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REVIEW ARTICLE

Environmental influences on clonal hematopoiesis

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Clonal hematopoiesis (CH) has emerged as an important factor linked to adverse health conditions in the elderly. CH is characterized by an overrepresentation of genetically distinct hematopoietic stem cell clones in the peripheral blood. Whereas the genetic mutations that underlie CH have been closely scrutinized, relatively little attention has been paid to the environmental factors that may influence the emergence of one dominant stem cell clone. As there is huge individual variation in latency between acquisition of a genetic mutation and emergence of CH, environmental factors likely play a major role. Indeed, environmental stressors such as inflammation, chemotherapy, and metabolic syndromes are known to affect steady-state hematopoiesis. To date, epidemiologic studies point toward smoking and prior chemotherapy exposure as likely contributors to some forms of CH, though the impact of other environmental factors is also being investigated. Mechanistic studies in murine models indicate that the role of different environmental factors in CH emergence may be highly specific to the mutation that marks each stem cell clone. For instance, recent studies have found that clones with mutations in the *PPM1D* gene are more resistant to genotoxic stress induced by chemotherapy. These clones thus have a competitive advantage in the setting of chemotherapy, but not in other types of stress. Here we review currently available literature on the interplay between environment and the genetic landscapes in CH and highlight critical areas for future study. Improved understanding of the effects of environmental stress on emergence of CH with mutation-specific clarity will guide future efforts to provide preventive medicine to individuals with CH.

Clonal hematopoiesis (CH) is a condition in which one or a few individual hematopoietic stem cells (HSCs) contribute disproportionately to peripheral blood production [1–3]. Not only are individuals with CH at significantly greater risk of developing hematologic malignancies compared with their counterparts without CH, but importantly they have greater all-cause mortality largely from heart disease and stroke [2,4]. The prevalence of clonal hematopoiesis increases with age and is thought to occur at some level in virtually all people [5], such that around 20% of individuals older than 70 have at least one HSC clone that is contributing to around 20% of their blood and that fraction increases steadily in each decade of life [1,2]. Although it is believed that the vast majority of 50-year-olds harbor clones with mutations in the genes most commonly associated with CH, only a fraction of these individuals goes on to develop CH. Thus, although CH is clearly associated with mortality, the interaction between environmental and genetic factors that drives its emergence remains unclear [6,7].

Heterozygous somatic mutations in about 20 genes are recurrently associated with CH, and some of these

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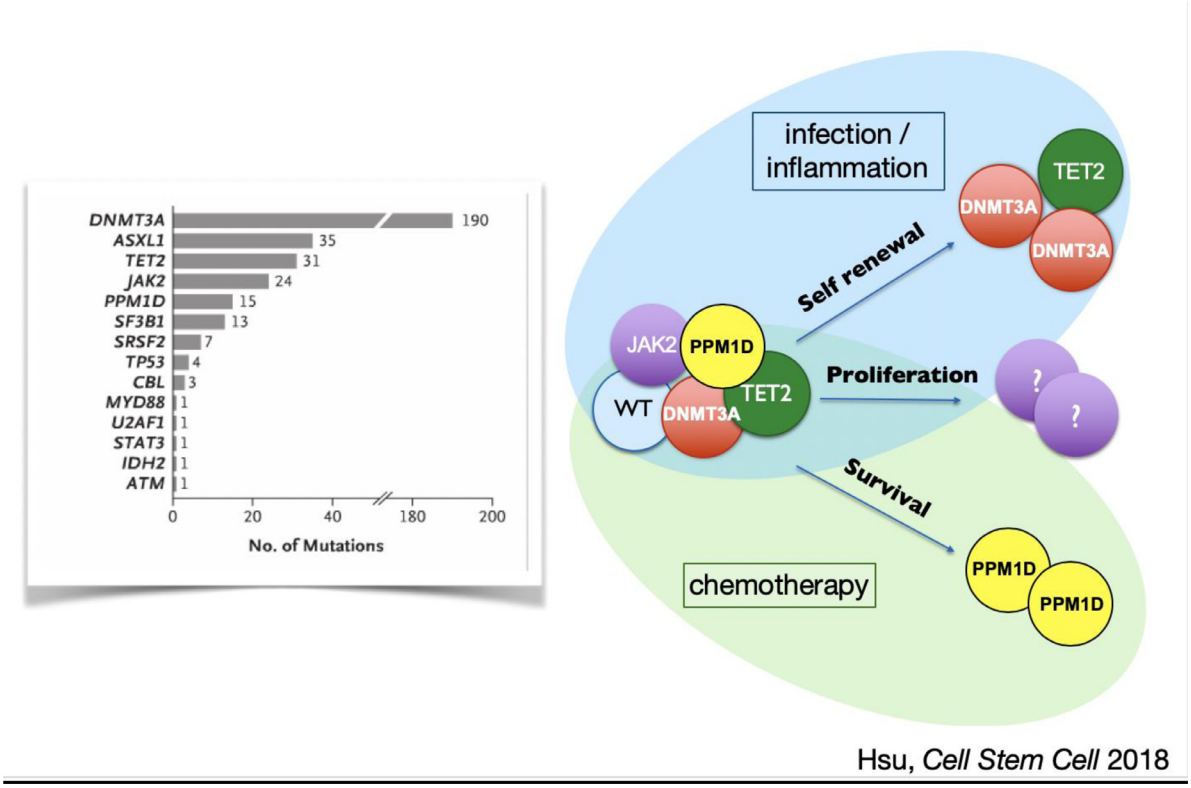

