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Clonal Hematopoiesis and Its Impact on Human Health

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Abstract

Aging is associated with increased mutational burden in every tissue studied. Occasionally, fitness-increasing mutations will arise, leading to stem cell clonal expansion. This process occurs in several tissues but has been best studied in blood. Clonal hematopoiesis is associated with an increased risk of blood cancers, such as acute myeloid leukemia, which result if additional cooperating mutations occur. Surprisingly, it is also associated with an increased risk of nonmalignant diseases, such as atherosclerotic cardiovascular disease. This may be due to enhanced inflammation in mutated innate immune cells, which could be targeted clinically with anti-inflammatory drugs. Recent studies have uncovered other factors that predict poor outcomes in patients with clonal hematopoiesis, such as size of the mutant clone, mutated driver genes, and epigenetic aging. Though clonality is inevitable and largely a function of time, recent work has shown that inherited genetic variation can also influence this process. Clonal hematopoiesis provides a paradigm for understanding how age-related changes in tissue stem cell composition and function influence human health.

INTRODUCTION

Clonal hematopoiesis of indeterminate potential (CHIP) is a recently discovered aging phenomenon with broad health implications (1–3). It is defined by the presence of specific, cancer-associated somatic mutations in hematopoietic cells in the absence of a hematological malignancy or other clonal disorder (4). These mutations are thought to confer a fitness advantage to hematopoietic stem cells (HSCs), allowing them to expand clonally but still undergo normal hematopoiesis. It is considered an aging phenomenon because the prevalence increases with age, reaching 10–30% in individuals over 70 (1, 5–7). The most frequent mutations in CHIP are loss-of-function or truncating alleles in the epigenetic regulator genes *DNMT3A*, *TET2*, and *ASXL1*, which are also frequently mutated in myeloid cancers. While CHIP itself is defined by the absence of hematological malignancies, it does associate with increased risk of developing hematological malignancies. CHIP is also associated with an increased risk of all-cause mortality, which may be due to an increased risk of nonmalignant diseases of aging such as coronary artery disease (CAD). Advances over the last several years have revealed insights into the causes and consequences of CHIP.

CHIP AND MALIGNANCIES

Clonal hematopoiesis in the healthy population was first described in the 1990s in studies on nonrandom X chromosome inactivation (XCI) in females (8, 9). These studies showed a clear link between age and skewed XCI in blood, implying that hematopoiesis became more oligoclonal with aging, although it was not clear why this was a frequent occurrence at the time these studies were published. Advances in sequencing technologies made it feasible to search for cancer-associated drivers in these cases, leading to the identification of *TET2* mutations in a subset of women with XCI (10). Larger studies using whole-exome sequencing of blood DNA from tens of thousands of persons found that such cancer-associated mutations were strikingly common in the course of normal aging, with >10% of subjects aged 70 or older harboring a cancer-causing mutation in their blood (1, 5). The presence of these mutations also increased the risk of developing hematological cancer by approximately tenfold, signifying that CHIP represents a bona fide premalignant state. The majority of malignancies that developed were myeloid in origin.

There has been intense interest in identifying factors that promote progression to malignancy. In one early study, the size of the mutant clone, approximated by variant allele fraction (VAF), showed a positive correlation with malignancy risk (1). In subsequent studies of clonal hematopoiesis preceding acute myeloid leukemia (AML), the VAF of the CHIP clone at baseline was confirmed to be an important factor for risk of transformation (11, 12). These studies also found that the specific driver mutation tracked with risk, as mutations in *TP53*, *SF3B1*, *SRSF2*, or *U2AF1* had a particularly high risk of transforming to AML, suggesting that the risk differs considerably by the mutated driver gene.

While most of the work on risk of malignancy due to CHIP has focused on single-nucleotide variants (SNVs) and small insertions and deletions (indels), it is known that large structural changes to chromosomes, known as mosaic chromosomal alterations (mCAs), can also drive clonal expansion (13, 14). Recent work in UK Biobank (UKB) (15) and Biobank Japan (16) found that the presence of either SNVs/indels alone or mCA alone was associated with a relatively low risk of cancer transformation, but that the combined presence of both forms of clonal hematopoiesis was associated with a greater risk of transformation. In addition, some forms of mCA predisposed to lymphoid cancers (L-CHIP), while others were more likely to result in myeloid cancers (M-CHIP) (15).

In patients with solid cancers, the development and evolution of CHIP appear to be driven by genotoxic stress. Recent studies suggest that clonal hematopoiesis is more prevalent in

