CHIP: a clonal odyssey of the bone marrow niche

Wolfgang E. Schleicher,[1] Bridget Hoag,[2] Marco De Dominici,[2] James DeGregori,[1,2] and Eric M. Pietras[1]

[1]Division of Hematology, Department of Medicine, and [2]Department of Biochemistry and Molecular Genetics, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA.

Clonal hematopoiesis of indeterminate potential (CHIP) is characterized by the selective expansion of hematopoietic stem and progenitor cells (HSPCs) carrying somatic mutations. While CHIP is typically asymptomatic, it has garnered substantial attention due to its association with the pathogenesis of multiple disease conditions, including cardiovascular disease (CVD) and hematological malignancies. In this Review, we will discuss seminal and recent studies that have advanced our understanding of mechanisms that drive selection for mutant HSPCs in the BM niche. Next, we will address recent studies evaluating potential relationships between the clonal dynamics of CHIP and hematopoietic development across the lifespan. Next, we will examine the roles of systemic factors that can influence hematopoietic stem cell (HSC) fitness, including inflammation, and exposures to cytotoxic agents in driving selection for CHIP clones. Furthermore, we will consider how — through their impact on the BM niche — lifestyle factors, including diet, exercise, and psychosocial stressors, might contribute to the process of somatic evolution in the BM that culminates in CHIP. Finally, we will review the role of old age as a major driver of selection in CHIP.

Introduction: CHIP as an epic journey

Like the lengthy epic tales of the Greek poet Homer, clonal hematopoiesis of indeterminate potential (CHIP) is postulated to be the culmination of years, if not a lifetime, of clonal selection for mutant hematopoietic stem and progenitor cells (HSPCs) in the BM microenvironment. The most common CHIP mutations include loss-of-function mutations in epigenetic modifiers (*DNMT3A*, *TET2*, and ASXL1), splicing factor (SF) genes (*U2AF1*, *SRSF2*, *SF3B1*), and DNA damage–response (DDR) genes (*PPM1D* and *TP53*) as well as gain-of-function mutations in JAK2, among others (1–4). Although CHIP is defined by the absence of hematologic malignancy, such as myeloproliferative neoplasms (MPN), myelodysplastic syndrome (MDS), or acute myeloid leukemia (AML) (5), its association with myriad disease pathologies underscores its importance in contemporary hematology research. CHIP is strongly associated with older age, with around 15% of individuals over 75 exhibiting overrepresentation of CHIP mutations (1). CHIP is likewise associated with an increased risk for several aging-associated diseases, including solid cancers, heme malignancies, a variety of heart and lung conditions, and all-cause mortality (1, 6–14). Given the proportion of CHIP-associated diseases and diversity of mutations that drive CHIP, a key focus of the field has been understanding both intrinsic advantages of HSPCs harboring CHIP mutations and extrinsic BM niche changes with age, environmental exposures, infection, and other lifestyle factors that facilitate mutant HSPC competitiveness and expansion (15).

