blood® Review Series

MECHANISMS AND CLINICAL IMPLICATIONS OF CLONAL HEMATOPOIESIS

Clonal hematopoiesis and risk for hematologic malignancy

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Clonal hematopoiesis (CH) is common in older persons and is associated with an increased risk of hematologic cancer. Here, we review studies establishing an association between CH and hematopoietic malignancy, discuss features of CH that are predictive of leukemic progression, and explore the role of hematopoietic stressors in the evolution of CH to acute myeloid leukemia or myelodysplastic syndrome. CH due to point mutations or structural variants such as copy-number alterations is associated with an ~10-fold increased risk of hematopoietic malignancy. Although the absolute risk of hematopoietic malignancy is low, certain features of CH may confer a higher risk of transformation, including the presence of *TP53* or spliceosome gene mutations, a variant allele fraction >10%, the presence of multiple mutations, and altered red blood indices. CH in the setting of peripheral blood cytopenias carries a very high risk of progression to a myeloid malignancy and merits close observation. There is emerging evidence suggesting that hematopoietic stressors contribute to both the development of CH and progression to hematopoietic malignancy. Specifically, there is evidence that genotoxic stress from chemotherapy or radiation therapy, ribosome biogenesis stress, and possibly inflammation may increase the risk of transformation from CH to a myeloid malignancy. Models that incorporate features of CH along with an assessment of hematopoietic stressors may eventually help predict and prevent the development of hematopoietic malignancies. (*Blood*. 2020;136(14):1599-1605)

Introduction

The accumulation of mutations in hematopoietic stem cells (HSCs) with age results in the production of a genetically heterogeneous cell population, with each HSC possessing its own unique set of private mutations.[1] HSCs that acquire somatic mutations conferring a competitive fitness advantage relative to their normal counterparts may expand, resulting in clonal hematopoiesis (CH). Genes commonly mutated in CH are also recurrently mutated in myeloid malignancies. Thus, it is not surprising that CH is associated with the development of hematopoietic malignancy. However, the absolute risk of hematopoietic malignancy development in persons with CH is low, and there is a need to identify persons most at risk for transformation. The mechanisms contributing to leukemic transformation from CH are unclear, limiting the development of strategies to prevent progression. Here, we review studies establishing an association between CH and hematopoietic malignancy, discuss features of CH that are predictive of leukemic progression, and explore the role of hematopoietic stressors in the progression of CH to acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

CH is associated with an increased risk of hematologic malignancy

Several large cohort studies in persons unselected for prior history of hematopoietic disorder have established an association between CH and the development of hematopoietic malignancies. For purposes of this review, unless otherwise stated, CH is defined as the presence of 1 or more somatic mutations with a variant allele fraction (VAF) of at least 0.02. Genovese et al performed whole-exome sequencing on 12 380 Swedish persons, identifying CH in 455.[2] The presence of CH conferred an increased risk for subsequent development of hematologic cancer with a hazard ratio of 12.9. Jaiswal et al performed panel sequencing on 3341 persons with longitudinal follow-up: 134 had CH.[3] The hazard ratio for the development of hematologic malignancy in patients with CH was 11.1. Zink et al analyzed whole-genome sequencing data from 11 262 Icelanders.[4] In this study, CH was defined as the presence of a high number (>20) of somatic mutations, regardless of coding or noncoding. Although this method identified a larger total peak prevalence of CH, there was still a significantly increased risk for development of hematologic malignancy with a hazard ratio of 2.43. Altogether, these studies show that the risk of developing a hematopoietic malignancy in persons with CH is increased. However, the incidence of hematopoietic malignancies is low. For example, with a median follow-up of nearly 8 years, only 4% of persons with CH in the Jaiswal study developed a hematopoietic malignancy. Thus, the predictive value of CH per se to identify patients at risk for hematopoietic malignancy is low.