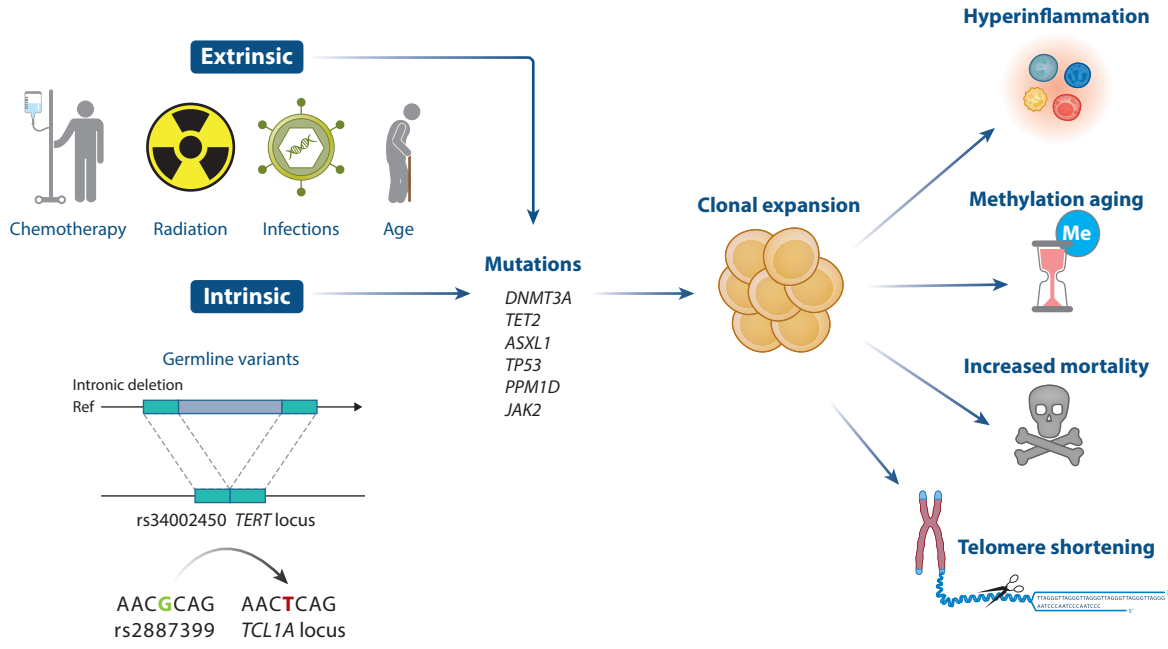

Figure 1

Extrinsic and intrinsic risk factors synergize with somatic mutations in CHIP driver genes to facilitate clonal expansion, leading to pathological aging outcomes such as hyperinflammation and increased mortality.

cancer cohorts and is associated with increasing age, smoking, and prior exposure to radio- or chemotherapy (**Figure 1**) (17). Chemotherapy is a cell-extrinsic factor that reduces the polyclonality of surviving HSCs by conferring a strong competitive advantage to cells harboring specific resistance mutations, leading to their enhanced fitness (18). It directly favors growth of clones with mutations mostly in DNA damage response genes, such as *TP53* and *PPM1D*, which then have an impact on the risk of developing secondary hematological malignancies as well as outcomes due to the primary tumor (19). In different solid tumor studies, almost 98% of patients' deaths were due to progression of their primary malignancy (20); hence, it is possible that clonal hematopoiesis influences cancer progression and recurrence, possibly due to cell–cell interactions between CHIP clones and cancer cells (21), the impact of impaired immune function on immune surveillance, promotion of an increased inflammatory milieu due to the clonal expansion of effector cells, or reduced tolerance toward cancer-directed therapy (17, 20).

CHIP AND CARDIOVASCULAR DISEASE

While the link between CHIP and hematological malignancies was expected, several large studies unexpectedly also associated CHIP with cardiovascular disease (CVD) such as CAD and stroke (1, 22, 23). CHIP carriers had a 1.5–2-fold increased risk of developing CAD compared to noncarriers (1, 22, 24) and nearly four times the risk of early-onset myocardial infarction (22), though the effect sizes are somewhat dependent on the cohort. For example, studies in UKB consistently yield lower effect estimates compared to other cohorts (25, 26), possibly due to a "healthy volunteer bias" in this data set (27). The increased risk of CAD in CHIP carriers is seen with multiple different somatic drivers, including *DNMT3A*, *TET2*, *ASXL1*, and *JAK2*.

To interrogate causal associations between specific CHIP mutations and atherosclerosis, studies have been performed in mouse models. In 2017, two groups demonstrated that knockout of *Tet2* in myeloid cells significantly accelerated atherosclerosis in a mouse model of atherosclerosis (22, 28). Mechanistically, loss of *Tet2* promoted a proinflammatory phenotype in macrophages, with upregulation of critical cytokines such as Il1b, Il6 and interleukin (IL)-8 family chemokines. Treatment with a small-molecule inhibitor of the NLRP3 inflammasome, which is responsible for generating the mature forms of IL-1β and IL-18, reversed the accelerated atherosclerosis phenotype (28). Loss of *Dnmt3a* promoted similar, proinflammatory gene expression changes in murine macrophages as well as increased plaque lesion size in another study (29). Activating mutations in *JAK2* have well-known effects on myeloproliferation, but recent studies have also demonstrated that these mutations promote neutrophil extracellular traps (30) and activation of the AIM2 inflammasome (31), thereby explaining some of the proatherosclerotic phenotypes. Little is known about how *ASXL1* mutations promote atherosclerosis.

Recent work has also uncovered links between CHIP and outcomes in heart failure (HF). In a study of 200 patients with HF, 38 of whom had clonal hematopoiesis, mutations in *TET2* and *DNMT3A* were associated with worse survival and hospitalization rates (32). In another study of patients with ischemic HF and reduced ejection fraction, the presence of *TET2* and *DNMT3A* mutations was associated with accelerated HF progression (33). In murine models of HF, introduction of hematopoietic mutations in *Tet2* or *Dnmt3a* worsened ejection fraction and increased macrophage inflammation, effects that were reversed by treatment with NLRP3 inhibition (34, 35).