Figure 1. A variety of mutations are associated with clonal hematopoiesis. Clonal dominance may occur through several mechanisms, either via increased self-renewal, a proliferative advantage, or improved survival. *DNMT3A* and *TET2* mutations are thought to offer a competitive advantage through increased self-renewal at the stem cell level. The mechanism by which *JAK2* mutations confer an advantage is unknown but is speculatively indicated here as proliferation of the stem and progenitor cell population. PPM1D mutations likely confer an advantage by enhancing survival in adverse circumstances such as chemotherapy.

mutations are associated with cancer development [7]. Among the most frequent mutations, a few are known to confer a growth or self-renewal advantage to HSCs, enabling those mutant clones to attain numerical advantage (Figure 1). However, CH is unlikely to be driven by genetics alone [8]. The pace at which CH emerges in individuals with known mutations may differ by decades, suggesting that environmental conditions are a critical driver of CH. Indeed, environmental conditions may provide the necessary backdrop for a survival advantage for certain mutant clones.

Age is the strongest epidemiologic predictor of clonal hematopoiesis, and increased inflammation is a common driver of many of the pathologies of older age, frequently termed *inflammaging* [9]. Inflammatory stress may thus be a critical driver of CH. Indeed, a recent study reported that intestinal permeability and elevated inflammatory signaling are necessary for CH in a mouse model of somatic *Tet2* mutation, indicating that interactions between genes and environment drive CH [4,10]. On the other hand, not all environmental conditions affect genetically variant HSC clones the same way, and environmental drivers may be quite specific to certain CH clones. For example, *Ppm1d*-mutant stem cells have been found to have a clonal advantage only in the setting of chemotoxic stress (Figure 1) [11]. Thus, investigation of potential environmental drivers of CH is likely to shed light on the role of certain driver mutations in HSC biology and provide insight into individual variation in CH emergence.

Aside from age, other environmental factors, including former tobacco use, and diseases that are linked to tobacco use, such as lung cancer and chronic obstructive pulmonary disease, are strongly associated with CH [12], as is radiation exposure [13]. However, the full range of epidemiologic factors associated with CH is not known. The impact of these mutations on CH emergence likely depends on specific mutations and the mechanisms by which the two interact biologically.

In this article, we review our current understanding of the impact of environmental conditions, including inflammation, microbiome and DNA damage due to various sources, on the emergence of CH. We propose that some types of clones will be particularly prone to expand under specific conditions and propose a framework for viewing the different types of drivers.

Inflammation as a driver of clonal hematopoiesis

The strong epidemiologic association of CH with age contributes to speculation that inflammation is a critical driver of this process. Inflammation increases with age, and is attributable to decayed regulatory mechanisms [14]. For example, a recent study suggests that de-repression of retro-transposable elements with age triggers interferon (IFN) responses that drive inflammation [15]. These factors contribute to a wide variety of age-associated diseases including diabetes, Alzheimer's, cardiovascular disease, and cancer.

In the blood system, genetic variants associated with pleiotropic peripheral blood counts are also associated with inflammatory and autoimmune conditions [16]. Inflammatory and autoimmune conditions are present in up to 25% of myelodysplastic syndrome (MDS) patients [17], and a subset of MDS patients are highly sensitive to immunomodulatory medication [18]. Thus, inflammation is a well-known contributor to age-associated disease processes including in the hematopoietic system.

A significant and growing body of literature provides a conceptual understanding of how inflammation may contribute to clonal hematopoiesis. Infections are a common hematologic stress that generate inflammatory cytokines that affect bone marrow function and demand increased production of blood and immune cells. Numerous studies have reported that infections promote HSC division and impair self-renewal. Increased stem cell division and hematopoietic progenitor prevalence have been recorded in the setting of a variety of infections including viruses such as lymphochoriomeningitis virus and cytomegalovirus, bacteria including mycobacteria and *Ehrlichia* [19,20], and parasites such as *Plasmodium*, which causes malaria [21]. Infections may affect hematopoietic progenitors through pathogen-associated molecular patterns (PAMPs) such as LPS and TLR2 agonist [22,23] or cytokines induced during the infection, as previously reviewed [24]. Indeed, several studies have reported that cell division and differentiation programs in HSCs can be activated by inflammatory cytokines, including interferon (IFN)-α, IFN-γ, interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α [25–28]. As infections naturally occur over the course of life, it is reasonable to view aging as a state of survival past an increasing number of infections.