The hematopoietic niche was initially defined in 1978 as "the stem cell in association with other cells which determine its behavior" (16). Since then, decades of research have identified critical functions and cellular constituents of the BM niche that regulate hematopoiesis. The adult BM niche is predominantly localized to trabecular bone and is composed of a variety of cell types that support long-term hematopoietic stem cell (HSC) function, including endothelial cells, mesenchymal stem/stromal cells (MSC), osteolineage cells, and adipocytes (Figure 1). Many hematopoietic populations also contribute to HSC maintenance, including megakaryocytes, lymphocytes, and macrophages. The BM is highly vascularized and innervated with sympathetic and parasympathetic nerve fibers, providing a conduit of cytokine, chemokine, and endocrine signaling that regulates HSC activity in response to homeostatic cellular turnover, circadian cues, acute physiological needs for hematopoietic replenishment, and immunological "danger" signals associated with host defense and tissue-repair mechanisms (17–19). HSCs within the adult BM niche are primarily housed in perivascular beds (20), which can be subdivided into sinusoidal and arteriolar regions (21, 22). This spatial organization may be important in regulating quiescence versus cell-cycle activation in HSC, as sinusoidal perivascular beds could provide more exposure to nutrients, cytokines, and oxygen to support HSC cell-cycle activity (21, 22). However, others have shown quiescent stem cells localized proximal to sinusoids (23). While the exact structure of the BM niche and the organization of HSCs within these structures remains a matter of debate, many key cellular components have been identified based on cell type–specific gene knockouts and functional studies. For instance, HSCs interact extensively with leptin receptor–expressing (LepR+) MSCs, which promote HSC localization and maintenance in the BM through production of CXCL12 and stem cell factor (SCF). The complete array and role(s) of BM niche cell types is a topic extensively reviewed elsewhere (24, 25).
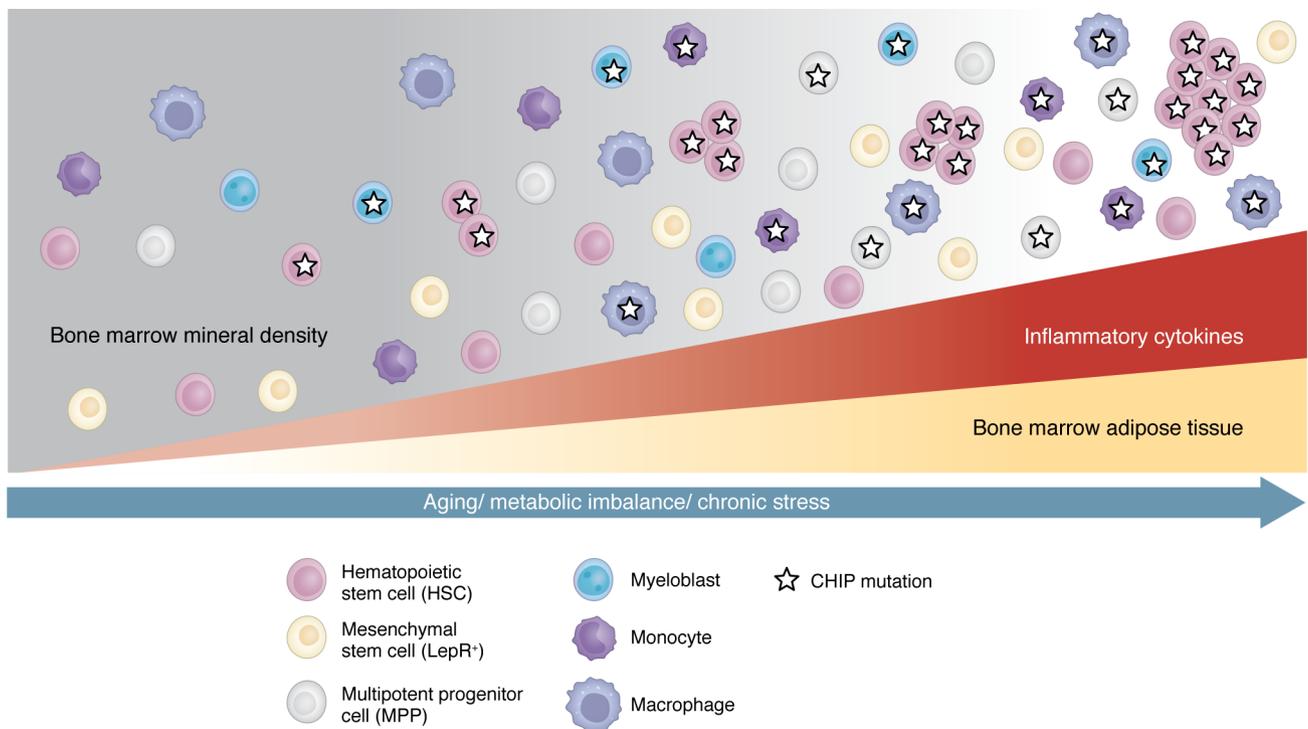
Figure 1. Changes to the BM niche with aging, metabolic imbalance, and/or chronic stress can promote CHIP. The BM niche is composed of multiple cell types that support long-term HSC function. Aging, metabolic imbalance, and chronic stress can result in changes to the BM niche that impair HSPC fitness in a way that could lead to the selection for mutant HSPCs and the eventual clonal outgrowth of mature blood cells associated with CHIP. This includes changes to the MSCs and increased inflammation and adipose tissue, together with reduced BM mineral density. Other changes with aging that are not depicted here include the loss of osteolineage cells, reduced innate and adaptive immunity, and phenotypic changes in HSPCs and their more mature progeny.