The observed association between hyperinflammation and atherosclerosis (36) has motivated the development of anti-inflammatory treatments to test the hypothesis that blocking inflammation might reduce the risk of CAD. In the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial, treatment with canakinumab, an IL-1β–blocking antibody, lowered risk of major adverse cardiovascular events (MACE) in individuals who had prior CAD and elevated C-reactive protein, providing the first evidence for the inflammatory hypothesis of CAD in a human trial setting (36). The MACE benefit in CANTOS was modest, with a relative risk reduction in MACE of ~15% in the trial as a whole, and no benefit for survival due to an increase in fatal infections in those receiving canakinumab. In a post hoc subgroup analysis, carriers of *TET2* mutations were found to have a greater benefit from receiving canakinumab, with a relative risk reduction in MACE of ~60%, although this did not reach statistical significance (37). Thus, CHIP with certain mutations may serve as a biomarker for subpopulations that preferentially respond to specific anti-inflammatory therapies, but this hypothesis requires confirmation in a prospective randomized controlled trial.

Other therapeutic options, such as the NLRP3 inhibitor MCC950, improved atherosclerosis conditions and provided protection against the development of heart failure in mouse models by reducing IL-1 production in Tet2-depleted macrophages. The MCC950 treatment led to significant protection against cardiac remodeling and cardiac hypertrophy. MCC950 treatment also improved echocardiographic measurements such as left ventricular (LV) systolic volume, LV diastolic volume, as well as the LV ejection fraction (34).

In addition to CVD, CHIP has been associated with increased risk of chronic obstructive pulmonary disease (38) and osteoporosis (39), and decreased risk of Alzheimer's disease (40). **Table 1** summarizes CHIP's known associations.

GERMLINE RISK OF CHIP

Although CHIP is the result of somatic mutations, there is a strong interest in understanding the impact of inherited germline variants on the risk of developing mutations that can lead to CHIP.

Table 1 CHIP has a systemic effect on aging that increases the risk of diseases ranging from cancer to heart disease even in otherwise healthy individuals

Disease/condition	Associations with CHIP	References
Hematological malignancies	Approximately three- to tenfold increased risk of myeloid neoplasia, though the risk varies considerably with driver mutations and size of the clone Modest increase in risk of lymphoid malignancy. Features of CHIP that confer a higher risk of transformation include mutations in *TP53*, *SF3B1*, *SRSF2*, *U2AF1*, VAF >10%, presence of multiple mutations, and coexistence of mosaic chromosomal alterations	1, 5, 12, 15–17, 25, 26, 78
Solid tumors	Increased prevalence of clones with mutations in DNA damage response genes (*TP53*, *PPM1D*) in patients with exposure to cytotoxic vaccine Associated with risk of progression, recurrence, and all-cause mortality in those with solid tumors	17–19
CAD	1.1–2-fold increased risk of incident CAD in human observational studies. Risk is greater in those with VAF >10%	1, 22, 24, 25
Ischemic heart failure	*DNMT3A* and *TET2* mutations associated with worsened survival and increased hospitalization due to ischemic HF	32, 33
Stroke	1.1–2-fold increased risk of hemorrhagic and ischemic stroke. Mutations in *TET2* show the strongest association	1, 23
Methylation aging	Increased epigenetic age acceleration as measured by multiple methylation clocks Patients with CHIP and age acceleration have the greatest risk of mortality and CAD, while patients with CHIP and no acceleration have no increased risk of mortality and CAD	69, 70
Other aging diseases	1.6-fold increased risk of COPD 1.4-fold increased risk of osteoporosis 35% decreased risk of Alzheimer's dementia	38–40

Abbreviations: CAD, coronary artery disease; CHIP, clonal hematopoiesis of indeterminate potential; COPD, chronic obstructive pulmonary disease; HF, heart failure; VAF, variant allele fraction.

Performing a genome-wide association study (GWAS) in a cohort of more than 10,000 Icelanders, Zink et al. were the first to describe a common (minor allele frequency of 0.41) small intronic deletion (rs34002450) mapping to the *TERT* locus as a risk allele for CHIP [odds ratio (OR) = 1.3] (41). Recent GWAS (7, 25) of the National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine (TOPMed) (42) and the UKB/Geisinger MyCode Community Health Initiative (GHS) (43) cohorts have identified >10 additional independently associated polymorphisms for the *TERT* 5p15 locus with effects on the risk of developing CHIP. *TERT* encodes a telomerase reverse transcriptase—a catalytic subunit of the telomerase complex. While telomerase is transcriptionally silenced in early human development, leading to gradual telomere shortening with aging, it can be upregulated in frequently dividing cells such as HSCs to mitigate telomere attrition and cellular senescence (44, 45). Short telomeres promote genomic instability and have been linked to a variety of malignancies (46, 47). The striking association of the *TERT* locus with CHIP risk implies a role for telomere regulation in CHIP. Indeed, CHIP risk is inversely correlated with leukocyte telomere length (LTL) (41). In a recent study that investigated the relationship of CHIP and LTL in the TOPMed and UKB cohorts using causal inference by Mendelian randomization (48), this finding was replicated (49). When considering mutations in specific genes, associations of CHIP and measured LTL (mLTL) were more heterogeneous and gene-specific: Whereas *TET2*,