The long-term consequences of infection and inflammatory signaling on HSCs can be severe. Indeed, excessive IFN-γ has long been recognized to be an etiologic driver of acquired aplastic anemia [29], whereas increased inflammation is also significantly associated with MDS [30]. Where HSC activation and bone marrow dysfunction may at first appear contradictory, it is now recognized that stem cell divisions are often associated with a loss of self-renewal [31]. Indeed, an increase in the differentiation rate of HSCs leads to a loss of HSC reserves. Using a mouse model, we demonstrated that chronic infection depletes HSCs via excessive terminal differentiation [32]. Increased stress-induced apoptosis may also contribute to HSC loss [33], whereas HSCs that survive long-term inflammatory stress must do so by downregulating their responses to stress [33]. Whereas Rantes and CCL5 were previously reported to strongly influence HSC skewing with age [34], the relative importance of various inflammatory cytokines in driving age-associated changes in hematopoiesis has yet to be fully defined [35].

A variety of studies have demonstrated that individual subclasses of HSCs are differentially affected by inflammatory signaling. We reported that myeloid- versus lymphoid-biased HSCs respond differentially to IFN-γ signaling [36]. In other studies, IFN-γ has been found to preferentially stimulate a stem cell-like megakaryocyte progenitor [37], whereas histamine signaling affects a certain subclass of HSCs [38]. Furthermore, a subclass of HSCs marked by CCR2 is activated to divide after the stress of myocardial infarction [39]. Collectively these studies indicate that not all HSCs are equally responsive to cytokine stress, leading to the concept that environmental conditions can provide a selection advantage to some subclasses over others. HSCs harboring CH-associated mutations may be considered as competing HSC subclasses, but there are already examples wherein a differential response to inflammation by these genetically variant HSCs leads to CH [10,40].

Aside from age, epidemiologic factors associated with CH include smoking, smoking related-diseases, treatment of addiction, psychiatric disease, and chronic pulmonary disease, many or all of which are related to smoking [41]. Smoking is strongly correlated with inflammation [42], but it remains to be determined whether smoking and inflammation contribute additively or synergistically to CH, or if they are one and the same.

Environmental stress and TET2 mutations in CH

Environmental impacts on ten-eleven translocation 2 (TET2)-mutant CH are particularly well studied. TET2 is an epigenetic modifier that is frequently mutated across myeloid malignancies. In CH, *TET2* is the second most frequently mutated gene, and growing evidence suggests that factors including secondary genetic alterations [43,44], inflammation [40,45,46], and changes in the microbiota [10] may contribute to the clonal expansion and preleukemic condition of TET2-mutant hematopoietic stem and progenitor cells (HSPCs). Here, we discuss the biological studies investigating environmental influences on HSPCs with TET2 loss of function (LOF) in CH.

The TET family of dioxygenases are able to successively oxidize 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) in the mammalian genome [47–49]. Among the three *TET* genes, somatic mutations of *TET2* are the most frequently observed in individuals with CH [2,50] and hematological malignancies [51–53]. Although *TET2*

mutations contribute to the selective advantage of HSPCs through increased self-renewal, not all the individuals with somatic *TET2* mutations in HSPCs develop hematological neoplasms. In mouse models, *Tet2* ablation leads to variable outcomes. Some studies documented only mild phenotypes with increased HSPC self-renewal and myeloid bias in *Tet2* knockout mice [54,55]. However, several other groups reported that Tet2-deficient mice displayed hypermutagenicity and developed myeloid or lymphoid malignancies [56–58].

Multiple reports have indicated that TET2-deficient HSPCs tend to expand relative to WT HSPCs in response to environmental stress, such as inflammation arising from stress stimulation or pathogenic organisms. In the bone marrow, *Tet2*-ablated HSPCs exhibited strong proliferation advantages and myeloid bias in response to lipopolysaccharide (LPS)-induced acute inflammation [40]. Mechanistically, *Tet2*-deficient HSPCs tend to produce high levels of pro-inflammatory cytokines, such as IL-6, to maintain HSPC survival and suppress apoptosis through the upregulation of a novel anti-apoptotic long non-coding RNA, *Morrbid,* during inflammation [40]. In parallel, the progeny of *Tet2*-deficient HSPCs, particularly innate myeloid cells, also produce high levels of IL-6 during LPS challenge [46]. The upregulation of IL-6 in Tet2-deficient myeloid cells is due to the loss of transcriptional suppression at the IL-6 promoter mediated by HDAC2. The upregulation of IL-6 in Tet2-deficient innate myeloid cells might evoke a positive feedback to HSPCs during infection-induced inflammation and further promote the expansion of HSPCs to cause CH (Figure 2).