CH due to large chromosomal anomalies also is associated with an increased risk of hematopoietic malignancy. Jacobs et al used single-nucleotide polymorphism (SNP) arrays to identify copy-number alterations and copy-number neutral loss of heterozygosity in the peripheral blood of 57 583 individuals.[5] This technique, which is able to detect chromosomal abnormalities (>2 Mb in size) with a frequency of >7% of cells, identified CH in

517 individuals (1.2%). Of note, the frequency of CH was 20% or 22% for individuals who subsequently developed myeloid or lymphoid leukemia, respectively, compared with 0.74% in cancer-free controls. Laurie et al used a similar approach to identify CH due to chromosomal abnormalities in 149 of 8562 persons (1.7%) with longitudinal follow-up.[6] Compared with persons without CH, the risk of hematopoietic malignancy in persons with CH was increased ~10-fold after adjusting for age. Finally, Loh et al also used SNP arrays to interrogate 151 202 UK Biobank participants.[7] They included long-range phasing of the SNP data to increase sensitivity, allowing them to detect chromosomal abnormalities at cell fractions as low as 1%. Using this approach, they identified CH in 7484 cases (4.9%). Similar to the other studies, an association of CH with hematopoietic malignancy was observed. In all 3 studies, the strongest association of CH was with the development of chronic lymphocytic leukemia (CLL). Indeed, chromosomal abnormalities frequently found in CLL, such as trisomy 12 or deletions of 13q, are associated with the subsequent development of CLL.

CH following cytotoxic therapy is associated with an increased risk of therapy-related myeloid malignancy

There is considerable evidence suggesting that CH is also associated with an increased risk of developing a therapy-related myeloid neoplasm (tMN). Exposure to cytotoxic therapy is associated with an increase in CH due to mutations in genes, such as *TP53* and *PPM1D*, which are frequently mutated in tMNs.[8-10] Two retrospective case-control studies showed that CH at the time of primary cancer treatment is associated with an ~10-fold increased risk of tMN.[11,12] Gibson et al showed that CH at the time of autologous stem cell transplantation for lymphoma conferred an increased risk of tMN, with a cumulative incidence of 14.1% for those with CH vs 4.3% for those without.[10] In the largest series reported to date, Bolton et al reported on 9549 persons with cancer who received "oncologic" therapy (includes chemotherapy, radiation therapy, or immunotherapy), of whom 75 developed a tMN.[13] CH was strongly associated with tMN (hazard ratio, 6.9), with a median time to progression to tMN of 26 months.

Clonal evolution from CH to hematopoietic malignancy

In all of the large cohort sequencing studies, lymphoid malignancies were more common than myeloid malignancies, despite the fact that the mutations identified in the CH samples were mostly associated with myeloid malignancies.[2,3] Moreover, Zink et al showed that CH without any identifiable driver mutation is still associated with an increased risk of hematopoietic malignancy.[4] These observations raise the possibility that hematopoietic malignancies may not always derive from the expanded hematopoietic stem and progenitor cell (HSPC) clone present at the time of CH. Instead, the presence of CH may represent a biomarker of a stressed hematopoietic system that is prone to malignant transformation. As summarized later in this section, there is evidence to support both pathways.

Accumulating evidence indicates that the majority of tMNs are derived from the expanded HSPC clone present in CH. We reported 4 cases of tMNs in which the exact *TP53* mutations found at diagnosis were also detectable at a low level in the blood or bone marrow 3 to 6 years prior to tMN development.[14] Bolton et al reported on 35 cases of tMN in which prior peripheral blood samples were available. One or more disease-defining mutations present in the tMN sample were identified in the CH sample in 32 cases (94%).[13] Similar results were reported in studies by Gillis et al and Takahashi et al.[11,12] Collectively, these 2 studies identified tMN mutations in the prior CH sample in 14 of 19 cases (74%). Of note, a recent report showed that specific somatic chromosomal abnormalities present in patients with tMNs were detectable in prior blood samples in 3 of 14 cases.[15] Collectively, these data suggest that the majority of tMN cases develop from an expanded HSPC clone carrying tMN-associated mutations that are present years prior to tMN development.

With respect to de novo hematopoietic malignancies, with the exception of clonal somatic chromosomal abnormalities and the development of CLL, data to make firm conclusions are lacking. Several large case-control studies have confirmed the association of CH with de novo AML.[16,17] Indeed, AML-associated mutations were detected in the CH sample in the majority of cases. However, because the AML was not sequenced, a direct relationship between CH mutations and AML could not be established.