ASXL1, *PPM1D*, *JAK2*, and *TP53* were significantly associated with shorter mLTL, no association was found with *DNMT3A*. Counterintuitively, bidirectional Mendelian randomization studies suggest that longer mLTL increases the risk to acquire CHIP, while telomeres of affected cells shrink upon CHIP emergence, a phenomenon termed the telomere paradox. A possible model could be that longer telomeres confer cellular longevity and extend the time window for potential mutagenic hits. Once a CHIP driver mutation is acquired, increasing proliferation and cell divisions expedite telomere shortening (**Figure 1**) (49).

The largest study in the UKB/GHS cohort of almost 630,000 participants, which includes ~40,000 CHIP carriers, has identified 57 independent common CHIP susceptibility variants at 27 loci that reached genome-wide significance (25): In addition to *TERT*, lead single-nucleotide polymorphisms (SNPs) include rs73154592 in *SMC4* (OR = 1.13), rs2275652 upstream of *CD164* (OR = 0.88), rs228606 in *NPAT* (OR = 1.12), and rs3219104 in *PARP1* (OR = 1.11) with mostly modest effects. The mechanisms through which these variants increase or decrease risk of CHIP are not known. However, all of them are expression quantitative trait loci that influence gene expression in a cis- and trans-regulatory fashion (25). The PARP1 enzyme has a well-established role in initiating DNA repair after single-strand breaks and maintaining genomic integrity (50), which can be therapeutically inhibited in BRCA-positive cancer to induce cell death (51). Likewise, the NPAT cofactor regulates ATM expression, which is involved the in DNA damage response pathway (52). *CD164* encodes a transmembrane sialomucin and cell adhesion molecule that regulates proliferation, adhesion, and migration of HSCs (53), while SMC4 is involved in chromosome assembly and segregation (54) and its overexpression has been shown to promote cancer (55).

In addition to SNPs associating with overall CHIP risk, some variants are specific to CHIP subtypes (7, 25). Most of these susceptibility loci have been identified for *DNMT3A*-CHIP as the most common subtype and overlap with overall CHIP risk alleles. A majority of the risk variants confer consistent effects across different subtypes—with some noteworthy exceptions that show opposing effects: studies in TOPMed and UKB/GHS have identified a locus in *TCL1A* with lead variants rs11846938-G, rs2887399-T, and rs2296311-A predisposing carriers to develop *DNMT3A*-CHIP while protecting against *TET2*- and *ASXL1*-CHIP. Interestingly, the rs2887399-T variant has been shown to reduce risk for loss of chromosome Y (LOY) clonal mosaicism (56, 57).

One limitation in these large cohorts is that individuals included are predominantly of European ancestry, and genomes of African, Asian, and American individuals are underrepresented, limiting the applicability of these findings in non-European ancestries. In the TOPMed cohort, only a single variant (rs144418061), which is specific to individuals of African ancestry (minor allele frequency of 0.035) and maps to the *TET2* locus, was associated with CHIP (7). Carriers of an A allele had a 2.4-fold higher risk of developing CHIP, and the association was equally robust for *DNMT3A*-, *TET2*-, and *ASXL1*-CHIP. This has not been replicated in the UKB/GHS cohort (25). Interestingly, the authors of the TOPMed study hypothesized that the *TET2* variant affects enhancer activity. Using an in silico activity-by-contact model to predict which enhancers regulate *TET2* expression in $CD34^+$ HSCs enabled them to identify a causal variant (rs79901204-T) at this locus that disrupts a GATA–E-Box motif at the *TET2* distal enhancer, resulting in increased HSC self-renewal.

CHIP AND METHYLATION/AGING

Given the prominence of *DNMT3A* and *TET2* as the most commonly mutated genes in CHIP, there is a growing interest in understanding the effects of these mutations on DNA methylation (**Figure 1**). The canonical enzymatic functions of *DNMT3A* (58) and *TET2* (59) are to methylate and demethylate cytosines, respectively. Knockdown of *DNMT3A* expression using short hairpin RNA in $CD34^+$ HSCs was found to have variable effects depending on the affected isoform, with

underexpression of some isoforms leading to hypermethylation, in contradiction to the enzymatic function of *DNMT3A* (60). One proposed explanation for this paradoxical finding is that there may be a compensatory increase in expression of other methyltransferases such as *DNMT3B*, but the regulation of the activity of these other genes may differ from *DNMT3A* (60). Knockout of *Dnmt3a* and *Tet2* in mouse HSCs led to methylation changes consistent with the enzymatic function of each gene, while a double knockout resulted in a combination of "counteractive" effects, where the two mutations nullified each other and methylation was similar to controls, and "synergistic" hypomethylation, where the additional loss of *TET2* led to greater hypomethylation of some CpGs than was seen in the *DNMT3A*-only knockout (61).