Interestingly, increased IL-6 production is also observed in microbiota-dependent inflammation in a Tet2-deficient mouse model. Meisel et al. [10] reported increased intestinal permeability and spontaneous bacterial translocation (e.g., *Lactobacillus*) into the blood of Tet2-deficient mice, thereby resulting in increases in plasma and spleen IL-6 levels. These studies provide strong evidence to support a positive feedback loop between Tet2-deficient HSPCs and their progeny innate myeloid cells during the response to inflammation-induced cytokine production (Figure 2). Given that myeloid cells derived from Tet2-deficient HSPCs can exert non–cell-autonomous effects on HSPCs, it is interesting to speculate whether such cells could also promote expansion of HSPC clones carrying other mutations. In other words, would the presence of a Tet2-deficient clone that produces Tet2-deficient macrophages accelerate the expansion of a *Dnmt3a*-mutant clone? As people are likely to harbor a variety of genetically variant HSC clones, such cross-cutting effects may exist.

TET2-mutant HSPCs produce immune cells that contribute to abnormal adaptive and innate immune responses not only in the hematopoietic system, but also in the peripheral tissues. Indeed, it has been reported that *Tet2*-KO mice displayed worse tissue damage in both lung and gut after immune challenge [46]. Furthermore, previous reports point to a strong correlation between *TET2* mutations and cardiovascular disease progression [4]. The causal relationship between Tet2 deletion in HSPCs and the increased risk of cardiovascular diseases has been further demonstrated in animal models [59,60]. Mechanistically, deletion of *Tet2* in HSPCs leads to the upregulation

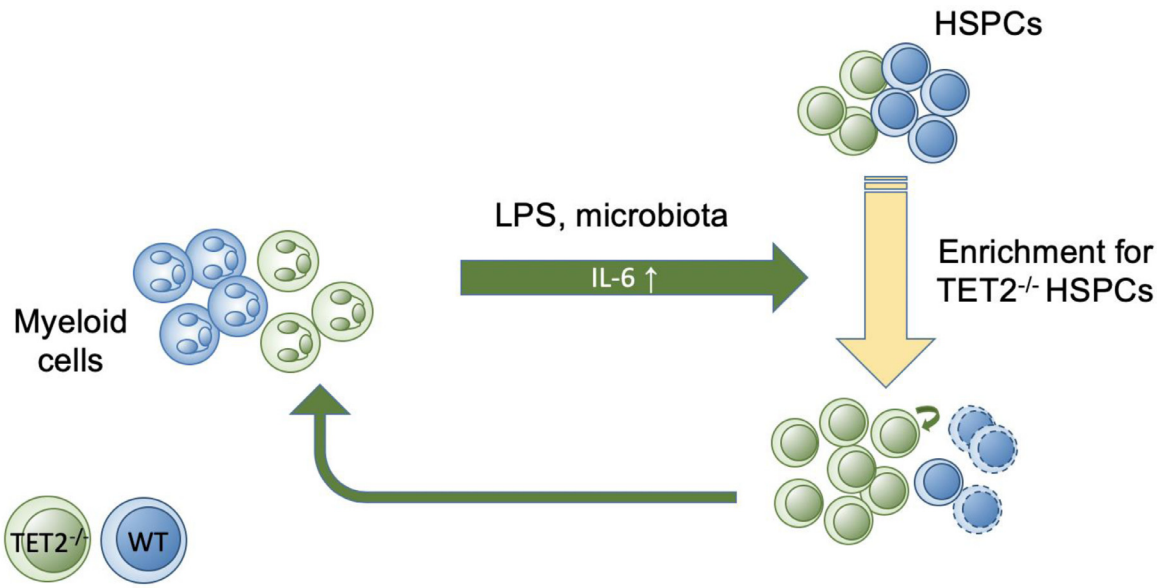

Figure 2. Positive feedback loop between TET2-deficient HSPCs and their innate myeloid cell progeny during the response to pathogen-associated molecular patterns. Inflammatory cytokines such as IL-6 are excessively produced by TET2-deficient myeloid cells, leading to further expansion of the HSPC compartment and perpetuation of the cycle.

of NLRP3 inflammasome and IL-1 production in myeloid cells, thereby leading to increased plaque sizes and impaired cardiac repair. *TET2* mutations are also detected in patients with chronic obstructive pulmonary disease or asthma and neurodegenerative disorders [61,62] but the causal relationships between TET2 mutations and these diseases are yet to be defined.

Clonal hematopoiesis driven by chemotoxic exposures

Although epigenetic regulators such as DNMT3A and TET2 sit at the top of the list for genes commonly mutated in clonal hematopoiesis, there are also a number of CH genes that are involved in DNA repair. The selective advantage their mutations impart is likely through entirely different mechanisms. Among this class of genes are *PPM1D* and *TP53* [12]. PPM1D mutations are among the top 10 CH mutations in individuals with an identified driver, representing on the order of 5% of CH cases. *PPM1D* mutations have recently been studied in some depth and likely represent a paradigm for this class of mutations.