There is also evidence that CH may serve as a biomarker of prior hematopoietic stress, particularly genotoxic stress. As discussed in the next section, prior exposure to chemotherapy is associated with an increased frequency of CH in a dose-dependent fashion. Interestingly, Gibson et al showed that the presence of CH in patients with relapsed lymphoma undergoing autologous hematopoietic cell transplantation is associated with increased nonrelapse mortality.[10] They also showed that the CH mutations detectable at the time of transplantation are not always the ones that give rise to tMN. Together, these observations suggest that, in the setting of prior cytotoxic therapy, the presence of CH may reflect a perturbed hematopoietic state, which might include a reduced HSPC pool and/or altered bone marrow microenvironment.

Specific features of CH that are predictive of hematopoietic malignancy development

Current evidence suggests that the great majority of patients with CH do not develop a hematopoietic malignancy, making the positive predictive value low. Thus, there is a need to better stratify persons with CH who are at risk of developing a hematopoietic malignancy. Indeed, recent data suggest that certain features of CH may confer a higher risk of malignant transformation, including the specific gene mutated, clone size, and the presence of multiple mutations (Table 1).

Case-control studies of patients with CH who developed AML show that mutations in certain genes confer a higher risk of AML development. In the study by Abelson et al, mutations of *TP53* and the splicing factor *U2AF1* conferred the highest risk of AML development with hazard ratios of 12.5 and 7.9, respectively.[16] This contrasts with hazard ratios for *DNMT3A* and *TET2* of 1.4 and 1.6, respectively. In the study by Desai et al, mutations of *TP53* and spliceosome genes (*U2AF1*, *SF3B1*, or *SRSF2*) also conferred a higher risk of AML development, with odds ratios of 47.2 and 7.4, respectively.[17] They also identified *IDH1*, *IDH2*,

Table 1. CH characteristics increasing risk for leukemia transformation

Definition	References
Total no. of mutations	
>1 gene	10,13,16,17
>250 somatic SNPs	4
VAF	
>10%	3,17
RDW	
>14%	13,16
Specific gene	
Study specific:	13,16,17
TP53, *U2AF1*/spliceosome	
IDH1/2, *RUNX1*, *PHF6*	17
Specific variant	18
DNMT3A (R882C/H, R729W, R326C, R320*, R736H/C, Y735C, W860R, R771*, R598*, P904L)	
SRSF2 P95R/H/L	
SF3B1 K700E, K666N	
JAK2 V617F	
IDH2 R140Q	
GNB1 K57E	

RDW, red cell distribution width.

and *RUNX1* with *PHF6* mutations as high-risk mutations. Remarkably, in this study, all persons with *TP53* mutations (n = 21) or *IDH1/2* mutations (n = 15) developed AML a median of 5 to 6 years from CH sampling. Due to the case-control nature of this study, caution should be used in extrapolating these data to the general population to conclude that all CH cases with *TP53* and *IDH1/2* mutations will inevitably undergo malignant transformation. In the Bolton study of CH and the development of tMN in persons receiving prior oncologic therapy, the strongest associations were observed for *TP53* and spliceosome gene mutations.[13] Of note, in this study, CH due to *IDH1/2* mutations had only a modest association with tMN development. Taking this analysis 1 step further, Watson et al looked beyond the gene level to assess the impact of specific variants on the development of CH.[18] They identified 20 high-risk variants that had a strong fitness advantage and conferred a higher risk of developing AML (Table 1). Although additional data are needed to confirm these findings, it is likely that incorporating specific gene variants into predictive algorithms will improve our ability to identify persons with CH at highest risk for malignant transformation.