In a study of whole-blood methylation in CHIP patients with *DNMT3A* and *TET2*, only a modest number of CpGs were differentially methylated in *DNMT3A* mutation carriers compared to controls, but these were exclusively hypomethylated, while far more CpGs were significantly hypermethylated *TET2* mutation carriers. Integrating these results into a coherent model of the effects of *DNMT3A* and *TET2* mutations on DNA methylation is difficult because existing studies have been performed in different cell types, and only weak correlation between gene methylation and expression has been observed (62).

Although a detailed understanding of the effects of CHIP on DNA methylation remains elusive, there is evidence that CHIP affects clinically significant methylation phenotypes such as epigenetic clocks. The development of these clocks was motivated by the observation that age and methylation are highly correlated (63). The earliest clocks focused on directly predicting age from methylation in blood (64, 65) or across tissues (66), while later efforts have focused on predicting mortality from blood methylation (67, 68). Most studies relating methylation clocks to disease focus on age acceleration or deceleration—the difference between a subject's epigenetic and chronological ages—rather than the epigenetic age estimate itself. Age acceleration is believed to represent pathological aging and has been associated with increased mortality and risk of CAD (68), while age deceleration is associated with healthy aging. In two recent studies (69, 70), CHIP was found to significantly increase several different measures of epigenetic age acceleration (EAA). Strong evidence was also found for a pathological interaction between CHIP and EAA. Subjects with CHIP in the absence of EAA showed no increase in mortality and incident CAD compared to controls, while mortality and risk of incident CAD were tripled in subjects with both CHIP and EAA, a much larger effect than that conferred by CHIP or EAA alone (70). These findings suggest that CHIP may be a risk factor for EAA and that they may interact to worsen pathological aging.

CLONAL TRAJECTORIES AND DYNAMICS

Human blood cells are derived from a steady-state pool of 50,000 to 250,000 HSCs per individual (71–73). At younger ages, HSCs contribute equally to blood production; however, with aging, hematopoiesis shows a more oligoclonal pattern. A sharp decline in clonal diversity above the age of 70 is relatively consistent across individuals, as revealed by a recent study that sequenced 3,579 genomes from single-cell-derived colonies of hematopoietic progenitor cells and HSCs from 10 healthy individuals followed by phylogenetic mapping to identify clonal relationships (71). The decrease of clonality is mainly caused by positive selection of nonsynonymous mutations that randomly occur throughout the lifespan of an HSC (72). However, the fitness advantage can be influenced by various cell-extrinsic factors that can lead to earlier clonal expansion, e.g., infection (74, 75), chemotherapy (17, 76), and smoking (25).

A longstanding question in cancer biology has been when the initiating mutations that will lead to tumorigenesis arise. Using similar single-HSC colony sequencing methods, a recent study examined this question for those who developed myeloproliferative neoplasms as adults. Strikingly,

the mean latency between the acquisition of the initial driver and development of cancer was 30 years, and in many cases the mutations were acquired in early childhood or even in utero (77).

In nearly every study of CHIP, the size of the mutant clone is associated with the likelihood of developing malignant and nonmalignant diseases (1, 78), but the factors that influence clonal expansion over time are less well understood. This is a difficult question to address, as determination of clonal expansion rate requires studying large cohorts with serially sampled blood specimens over longer time periods. A recent study analyzed blood DNA samples from 385 adults aged 54–93 years at study entry and without known hematological malignancies (79). The samples, which were collected a median of four times over a median span of 13 years, revealed important novel insights:

1. At older ages, the vast majority of CHIP clones expanded at a constant exponential rate, with the exception of *JAK2*-V617F-mutant clones, which exhibited very unstable trajectories.
2. Growth rate was determined by the gene that was affected: Slowest growth was observed for *DNMT3A* or *TP53* clones (5% per year), whereas clones harboring mutations in *TET2*, *ASXL1*, *PPM1D*, and *SF3B1* (10% per year) and particularly in *SRSF2* and *U2AF1* (15–20% per year) expanded much faster.
3. Specific clones, e.g., *DNMT3A* or *TP53* mutants, emerged earlier in life and markedly decelerated prior to reaching a stable growth rate in the elderly, whereas splicing factor-mutant clones originated late in life and showed very aggressive expansion. These observations are in line with findings that the risk of progression to AML is particularly high for these mutations (78).

A recent approach to overcome the lack of longitudinal blood sampling is to infer clonal expansion rates from single-time-point data using a novel methodology termed PACER (passenger-approximated clonal expansion rate) (68). PACER takes advantage of the fact that HSCs acquire passenger mutations at a constant rate throughout their lifespan, allowing inference of clone birth date, and hence growth rate, using the passenger count in the CHIP clone (17, 71, 79–82). Performing a GWAS of PACER revealed a common inherited variant (rs2887399) in the *TCL1A* promotor that was associated with a slower clonal expansion. The same SNP was previously linked to reduced risk of LOY mosaicism and increased risk of *DNMT3A*-CHIP (7, 25, 56, 57). Carriers of the rs2887399-T variant showed an allele dosage–dependent protective effect against mutations in *TET2*, *ASXL1*, *SF3B1*, and *SRSF2* but increased odds of developing mutations in *DNMT3A* (81). An in vitro study on human $CD34^+$ cells found that *TCL1A*, which is physiologically not expressed in HSCs, is aberrantly upregulated by mutations in *TET2* and *ASXL1*, but not *DNMT3A*, thereby promoting clonal expansion (81). However, the rs2887399-T variant prevented *TCL1A* expression in *TET2*- and *ASXL1*-mutant cells and reduced the expansion potential of these mutant clones close to baseline levels. This study implicates aberrant expression of *TCL1A* as the dominant factor driving clonal expansion downstream of several common driver genes. This study also shows that germline variation can influence the clonal composition of aging HSCs by altering the relative fitness of driver mutations in certain genes.