Dysregulation of the cellular composition and/or biophysical properties of the niche, due to systemic changes such as aging, chronic inflammation, metabolic imbalance, or environmental exposure, can affect the functional properties of HSCs, thereby establishing conditions that may promote clonal selection. This Review will summarize our current understanding of how these factors directly affect CHIP development and progression, with key studies summarized in Table 1. We will integrate these studies with the spectrum of lifestyle factors and CHIP-associated disease risks, highlighting current gaps in knowledge and opportunities for further study.

CHIP and hematopoietic development: where does the journey begin?

When CHIP clones emerge remains a critical open question. Like Homer's epic *Odyssey*, our understanding of CHIP begins in medias res — somewhere in the middle of the chain of events. Sequencing studies have identified rare HSPC clones harboring CHIP mutations in most individuals aged 50–60, with longitudinal stability and presence in multiple hematopoietic lineages. These data suggest that initiation of mutant clones occurs much earlier in life (26). Indeed, it is reasonable to assume that any given mutation occurs with similar probability throughout life in concordance with physiological rates of mutation accumulation. Hence, while CHIP is associated with aging, mutant HSPC clones may trace their origins to a much earlier point in hematopoietic

development, potentially during fetal life. Although the topic is more comprehensively reviewed elsewhere (17, 27), we will briefly summarize our current understanding of hematopoietic development to provide context for addressing current gaps in knowledge. In mammals, definitive HSCs (defined as functionally capable of reconstituting the entire hematopoietic system) first arise during fetal development from a region of the embryonic mesoderm called the aorta-gonad-mesonephros (AGM) (28). In parallel with definitive HSCs, a transient population of fetal HSCs (termed developmentally restricted HSCs [drHSCs]) and an embryonic multipotent progenitor (eMPP) population arise, which are responsible for early life blood production, limited adult multilineage output, and lifelong lymphoid output (29, 30). Contrary to previous dogma, definitive HSC expansion occurs after BM colonization, while drHSC/eMPP expansion occurs in the fetal liver (29, 31). BM colonization is accompanied by BM ossification and vascularization, thereby giving rise to the foundational BM niche (17, 32). Concomitant with phases of HSC expansion, some evidence suggests that mutations can arise during fetal development. By reconstructing hematopoietic phylogenies using whole-genome sequencing of 12 MPN patients, one study reported *DNMT3A* and *JAK2^{V617F}* mutations arising as early as 8 and 33 weeks of gestation, respectively (33). Moreover, a retrospective cohort study of the UK Biobank reported an association between abnormal birth weight, both low and high, and CHIP incidence, with a particular association (OR, 1.04 per 1 kg

