytes and macrophages, leading to, for instance, increased macrophage recruitment to atherosclerotic plaques and increased inflammation in cardiac macrophages.[4,25,26] Potential secondary therapeutic strategies for CH-associated CVD include the inhibition of pro-inflammatory cytokines and the NLRP3 inflammasome complex, both of which have been demonstrated to reduce CVD risk.[4,29,30] In particular, *JAK2*^{V617F} mutations are among the few CH mutations that can be targeted pharmacologically with inhibitors.[4] Activating *JAK2*^{V617F} mutations exhibit enhanced neutrophil extracellular trap (NET) formation which is associated with increased arterial and venous thrombosis and is linked to a 10-fold higher risk of coronary artery disease compared to other common CH mutations.[4,19,23,27] JAK2 inhibitors such as ruxolitinib have been shown to reduce NET formation and thrombosis in murine deep vein stenosis models.[27] *ASXL1* mutations have been less studied but have been recently demonstrated to accelerate atherosclerosis by promoting the expansion and inflammatory activation of myeloid cells.[28]

CH mutations are detected at a high prevalence, particularly in the aging population, and have a low rate of progression to both malignant and non-malignant diseases.[13] This provides a window for risk-stratification and early intervention treatments, which is especially critical for rapidly advancing hematologic neoplasms such as AML.[7,13] Aside from the pharmacological inhibition of JAK2, there are currently no specific therapies available for CH patients that can reduce the risk of hematologic malignancies or non-malignant diseases such as CVD.[4] A deeper understanding of how common CH driver mutations confer a fitness advantage to mutant HSC could enable the successful development of therapeutic interventions for CH-associated diseases.[13]

The review series in this issue of *Haematologica* highlights important advances and controversies in the field. It reviews the biology of the disease, opportunities for clinical translation and the practical management of patients with CH. The study of CH begins with diagnosing the condition. In a recently published article in *Haematologica*, Wong *et al*.[31] reviewed current and future approaches for the diagnosis of CH. Understanding the diagnostic criteria and limitations in diagnosing CH informs both the biological investigation

and clinical management of this condition. In the review series, Beeler and Bolton highlight the mechanisms by which CH can increase the risk of myeloid neoplasms and *vice versa*.[32] In addition, emerging data indicate that CH biologically impacts solid tumors and may influence treatment outcomes in patients with solid tumors. The review by Martinez and Coombs[33] covers important aspects linking CH to non-hematologic cancers. Hosseini and Chan discuss novel therapeutic strategies to target both the mutant CH clones and the inflammatory state produced by CH.[34] Bacharach *et al.*[35] discuss mechanisms explaining the persistence of the mutant CH cells. Finally, an increasing number of individuals are being diagnosed with CH and are often referred to hematologists or oncologists for management. Vanner *et al.*[36] provide an overview of the practical management of individuals with CH and consider the future with dedicated multidisciplinary CH clinics.

Thus, the review series provides a comprehensive picture of this emerging disease spanning the biology of CH to the practical clinical management of CH patients.

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Contributions

AAP and ADS wrote and edited the article.

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