PPM1D had not been described as a major participant in hematopoiesis previously so its frequent mutation in CH was of particular interest. PPM1D is a protein phosphatase that acts to downmodulate the DNA damage response by dephosphorylating p53, ATM, CHEK1, and other damage response proteins [63]. *PPM1D* mutations are typically clustered in the C-terminus of the protein and result in a truncated and highly stabilized protein. This stabilized protein results in an enhanced phosphatase activity that constitutively reduces the stress response. Normally, cells exposed to chemotoxic stress will pause to allow DNA repair to occur, with many cells undergoing apoptosis. However, cells with the *PPM1D* mutations are less sensitive to stress, and exhibit a lower rate of apoptosis [11,64]. The net result of their stress resistance is that HSCs bearing a *PPM1D* mutation are more resistant to chemotherapeutic insults than WT cells. Although chemo-toxic treatment results in apoptosis in both WT and mutant cells, the rate of cell death in mutant cells is lower. At the end of each round of chemotherapy, a greater proportion of mutant cells have survived compared with WT cells. We found that this larger number of surviving cells, even if relatively small, was sufficient to give a competitive advantage to the mutant cells in the context of repeated rounds of chemotherapy.

In mice, when *Ppm1d*-mutant stem cells were transplanted in competition with WT cells, they were able to engraft and contribute to blood production with equivalent efficiency. However, when mice were exposed to DNA-damaging agents, the mutant cells quickly outcompeted their WT counterparts, an effect that was maintained for months after cessation of chemotherapy treatment. However, not all types of stress gave the *Ppm1d* mutant cells a selective advantage; DNA-damaging agents were the most powerful, whereas stress such as serial transplantation did not offer any advantage to the mutant cells. Although PPM1D mutant cells may exhibit a slight proliferative advantage [64], a moderate difference in apoptosis can explain most of the differential expansion of PPM1D mutant cells in the blood.

These data can be extrapolated to explain at least some of the presence of *PPM1D* mutations in individuals with CH. In patients who have previously undergone chemotherapy for solid tumors, CH with *PPM1D* mutations is much more prevalent than without such exposures [12]. Similarly, in patients with therapy-related acute myeloid leukemia who have been exposed to DNA-damaging agents, *PPM1D* mutations are particularly common [11]. Notably, *PPM1D* mutations do show up in the general population with CH [1]. It is possible that these individuals represent those in the general population who have been exposed to chemotherapy or other stresses, or that *PPM1D* mutations offer advantages in some additional contexts that are yet to be identified.

Diet, metabolism, and clonal hematopoiesis

While the effects of diet or metabolic milieu on CH remain to be studied, obesity and metabolic syndromes are known to influence the fate of HSPCs. Specifically, obesity and metabolic syndromes enhance myelopoiesis. Both hyperglycemia in type 1 diabetes models and obesity caused by high-fat diet increase myeloid progenitors and myelopoiesis [65–68]. These metabolic disorders affect myelopoiesis largely through cell extrinsic mechanisms involving the HSC niche or by causing an inflammatory state.

HSCs reside in the bone marrow niche consisting of several cell types such as endothelial cells and bone marrow mesenchymal stromal cells (BMSCs), which have the capacity to differentiate into adipocytes, osteoblasts, and chondrocytes [69]. Obesity not only expands subcutaneous and visceral fat mass, it also promotes differentiation of BMSCs into adipocytes [70]. Increased marrow adipocytes, in turn, reduce the number of HSCs [70–72]. In contrast, a recent study suggests that exercise reduces leptin, a hormone that governs energy expenditure, and reduction of leptin instructs BMSCs to express HSC niche factors to promote HSC quiescence [73]. These studies illuminate the links between metabolic and physical conditions to the bone marrow microenvironment to support HSCs, with obesity and exercise negatively and positively affecting HSCs, respectively.

Obesity-induced changes in the microbiome have also been reported to alter the HSC niche and promote myelopoiesis [66,74]. Whether these changes in the microbiome are responsible for age-related changes in HSCs and their niche, leading to the emergence of CH, remains to be tested. Thus, whether by regulation of adipocytes or through microbiome-related changes, the net effect of obesity is to reduce the HSC population. It is therefore tempting to speculate that some CH mutations confer mutant HSCs with

resistance against the negative pressure imposed by fatty marrow in obese or aged populations.

Additionally, metabolic syndromes may promote CH indirectly by causing chronic inflammation. Obesity is a state of chronic inflammation characterized by expansion of pro-inflammatory immune cells in adipose tissues [75]. Adipocytes themselves also regulate inflammation by secreting a pro-inflammatory cytokine leptin and an anti-inflammatory cytokine adiponectin, the expression of which is increased and decreased in adipocytes of obese subjects, respectively. Obesity has been found to increase intestinal permeability, causing a systemic endotoxemia state [76]. Additionally, hyperglycemia in a mouse model of type 1 diabetes caused neutrophils to produce a sterile inflammatory signal S100A8/S100A9, which then instructed myeloid progenitor cells to secrete myelopoietic cytokines such as macrophage colony-stimulating factor (M-CSF) [67]. The resulting pro-inflammatory state was characterized by increased secretion of cytokines such as transforming growth factor β, IL-1, and interferons, all of which act on HSPCs as discussed previously.