CONCLUDING REMARKS

Clonal hematopoiesis is a seemingly inevitable consequence of aging. While its implications are becoming better understood, many unanswered questions remain. Ongoing studies may reveal the full extent to which mutant HSC clones can influence a variety of human diseases, beyond cancer and CVD. More work is needed to uncover additional genetic and environmental factors that influence clonal expansion, which could suggest novel therapeutic avenues for preventing

leukemic transformation. It also remains unclear whether the increased risk of atherosclerotic disease associated with CHIP is druggable, though preclinical and preliminary clinical data are promising. Finally, with the increasing appreciation that clonality is an inevitable consequence of aging with implications for disease, many of the lessons learned from clonal hematopoiesis may be applied to the study of other tissues.

DISCLOSURE STATEMENT

S.J. is a paid consultant to Novartis, AVROBIO, Roche Genentech, GSK, Foresite Labs, and TenSixteen Bio and is on the scientific advisory boards of Bitterroot Bio and TenSixteen Bio.

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LITERATURE CITED

1. Jaiswal S, Fontanillas P, Flannick J, et al. 2014. Age-related clonal hematopoiesis associated with adverse outcomes. *N. Engl. J. Med.* 371:2488–98
2. Natarajan P, Siddhartha J, Kathiresan S. 2018. Clonal hematopoiesis: somatic mutations in blood cells and atherosclerosis. *Circ. Genom. Precis. Med.* 11:e001926
3. Jaiswal S, Ebert BL. 2019. Clonal hematopoiesis in human aging and disease. *Science* 366:eaan4673
4. Steensma DP, Bejar R, Jaiswal S, et al. 2015. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood* 126:9–16
5. Genovese G, Kähler AK, Handsaker RE, et al. 2014. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N. Engl. J. Med.* 371:2477–87
6. McKerrell T, Park N, Moreno T, et al. 2015. Leukemia-associated somatic mutations drive distinct patterns of age-related clonal hemopoiesis. *Cell Rep.* 10:1239–45
7. Bick AG, Weinstock JS, Nandakumar SK, et al. 2020. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature* 586:763–68
8. Champion KM, Gilbert JGR, Asimakopoulos FA, et al. 1997. Clonal haemopoiesis in normal elderly women: implications for the myeloproliferative disorders and myelodysplastic syndromes. *Br. J. Haematol.* 97:920–26
9. Busque L, Mio R, Mattioli J, et al. 1996. Nonrandom X-inactivation patterns in normal females: lyonization ratios vary with age. *Blood* 88:59–65
10. Busque L, Patel JP, Figueroa M, et al. 2012. Recurrent somatic *TET2* mutations in normal elderly individuals with clonal hematopoiesis. *Nat. Genet.* 44:1179–81
11. Abelson S, Collord G, Ng SWK, et al. 2018. Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature* 559:400–4
12. Desai P, Mencia-Trinchant N, Savenkov O, et al. 2018. Somatic mutations precede acute myeloid leukemia years before diagnosis. *Nat. Med.* 24:1015–23
13. Jacobs KB, Yeager M, Zhou W, et al. 2012. Detectable clonal mosaicism and its relationship to aging and cancer. *Nat. Genet.* 44:651–58
14. Laurie CC, Laurie CA, Rice K, et al. 2012. Detectable clonal mosaicism from birth to old age and its relationship to cancer. *Nat. Genet.* 44:642–50
15. Niroula A, Sekar A, Murakami MA, et al. 2021. Distinction of lymphoid and myeloid clonal hematopoiesis. *Nat. Med.* 27:1921–27
16. Ryunosuke S. 2021. Combined landscape of single-nucleotide variants and copy number alterations in clonal hematopoiesis. *Nat. Med.* 27:1239–49
17. Coombs CC, Zehir A, Devlin SM, et al. 2017. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and impacts clinical outcome. *Cell Stem Cell* 21:374–82.e4