The size of a hematopoietic clone can be inferred from the VAF, with some caveats such as the presence of homozygous mutations or germline variants. In the study by Jaiswal et al, the hazard ratio for the development of hematologic malignancy increased to nearly 50 for those persons with a VAF of 10% or greater (corresponding to a clone representing 20% of cells in the blood).[3] Case-control studies of patients with CH who developed AML also suggested that clone size correlates with leukemic progression for most gene mutations. For example, in the study by Desai et al, multivariate analysis showed that the odds ratio of AML development increased from 2.5 for persons with *DNTM3A* mutations with a VAF <10% to 4.8 for persons with a VAF ≥10%.[17] However, both studies suggested that the impact of clone size on AML development is reduced for mutations in certain genes, including *TP53*, *U2AF1*, and *IDH1*. Clone size was also predictive of the development of tMN, with the odds ratio for tMN development increasing more than threefold comparing CH with a VAF of 2% to 5% to cases with a VAF >10%.[13]

The risk of transformation to AML also correlates with the total number of mutations detected in the CH sample. In the Gibson et al study of tMN development in persons undergoing autologous stem cell transplantation for lymphoma, the presence of >1 CH mutation was associated with a higher risk of tMN than those with only 1 mutation (16.5% vs 4% at 5 years).[10] In the studies by Abelson et al and Desai et al, CH with >1 mutation was associated with a higher risk of AML development.[16,17] In particular, certain combinations of gene mutations, such as *DNTM3A* plus a spliceosome gene mutation, conferred a high risk of leukemic transformation. Strikingly, in the Zink et al study, the total number of somatic single-nucleotide variants (SNVs) dramatically increased the risk for hematologic malignancy development; the hazard ratio for cases with <180 SNVs was 1.98 vs a hazard ratio of 42.2 for cases with >250 SNVs.[4] Finally, in the Bolton et al study, the presence of >1 CH mutation conferred an increased risk of tMN development, with a hazard ratio of 1.8.[13] Of note, in all of these studies, whether the multiple mutations identified in the CH sample are present in the same clone is unknown, but are likely to be relevant.

Along with these clone-specific parameters, there are data suggesting that certain red blood cell parameters, including red cell distribution width and mean corpuscular volume, are associated with AML development.[13,16] Bolton et al incorporated CH mutation type, maximum clone size, number of mutations, and peripheral blood count indices into a model to identify a high-risk group with an absolute 10-year risk of tMN of 4% to 12%. Large prospective studies are needed to validate and refine this model, but these data suggest that we may eventually be able to identify persons with CH at high-enough risk to be actionable.

CH with cytopenia

Prior studies had identified CH in persons with peripheral blood cytopenia, a condition termed clonal cytopenia of undetermined significance (CCUS).[19,20] In a prospective study of 154 persons with idiopathic blood cytopenia, panel sequencing identified 1 or more mutation in 56 (36%).[21] The 5-year probability of progression to a myeloid neoplasm in this cohort of persons with CCUS was 82%. This compares to the 5-year probability of transformation of only 9% in persons with idiopathic cytopenia without CH. Mutations in certain genes, such as *SF3B1*, or multiple mutations confer an even higher risk, with over 90% of persons with CH carrying these mutations progressing to a myeloid neoplasm by 5 years. Thus, CCUS appears to be a special category of CH with a very high risk of transformation to a myeloid malignancy.

Role of hematopoietic stressors in leukemic transformation from CH

Accumulating evidence suggests that hematopoietic stressors play an important role in the development of CH, which is

discussed in further detail elsewhere in this review series. For example, there is strong clinical and preclinical evidence that cytotoxic therapy selects for hematopoietic progenitor cells carrying mutations in DNA damage response genes, including *TP53*, *PPM1D*, and *CHEK2*.[8,11,12,14] Animal studies have confirmed that HSPCs carrying *TP53* or *PPM1D* mutations have a competitive advantage in vivo after exposure to chemotherapy.[14,22-24] Intriguingly, it appears that there may be chemotherapy-specific effects on the development of CH. For example, Hsu et al showed that expansion of *PPM1D*-mutated clones was strongly associated with exposure to platinum agents and etoposide, but not to other cytotoxic agents or transplant.[24] This is consistent with recent data showing that platinum agents and etoposide, but not alkylator agents, are associated with an increased frequency of CH.[13] There is also emerging evidence that inflammatory cytokines may contribute to the expansion of hematopoietic stem/progenitor clones carrying mutations in epigenetic modifiers, such as *TET2*.[25-27]