The effects of metabolic syndromes on promoting myelopoiesis parallel the observation that HSCs and myeloid progenitors with CH mutations exhibit preferential expansion compared with lymphocytes [77]. Intriguingly, some individuals with CH exhibit preferential expansion of myeloid progenitors over the more immature HSCs, suggesting that some mutations, environmental selective pressure, or the combination of both may encourage clonal expansion of committed progenitors. It should be noted that neither diet nor metabolic syndromes have been demonstrated to be epidemiological factors associated with CH, and the link remains speculative. Nevertheless, identification of the mutations that allow CH clones to expand in the pro-inflammatory conditions associated with metabolic syndromes may lead to strategies to assess the risk of developing CH or to prevent the expansion of such clones in people with metabolic syndromes.

Unanswered questions and future directions

CH represents a premalignant status that provides an excellent opportunity to monitor patients for the early stages of malignant development. Current studies are focused on the genetic defects in CH. However, accumulating evidence suggests a strong functional interplay between genetic defects and environmental factors to promote the clonal expansion of HSPCs. Here we have discussed several examples of how environmental cues, such as inflammatory stress, chemotherapy, or diet and metabolites, influence the clonal expansion of subsets of HSPCs bearing specific genetic defects. Based on these studies, we hope that environmental factors will be taken into consideration in addition to genetic defects as critical contributors to the pathogenesis of CH. From a clinical perspective, the lifestyle of the individual is likely to affect risk assessment during CH management. For the population with a high risk of developing CH, intervening in environmental cues might provide an opportunity to reduce or prevent CH progression. In addition, many other environmental influences, such as anti-cancer radiation treatment, psychosocial stress, toxin exposure, and cardiac myocardial infarction, are yet to be fully explored with respect to their impact on CH. Further systematic studies are needed to elucidate the underlying mechanisms.

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References

1. Genovese G, Kähler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371:2477–2487.
2. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488–2498.
3. Xie M, Lu C, Wang J, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20:1472–1478.
4. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med. 2017;377:111–121.
5. Young AL, Challen GA, Birmann BM, Druley TE. Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. Nat Commun. 2016;7:12484.
6. Bowman RL, Busque L, Levine RL. Clonal hematopoiesis and evolution to hematopoietic malignancies. Cell Stem Cell. 2018;22:157–170.
7. Steensma DP. Clinical implications of clonal hematopoiesis. Mayo Clin Proc. 2018;93:1122–1130.
8. Loh PR, Genovese G, Handsaker RE, et al. Insights into clonal haematopoiesis from 8,342 mosaic chromosomal alterations. Nature. 2018;559:350–355.
9. Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev. 2007;128:92–105.
10. Meisel M, Hinterleitner R, Pacis A, et al. Microbial signals drive pre-leukaemic myeloproliferation in a Tet2-deficient host. Nature. 2018;557:580–584.
11. Hsu JI, Dayaram T, Tovy A, et al. PPM1D mutations drive clonal hematopoiesis in response to cytotoxic chemotherapy. Cell Stem Cell. 2018;23:700–713.e6.
12. Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. Cell Stem Cell. 2017;21:374–382.e4.
13. Boucai L, Falcone J, Ukena J, et al. Radioactive iodine-related clonal hematopoiesis in thyroid cancer is common and