18. Kahn JD, Miller PG, Silver AJ, et al. 2018. PPM1D-truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. *Blood* 132:1095–105
19. Bolton KL, Ptashkin RN, Gao T, et al. 2020. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. *Nat. Genet.* 52:1219–26
20. Park SJ, Bejar R. 2020. Clonal hematopoiesis in cancer. *Exp. Hematol.* 83:105–12
21. Kleppe M, Comen E, Wen HY, et al. 2015. Somatic mutations in leukocytes infiltrating primary breast cancers. *npj Breast Cancer* 1:15005
22. Jaiswal S, Natarajan P, Silver AJ, et al. 2017. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N. Engl. J. Med.* 377:111–21
23. Bhattacharya R, Zekavat SM, Haessler J, et al. 2022. Clonal hematopoiesis is associated with higher risk of stroke. *Stroke* 29:788–97
24. Bick AG, Pirruccello JP, Griffin GK, et al. 2020. Genetic interleukin 6 signaling deficiency attenuates cardiovascular risk in clonal hematopoiesis. *Circulation* 141:124–31
25. Kessler MD, Damask A, O'Keeffe S, et al. 2022. Exome sequencing of 628,388 individuals identifies common and rare variant associations with clonal hematopoiesis phenotypes. *medRxiv* 2021.12.29.21268342
26. Kar SP, Quiros PM, Gu M, et al. 2022. Genome-wide analyses of 200,453 individuals yields new insights into the causes and consequences of clonal hematopoiesis. *Nat. Genet.* 54:1155–66
27. Fry A, Littlejohns TJ, Sudlow C, et al. 2017. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am. J. Epidemiol.* 186:1026–34
28. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. 2017. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science* 355:842–47
29. Rauch PJ, Silver AJ, Gopakumar J, et al. 2018. Loss-of-function mutations in *Dnmt3a* and *Tet2* lead to accelerated atherosclerosis and convergent macrophage phenotypes in mice. *Blood* 132:745
30. Wolach O, Sellar RS, Martinod K, et al. 2018. Increased neutrophil extracellular trap formation promotes thrombosis in myeloproliferative neoplasms. *Sci. Transl. Med.* 10:eaan8292
31. Fidler TP, Xue C, Yalcinkaya M, et al. 2021. The AIM2 inflammasome exacerbates atherosclerosis in clonal haematopoiesis. *Nature* 592:296–301
32. Dorsheimer L, Assmus B, Rasper T, et al. 2019. Association of mutations contributing to clonal hematopoiesis with prognosis in chronic ischemic heart failure. *JAMA Cardiol.* 4:32–40
33. Pascual-Figal DA, Bayes-Genis A, Díez-Díez M, et al. 2021. Clonal hematopoiesis and risk of progression of heart failure with reduced left ventricular ejection fraction. *J. Am. Coll. Cardiol.* 77:1747–59
34. Sano S, Oshima K, Wang Y, et al. 2018. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1β/NLRP3 inflammasome. *J. Am. Coll. Cardiol.* 71:875–86
35. Sano S, Wang Y, Walsh K. 2018. Clonal hematopoiesis and its impact on cardiovascular disease. *Circ. J.* 83:2–11
36. Ridker PM, Everett BM, Thuren T, et al. 2017. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N. Engl. J. Med.* 377:1119–31
37. Svensson EC. TET2-driven clonal hematopoiesis and response to canakinumab: an exploratory analysis of the CANTOS randomized clinical trial. *JAMA Cardiol.* 7:521–28
38. Miller PG, Qiao D, Rojas-Quintero J, et al. 2022. Association of clonal hematopoiesis with chronic obstructive pulmonary disease. *Blood* 139:357–68
39. Kim PG, Niroula A, Shkolnik V, et al. 2021. *Dnmt3a*-mutated clonal hematopoiesis promotes osteoporosis. *J. Exp. Med.* 218:e20211872
40. Bouzid H, Belk JA, Jan M, et al. 2021. Clonal hematopoiesis is associated with protection from Alzheimer's disease. *medRxiv* 2021.12.10.21267552
41. Zink F, Stacey SN, Norddahl GL, et al. 2017. Clonal hematopoiesis, with and without candidate driver mutations, is common in the elderly. *Blood* 130:742–52
42. Taliun D, Harris DN, Kessler MD, et al. 2021. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *Nature* 590:290–99
43. Backman JD, Li AH, Marcketta A, et al. 2021. Exome sequencing and analysis of 454,787 UK Biobank participants. *Nature* 599:628–34