Whether hematopoietic stressors also contribute to the progression from CH to hematopoietic malignancy is less clear. Our recent study of CH in persons with Shwachman-Diamond syndrome (SDS) provides insight into this question. SDS is a congenital bone marrow failure syndrome characterized by blood cytopenias, exocrine pancreatic insufficiency, bony abnormalities, and a high rate of transformation to MDS or AML. We identified CH due to *TP53* mutations in 13 of 27 persons with SDS (43%; median age, 6.3 years) vs 0 of 17 age-matched healthy controls.[28] SDS is caused in most cases by biallelic loss-of-function mutations of *SBDS*,[29] which results in impaired ribosome biogenesis.[30-32] Of note, there is evidence that ribosome biogenesis stress induces p53 expression, which in turn results in a growth arrest.[33,34] Together, these observations suggest a model in which elevated p53 expression due to ribosome biogenesis stress in SDS HSPCs results in impaired HSPC growth and/or survival (Figure 1). Mutation of *TP53* in HSPCs is predicted to attenuate this growth arrest, resulting in their selective expansion in patients with SDS.

However, simply having a *TP53* mutation within the hematopoietic compartment is clearly not sufficient to drive leukemogenesis. Li Fraumeni is a cancer predisposition syndrome caused by heterozygous germline mutations of *TP53*.[35] Despite 100% of HSPCs carrying a heterozygous *TP53* mutation, the risk of MDS/AML development in Li Fraumeni syndrome is low (<5%),[36] especially compared with SDS, where the cumulative incidence of MDS/AML is >20%.[37] So why is the risk of leukemic progression higher in SDS? We suggest that continued ribosome stress in SDS HSPCs carrying a heterozygous *TP53* mutation selects for clones that inactivate the second *TP53* allele (Figure 1). Mouse studies show that development of hematopoietic malignancy is faster and more penetrant in HSPCs carrying biallelic loss-of-function *TP53* mutations compared with heterozygous *TP53*-mutated cells.[38-40] However, biallelic loss of *TP53* alone is not sufficient to induce AML or MDS in mice, and other cooperating mutations are required for transformation.[41,42] In humans, there is a high frequency of chromosome 5 and 7 abnormalities in *TP53*-mutated AML/MDS. When these chromosomal abnormalities are acquired in relation to the biallelic loss of *TP53* is unknown. Nonetheless, these observations suggest a model for myeloid malignancy development in SDS in which ribosome stress contributes not only to the development of *TP53*-mutated CH, but also to its progression to a myeloid malignancy. Consistent with this conclusion, a recent study showed that the majority of MDS or AML cases arising in the setting of SDS carry biallelic *TP53* mutations.[43] In contrast, in Li Fraumeni syndrome, there is no selective pressure to mutate the second TP53 allele and the risk of MDS/AML is low. Of note, a recent case series of persons with Li Fraumeni showed that 5 of 5 patients with myeloid malignancy developed tMN after being treated with cytotoxic chemotherapy for a first malignancy.[44] Thus, in Li Fraumeni syndrome, genotoxic stress may contribute to tMN development by selecting for HSPCs that have inactivated the second *TP53* allele.[45,46]

There is evidence that other hematopoietic stressors contribute to clonal evolution from CH to hematopoietic malignancy in certain disorders. For example, CH due to activating mutations of *CSF3R* (encoding the granulocyte colony-stimulating factor [G-CSF] receptor) is frequent in patients with severe congenital neutropenia.[47-50] Of note, circulating levels of G-CSF are elevated in patients with severe congenital neutropenia, either due to pharmacologic administration, or increased endogenous production.[51] This high level of G-CSF, in combination with the activating *CSF3R* mutations, provides a fitness advantage to HSPCs[52] that likely contributes to the high rate of transformation to MDS/AML seen in this disorder. Another example of hematopoietic stressors shaping clonal evolution is in patients with germline mutations of *SAMD9* or *SAMD9L*, which are on chromosome 7 (clinical syndromes reviewed in Davidsson et al[53]). These gain-of-function mutations impair HSPC proliferation, which may be promoted by inflammation-induced SAMD9/SAMD9L expression.[54,55] In this setting, HSPCs that have lost the copy of chromosome 7 containing the mutant *SAMD9* or *SAMD9L* allele have a fitness advantage, resulting in their clonal expansion and, in some cases, progression to MDS/AML with monosomy 7.[54-56] Finally, there is evidence that inflammation may contribute to leukemic progression from *TET2*-mutated CH. Loss of *Tet2* in mice results in enhanced HSC self-renewal and a myeloproliferative-like syndrome.[57] Meisel et al showed that this myeloproliferative phenotype is abrogated when *Tet2*$^{-/-}$ mice are housed under germ-free conditions.[58] They provided evidence that *Tet2* loss disrupts intestinal integrity, leading to increased translocation of intestinal bacteria, which in turn, results in increased inflammatory cytokine production that contributes to the myeloproliferative phenotype.