associated with decreased survival. J Clin Endocrinol Metab. 2018;103:4216–4223.
14. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and age-related diseases: role of inflammation triggers and cytokines. Front Immunol. 2018;9:586.
15. De Cecco M, Ito T, Petrashen AP, et al. L1 drives IFN in senescent cells and promotes age-associated inflammation. Nature. 2019;566:73–78.
16. Tajuddin SM, Schick UM, Eicher JD, et al. Large-scale exome-wide association analysis identifies loci for white blood cell traits and pleiotropy with immune-mediated diseases. Am J Hum Genet. 2016;99:22–39.
17. Wolach O, Stone R. Autoimmunity and inflammation in myelodysplastic syndromes. Acta Haematol. 2016;136:108–117.
18. Glenthoj A, Orskov AD, Hansen JW, Hadrup SR, O'Connell C, Gronbaek K. Immune mechanisms in myelodysplastic syndrome. Int J Mol Sci. 2016;17:944.
19. Baldridge MT, King KY, Boles NC, Weksberg DC, Goodell MA. Quiescent haematopoietic stem cells are activated by IFN-γ in response to chronic infection. Nature. 2010;465:793–797.
20. Smith JNP, Zhang Y, Li JJ, et al. Type I IFNs drive hematopoietic stem and progenitor cell collapse via impaired proliferation and increased RIPK1-dependent cell death during shock-like ehrlichial infection. PLoS Pathogens. 2018;14:e1007234.
21. Vainieri ML, Blagborough AM, MacLean AL, et al. Systematic tracking of altered haematopoiesis during sporozoite-mediated malaria development reveals multiple response points. Open Biol. 2016;6:160038.
22. Herman AC, Monlish DA, Romine MP, Bhatt ST, Zippel S, Schuettpelz LG. Systemic TLR2 agonist exposure regulates hematopoietic stem cells via cell-autonomous and cell-non-autonomous mechanisms. Blood Cancer J. 2016;6:e437.
23. Takizawa H, Fritsch K, Kovtonyuk LV, et al. Pathogen-induced TLR4-TRIF innate immune signaling in hematopoietic stem cells promotes proliferation but reduces competitive fitness. Cell Stem Cell. 2017;21:225–240.e5.
24. King KY, Goodell MA. Inflammatory modulation of HSCs: viewing the HSC as a foundation for the immune response. Nat Rev Immunol. 2011;11:685–692.
25. Essers MAG, Offner S, Blanco-Bose WE, et al. IFNα activates dormant haematopoietic stem cells in vivo. Nature. 2009;458:904–908.
26. Pietras EM, Mirantes-Barbeito C, Fong S, et al. Chronic interleukin-1 exposure drives haematopoietic stem cells toward precocious myeloid differentiation at the expense of self-renewal. Nat Cell Biol. 2016;18:607–618.
27. Schürch CM, Riether C, Ochsenbein AF. Cytotoxic CD8+ T cells stimulate hematopoietic progenitors by promoting cytokine release from bone marrow mesenchymal stromal cells. Stem Cell. 2014;14:460–472.
28. Yamashita M, Passegue E. TNF-alpha coordinates hematopoietic stem cell survival and myeloid regeneration. Cell Stem Cell. 2019;25:357–372.e7.
29. Nisticò A, Young NS. Gamma-interferon gene expression in the bone marrow of patients with apla6stic anemia. Ann Intern Med. 1994;120:463–469.
30. Barreyro L, Chlon TM, Starczynowski DT. Chronic immune response dysregulation in MDS pathogenesis. Blood. 2018;132:1553–1560.
31. Esplin BL, Shimazu T, Welner RS, et al. Chronic exposure to a TLR ligand injures hematopoietic stem cells. J Immunol. 2011;186:5367–5375.
32. Matatall KA, Jeong M, Chen S, et al. Chronic infection depletes hematopoietic stem cells through stress-induced terminal differentiation. Cell Rep. 2016;17:2584–2595.
33. Pietras EM, Lakshminarasimhan R, Techner JM, et al. Re-entry into quiescence protects hematopoietic stem cells from the killing effect of chronic exposure to type I interferons. J Exp Med. 2014;211:245–262.
34. Ergen AV, Boles NC, Goodell MA. Rantes/Ccl5 influences hematopoietic stem cell subtypes and causes myeloid skewing. Blood. 2012;119:2500–2509.
35. Kovtonyuk LV, Fritsch K, Feng X, Manz MG, Takizawa H. Inflamm-aging of hematopoiesis, hematopoietic stem cells, and the bone marrow microenvironment. Front Immunol. 2016;7:502.
36. Matatall KA, Shen CC, Challen GA, King KY. Type II interferon promotes differentiation of myeloid-biased hematopoietic stem cells. Stem Cells. 2014;32:3023–3030.
37. Haas S, Hansson J, Klimmeck D, et al. Inflammation-induced emergency megakaryopoiesis driven by hematopoietic stem cell-like megakaryocyte progenitors. Stem Cell. 2015;17:422–434.
38. Chen X, Deng H, Churchill MJ, et al. Bone marrow myeloid cells regulate myeloid-biased hematopoietic stem cells via a histamine-dependent feedback loop. Cell Stem Cell. 2017;21:747–760.e7.
39. Dutta P, Sager HB, Stengel KR, et al. Myocardial infarction activates CCR2(+) hematopoietic stem and progenitor cells. Cell Stem Cell. 2015;16:477–487.
40. Cai Z, Kotzin JJ, Ramdas B, et al. Inhibition of inflammatory signaling in Tet2 mutant preleukemic cells mitigates stress-induced abnormalities and clonal hematopoiesis. Cell Stem Cell. 2018;23:833–849.e835.
41. Zink F, Stacey SN, Norddahl GL, et al. Clonal hematopoiesis, with and without candidate driver mutations, is common in the elderly. Blood. 2017;130:742–752.
42. Kianoush S, Yakoob MY, Al-Rifai M, et al. Associations of cigarette smoking with subclinical inflammation and atherosclerosis: ELSA-Brasil (The Brazilian Longitudinal Study of Adult Health). J Am Heart Assoc. 2017;6:30483.
43. Muto T, Sashida G, Oshima M, et al. Concurrent loss of Ezh2 and Tet2 cooperates in the pathogenesis of myelodysplastic disorders. J Exp Med. 2013;210:2627–2639.
44. Zhang X, Su J, Jeong M, et al. DNMT3A and TET2 compete and cooperate to repress lineage-specific transcription factors in hematopoietic stem cells. Nat Genet. 2016;48:1014–1023.
45. Shen Q, Zhang Q, Shi Y, et al. Tet2 promotes pathogen infection-induced myelopoiesis through mRNA oxidation. Nature. 2018;554:123–127.
46. Zhang Q, Zhao K, Shen Q, et al. Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. Nature. 2015;525:389–393.
47. He YF, Li BZ, Li Z, et al. Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. Science. 2011;333:1303–1307.
48. Ito S, Shen L, Dai Q, et al. Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. Science. 2011;333:1300–1303.
49. Tahiliani M, Koh KP, Shen Y, et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science. 2009;324:930–935.
50. Busque L, Patel JP, Figueroa ME, et al. Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. Nat Genet. 2012;44:1179–1181.
51. Couronne L, Bastard C, Bernard OA. TET2 and DNMT3A mutations in human T-cell lymphoma. N Engl J Med. 2012;366:95–96.
52. Delhommeau F, Dupont S, Della Valle V, et al. Mutation in TET2 in myeloid cancers. N Engl J Med. 2009;360:2289–2301.
53. Langemeijer SM, Kuiper RP, Berends M, et al. Acquired mutations in TET2 are common in myelodysplastic syndromes. Nat Genet. 2009;41:838–842.