44. Wright WE, Piatyszek MA, Rainey WE, et al. 1996. Telomerase activity in human germline and embryonic tissues and cells. *Dev. Genet.* 18:173–79
45. Shay JW, Wright WE. 2019. Telomeres and telomerase: three decades of progress. *Nat. Rev. Genet.* 20:299–309
46. Hastie ND, Dempster M, Dunlop MG, et al. 1990. Telomere reduction in human colorectal carcinoma and with ageing. *Nature* 346:866–68
47. Chiba K, Lorbeer FK, Shain AH, et al. 2017. Mutations in the promoter of the telomerase gene *TERT* contribute to tumorigenesis by a two-step mechanism. *Science* 357:1416–20
48. Sanderson E, Glymour MM, Holmes MV, et al. 2022. Mendelian randomization. *Nat. Rev. Methods Primers* 2:6
49. Nakao T, Bick AG, Taub MA, et al. 2022. Mendelian randomization supports bidirectional causality between telomere length and clonal hematopoiesis of indeterminate potential. *Sci. Adv.* 8:eabl6579
50. Ray Chaudhuri A, Nussenzweig A. 2017. The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. *Nat. Rev. Mol. Cell Biol.* 18:610–21
51. Farmer H, McCabe N, Lord CJ, et al. 2005. Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy. *Nature* 434:917–21
52. Medina R, van der Deen M, Miele-Chamberland A, et al. 2007. The HiNF-P/p220NPAT cell cycle signaling pathway controls nonhistone target genes. *Cancer Res.* 67:10334–42
53. Forde S, Tye BJ, Newey SE, et al. 2007. Endolyn (CD164) modulates the CXCL12-mediated migration of umbilical cord blood CD133+ cells. *Blood* 109:1825–33
54. Losada A, Hirano T. 2005. Dynamic molecular linkers of the genome: the first decade of SMC proteins. *Genes Dev.* 19:1269–87
55. He H, Zheng C, Tang Y. 2021. Overexpression of SMC4 predicts a poor prognosis in cervical cancer and facilitates cancer cell malignancy phenotype by activating NF-κB pathway. *Hum. Cell* 34:1888–98
56. Thompson DJ, Genovese G, Halvardson J, et al. 2019. Genetic predisposition to mosaic Y chromosome loss in blood. *Nature* 575:652–57
57. Zhou W, Machiela MJ, Freedman ND, et al. 2016. Mosaic loss of chromosome Y is associated with common variation near *TCL1A*. *Nat. Genet.* 48:563–68
58. Okano M, Bell DW, Haber DA, Li E. 1999. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell* 99:247–57
59. Kohli RM, Zhang Y. 2013. TET enzymes, TDG and the dynamics of DNA demethylation. *Nature* 502:472–79
60. Božić T, Frobel J, Raic A, et al. 2018. Variants of *DNMT3A* cause transcript-specific DNA methylation patterns and affect hematopoiesis. *Life Sci. Alliance* 1:e201800153
61. Zhang X, Su J, Jeong M, et al. 2016. DNMT3A and TET2 compete and cooperate to repress lineage-specific transcription factors in hematopoietic stem cells. *Nat. Genet.* 48:1014–23
62. Buscarlet M, Provost S, Zada YF, et al. 2017. DNMT3A and TET2 dominate clonal hematopoiesis and demonstrate benign phenotypes and different genetic predispositions. *Blood* 130:753–62
63. Fraga MF, Esteller M. 2007. Epigenetics and aging: the targets and the marks. *Trends Genet.* 23:413–18
64. Hannum G, Guinney J, Zhao L, et al. 2013. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol. Cell* 49:359–67
65. Horvath S, Oshima J, Martin GM, et al. 2018. Epigenetic clock for skin and blood cells applied to Hutchinson Gilford progeria syndrome and *ex vivo* studies. *Aging* 10:1758–75
66. Horvath S. 2013. DNA methylation age of human tissues and cell types. *Genome Biol.* 14:R115
67. Levine ME, Lu AT, Quach A, et al. 2018. An epigenetic biomarker of aging for lifespan and healthspan. *Aging* 10:573–91
68. Lu AT, Quach A, Wilson JG, et al. 2019. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging* 11:303–27
69. Robertson NA, Hillary RF, McCartney DL, et al. 2019. Age-related clonal haemopoiesis is associated with increased epigenetic age. *Curr. Biol.* 29:R786–87
70. Nachun D, Lu AT, Bick AG, et al. 2021. Clonal hematopoiesis associated with epigenetic aging and clinical outcomes. *Aging Cell* 20:e13366

71. Mitchell E, Chapman MS, Williams N, et al. 2021. Clonal dynamics of haematopoiesis across the human lifespan. *bioRxiv* 2021.08.16.456475
72. Watson CJ, Papula AL, Poon GYP, et al. 2020. The evolutionary dynamics and fitness landscape of clonal hematopoiesis. *Science* 367:1449–54
73. Lee-Six H, Øbro NF, Shepherd MS, et al. 2018. Population dynamics of normal human blood inferred from somatic mutations. *Nature* 561:473–78
74. Dharan NJ, Yeh P, Bloch M, et al. 2021. HIV is associated with an increased risk of age-related clonal hematopoiesis among older adults. *Nat. Med.* 27:1006–11
75. Meisel M, Hinterleitner R, Pacis A, et al. 2018. Microbial signals drive pre-leukaemic myeloproliferation in a Tet2-deficient host. *Nature* 557:580–84
76. Wong TN, Ramsingh G, Young AL, et al. 2015. The role of TP53 mutations in the origin and evolution of therapy-related AML. *Nature* 518:552–55
77. Williams N, Lee J, Mitchell E, et al. 2022. Life histories of myeloproliferative neoplasms inferred from phylogenies. *Nature* 602:162–68
78. Abelson S, Collord G, Ng SWK, et al. 2018. Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature* 559:400–4
79. Fabre MA, de Almeida JG, Fiorillo E, et al. 2021. The longitudinal dynamics and natural history of clonal haematopoiesis. *bioRxiv* 2021.08.12.455048
80. Osorio FG, Rosendahl Huber A, Oka R, et al. 2018. Somatic mutations reveal lineage relationships and age-related mutagenesis in human hematopoiesis. *Cell Rep.* 25:2308–16.e4
81. Weinstock JS, Gopakumar J, Burugula BB, et al. 2021. Clonal hematopoiesis is driven by aberrant activation of TCL1A. *bioRxiv* 2021.12.10.471810
82. Robertson NA, Latorre-Crespo E, Terradas-Terradas M, et al. 2021. Longitudinal dynamics of clonal hematopoiesis identifies gene-specific fitness effects. *bioRxiv* 2021.05.27.446006