It is worth noting that not all clonal adaptions to hematopoietic stressors are deleterious. For example, in SDS, the most common somatic chromosomal abnormality is isochromosome 7.[59] Studies show that the duplicated region of chromosome 7 includes the *SBDS* allele capable of producing full-length protein, effectively increasing *SBDS* expression,[60] and is associated with a lower risk of transformation to myeloid malignancy. Thus, considering the context in which CH arises to determine whether close monitoring or therapeutic intervention is needed will be important.

Conclusions, open questions, and future directions

In summary, current evidence shows that CH confers an increased risk of myeloid and lymphoid malignancies. However, these cancers are uncommon, and the absolute risk of developing a hematopoietic malignancy is small. There are emerging data that certain features of CH may confer a higher risk of transformation,

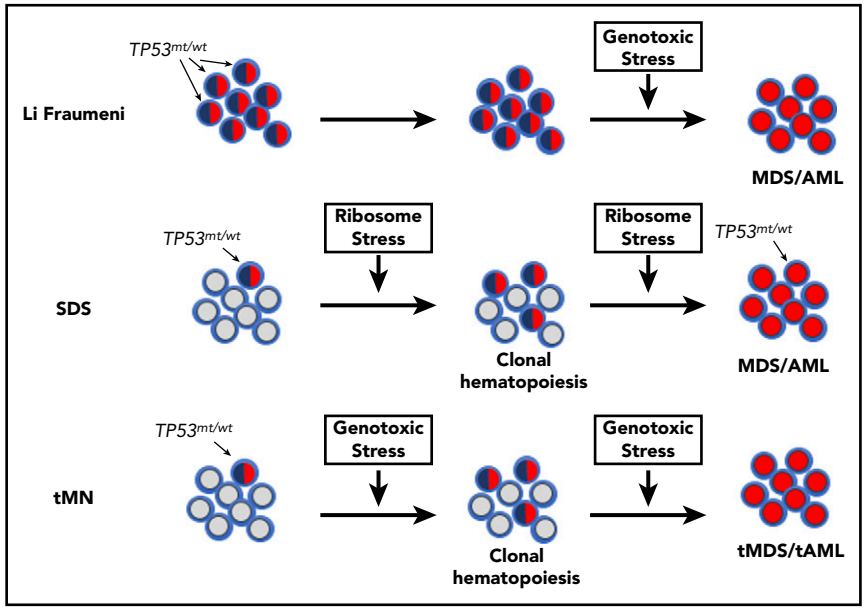

Figure 1. Model of MDS/AML pathogenesis in SDS, Li Fraumeni syndrome, and tMN. In Li Fraumeni syndrome, all of the HSPCs carry heterozygous *TP53* mutations (indicated by blue/red shaded cells). In the absence of genotoxic stress (eg, chemotherapy), there is no selective pressure to mutate the second allele. Thus, MDS/AML in Li Fraumeni syndrome is uncommon. In SDS, mutations of *SBDS* lead to chronic ribosome stress, which can select for HSPCs that have mutated 1 allele of *TP53* and result in *TP53*-mutated CH. Continued ribosome stress then selects for HSPCs in which both TP53 alleles are mutated (red shaded cells), which ultimately leads to MDS/AML. Patients undergoing treatment with cytotoxic chemotherapy or radiation experience significant genotoxic stress, resulting in selection of HSPCs carrying age-related *TP53* mutations. In this model, repeated exposure to cytotoxic therapy selects for HSPCs carrying biallelic TP53 mutations, which ultimately leads to MDS/AML. Other hematopoietic stressors, such as chronic inflammation, may promote progression from CH to myeloid malignancy in a similar fashion by providing a fitness advantage to HSPCs carrying mutations in other genes besides *TP53*. tAML, therapy-related AML; tMDS, therapy-related MDS.