54. Ko M, Bandukwala HS, An J, et al. Ten-eleven-translocation 2 (TET2) negatively regulates homeostasis and differentiation of hematopoietic stem cells in mice. Proc Natl Acad Sci USA. 2011;108:14566–14571.
55. Moran-Crusio K, Reavie L, Shih A, et al. Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. Cancer Cell. 2011;20:11–24.
56. Li Z, Cai X, Cai C, et al. Deletion of Tet2 in mice leads to dysregulated hematopoietic stem cells and subsequent development of myeloid malignancies. Blood. 2011;118:4509–4518.
57. Pan F, Wingo TS, Zhao Z, et al. Tet2 loss leads to hypermutagenicity in haematopoietic stem/progenitor cells. Nat Commun. 2017;8:15102.
58. Quivoron C, Couronne L, Della Valle V, et al. TET2 inactivation results in pleiotropic hematopoietic abnormalities in mouse and is a recurrent event during human lymphomagenesis. Cancer Cell. 2011;20:25–38.
59. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science. 2017;355:842–847.
60. Sano S, Oshima K, Wang Y, et al. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1beta/NLRP3 inflammasome. J Am Coll Cardiol. 2018;71:875–886.
61. Buscarlet M, Provost S, Zada YF, et al. DNMT3Aand TET2 dominate clonal hematopoiesis and demonstrate benign phenotypes and different genetic predispositions. Blood. 2017;130:753–762.
62. Keogh MJ, Wei W, Aryaman J, et al. High prevalence of focal and multi-focal somatic genetic variants in the human brain. Nat Commun. 2018;9:4257.
63. Le Guezennec X, Bulavin DV. WIP1 phosphatase at the crossroads of cancer and aging. Trends Biochem Sci. 2010;35:109–114.
64. Kahn JD, Miller PG, Silver AJ, et al. PPM1D-truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. Blood. 2018;132:1095–1105.
65. Lee JM, Govindarajah V, Goddard B, et al. Obesity alters the long-term fitness of the hematopoietic stem cell compartment through modulation of Gfi1 expression. J Exp Med. 2018;215:627–644.
66. Luo Y, Chen GL, Hannemann N, et al. Microbiota from obese mice regulate hematopoietic stem cell differentiation by altering the bone niche. Cell Metab. 2015;22:886–894.
67. Nagareddy PR, Murphy AJ, Stirzaker RA, et al. Hyperglycemia promotes myelopoiesis and impairs the resolution of atherosclerosis. Cell Metab. 2013;17:695–708.
68. Singer K, DelProposto J, Morris DL, et al. Diet-induced obesity promotes myelopoiesis in hematopoietic stem cells. Mol Metab. 2014;3:664–675.
69. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. Nature. 2014;505:327–334.
70. Ambrosi TH, Scialdone A, Graja A, et al. Adipocyte accumulation in the bone marrow during obesity and aging impairs stem cell-based hematopoietic and bone regeneration. Cell Stem Cell. 2017;20:771–784.e776.
71. Hu T, Kitano A, Luu V, et al. Bmi1 suppresses adipogenesis in the hematopoietic stem cell niche. Stem Cell Rep. 2019;13:545–558.
72. Naveiras O, Nardi V, Wenzel PL, Hauschka PV, Fahey F, Daley GQ. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. Nature. 2009;460:259–263.
73. Frodermann V, Rohde D, Courties G, et al. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. Nat Med. 2019;25:1761–1771.
74. Yan H, Baldridge MT, King KY. Hematopoiesis and the bacterial microbiome. Blood. 2018;132:559–564.
75. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol. 2017;13:633–643.
76. Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008;57:1470–1481.
77. Arends CM, Galan-Sousa J, Hoyer K, et al. Hematopoietic lineage distribution and evolutionary dynamics of clonal hematopoiesis. Leukemia. 2018;32:1908–1919.