including the presence of TP53 or spliceosome gene mutations, a VAF >10%, the presence of multiple mutations, and altered red blood indices. There is also emerging evidence that specific variants within a given gene confer differing degrees of risk for transformation. Prospective trials are needed to validate these finding and establish the absolute risk of hematopoietic malignancy development. CH in the setting of peripheral blood cytopenias (CCUS) carries a very high risk of progression to a myeloid malignancy. Prospective clinical studies are needed to determine whether early intervention in persons with CCUS prevents or delays the development of MDS/AML. Nonetheless, we suggest that current evidence supports testing for CH in persons with unexplained persistent blood cytopenias. Persons with CCUS should receive frequent follow-up for the development of MDS/AML.

There are several open questions in the field. Sequencing and array-based studies show that CH due to point mutations and structural variants (eg, copy-number alterations) are each associated with an increased risk of hematopoietic malignancy. However, to date, no studies have tested for both types of mutations in the same study population. Whether the cooccurrence of structural variants with point mutations increases the risk of hematopoietic malignancy is uncertain. Improved methods to detect structural variants using next-generation sequencing data should allow investigators to address this issue in the near future.

For persons with CH containing multiple mutations, are these mutations in the same cell? Longitudinal studies in persons with CH carrying multiple mutations show that, in some cases, 1 of the mutations is lost.[9,13] Thus, in these cases, the mutations likely arose in distinct HSPC clones. Is the likelihood of leukemic progression different between CH due to a single HSPC clone containing multiple mutations and CH in which multiple HSPCs carry single mutations? Single-cell sequencing techniques with improved mutation calling will allow the field to better address this question.

There is accumulating evidence suggesting that the cell of origin in which a mutation occurs contributes to the emergence of the tumor phenotype.[61] For example, the phenotype of *MLL-AF9*–induced leukemia in mice differs when HSCs are the cells of origin as compared with granulocyte-monocyte progenitors.[62,63] Studies are needed to determine whether the cell of origin in CH impacts the risk of malignant transformation.

The role of hematopoietic stressors in the development of CH and subsequent development of hematopoietic malignancy need further investigation. Our study of SDS suggests that ribosomal stress plays a key role both in the development of CH carrying heterozygous *TP53* mutations and in the progression to myeloid malignancy carrying biallelic *TP53* mutations. Does repeated exposure to cytotoxic therapy likewise promote progression from heterozygous *TP53*-mutated CH to biallelic *TP53*-mutated tMN? Does inflammation play a role in the development and leukemic progression of CH due to epigenetic modifier genes, such as *TET2*, *DNMT3A*, or *ASXL1*? Ultimately, identifying hematopoietic stressors that contribute to leukemic progression in persons with CH may suggest strategies to minimize its development.

Finally, and perhaps most importantly, strategies to prevent the development of hematopoietic malignancies in persons with CH and high-risk features are needed. The identification of stressors that contribute to leukemic progression in persons with CH may suggest strategies to minimize its development. For example, smoking has been linked to CH, suggesting that smoking cessation may reduce its incidence.[8] Aggressive treatment of inflammation may also reduce the incidence of CH and/or its progression to hematopoietic malignancy. In persons with *TP53*-mutated CH, minimizing genotoxic therapy may reduce the rate of leukemic transformation. Finally, treatment with agents that target specific high-risk gene mutations may provide an approach to suppress the HSPC clone carrying that mutation. For example, treatment with enasidenib, an IDH2 inhibitor, has been shown to suppress HSPCs carrying *IDH2* mutations in patients with AML.[64] As more targeted therapies become available, their use to suppress CH or prevent its progression could be tested.

Authorship

Contribution: J.T.W. and D.C.L. wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Footnote

Submitted 2 January 2020; accepted 5 June 2020; prepublished online on *Blood* First Edition 31 July 2020. DOI 10.1182/blood.2019000991.

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