Table 1. BM niche changes and associated CHIP phenotypes

Context	Niche changes	Associated CHIP mutation	Associated mouse models	Associated disease risk	References
Cytotoxic treatments	Induction of MSC senescence; acute BM injury (mature cell destruction); long-term BM injury (HSC senescence); sympathetic nerve damage in BM	TP53	HUPKI; $p53^{R248W/+}$; germline $p53^{-/-}$; germline $p53^{+/-}$	CVD, t-MN, CHIP	(38, 44, 46, 163)
		PPM1D	Constitutive active truncation mutant	CVD, t-MN/CHIP	(38, 52, 54, 164)
		NA (WT)	Drug-treatment model		(59)
Inflammation	Elevated inflammatory cytokines (IL-1, IL-6, TNF, IFN)	$JAK2^{V617F}$	$SclCre^{ER}:JAK2^{V617F}$ (inducible knockout)	AML, MPN, CVD, PMF	(85–87, 165)
		TET2	Germline $Tet2^{+/-}$; $SclCre^{ER}/Vav-Cre:Tet2^{fl/+}$ (inducible heterozygote)	AML, MPN, CVD, gout, diabetes	(13, 66, 67, 69, 70, 166)
		$DNMT3A^{R882H}$	Dnmt3a^{R878H}	AML, MPN, CVD	(76, 77, 116, 145)
Sleep disruption	Elevated inflammatory cytokines (IL-1, IL-6, TNF, IFN)	NA	Sleep fragmentation in C57BL/6J; CPW in C57BL/6J	AML	(108–110)
Psychological stress	Elevated inflammatory cytokines (IL-1, IL-6, TNF, IFN)	NA	Repeated intruder-induced social defeat (stress) in C57BL/6J	CVD	(98, 99)
Obesity	BMAT; elevated inflammatory cytokines (IL-1, IL-6, TNF, IFN)	TET2	Ob/Ob; HFD-fed C57BL/6	AML, CVD	(13, 68, 115)
		$DNMT3A^{R882H}$			(114, 115)
		NA (WT)	HFD-fed WT mice		(117–119)
Aging	Elevated BMAT; elevated inflammatory cytokines (IL-1, IL-6, TNF, IFN); impaired B-lymphopoiesis; myeloid skewing; low bone density; matrix stiffening; decrease in LepR⁺ MSCs	TET2		AML, MPN, CVD	(69–71)
		$DNMT3A^{R882H}$	Dnmt3a^{R878H}	AML, MPN, CVD	(76, 77, 116, 145)
		SFs (U2AF1, SRSF2, SF3B1)	$SclCre^{ER}:SRSF2^{P95H}$, U2AF1(S34F)/rtTA	MDS/AML	(38, 167–169)
		ASXL1	Mutant ASXL1		(149)
			Elevated JAK/STAT signaling		(170)

Table summarizes and integrates key current knowledge discussed in this Review related to the impact of different environmental and physiological factors on the BM environment as well as CHIP mutations and disease outcomes associated with these combinations of mutations and phenotypic factors. PMF, primary myelofibrosis; CPW, curling prevention by water; BMAT, elevated BM adipose tissue; HFD, high-fat diet.

increase) between *DNMT3A* CHIP and higher birth weight (34). Although these studies showcase great strides in improved detection of rare mutant HSPC clones that allow us to infer potential origins for CHIP-associated mutations, more work is required to precisely identify when CHIP mutations, and the processes that select for them, occur in an individual's life.

Genotoxins and inflammation: the BM's Scylla and Charybdis

Much like the two sea monsters Odysseus must navigate between, the BM must navigate cellular stresses that can severely impair hematopoietic function and potentially select for mutant HSPCs (35). We will begin our discussion with the well-characterized contributions of genotoxic agents, such as chemotherapeutics and other factors influencing mutation-driven clonal expansions in HSPC pools.

Cytotoxic agents. Cytotoxic agents, such as chemotherapeutics and radiation, are commonly employed to (somewhat) selectively eliminate malignant cells by eliciting DNA damage or impairing key cellular functions, such as DNA replication, transcription, and damage repair, or by inducing metabolic stress (36). Cytotoxic drugs are also employed as myeloablative agents in the setting of HSC transplantation (36, 37). In either case, cytotoxic agents are often inciting stimuli for expansion of HSPCs harboring mutations in DDR genes, such as in *TP53* and *PPM1D,* which confer resistance to DNA-damaging insults (38–40). Moreover, cytotoxic drugs may affect the niche in ways that promote MSC and HSC senescence (41, 42). *TP53* mutations are most highly associated

with therapy-related MPNs (t-MN) and treatment-induced clonal hematopoiesis (t-CH) (43–45). *TP53* mutations also contribute to increased risk of heart failure in cancer survivors (46). Loss of *Trp53* in mouse HSPCs promotes maintenance of stem cell potential and fitness following γ irradiation (47–49), leading to potent selection for *Trp53*-mutant HSPCs. Although the potential mechanisms underlying *TP53*-mutant HSPC expansion have not been fully clarified, p53 plays important roles in regulating HSC quiescence, self-renewal, and proliferation (47, 49–51).

TP53 mutations account for 40% of t-MN cases (44), likely due to t-MN's association with a myriad of cytotoxic agents (38), while *PPM1D* gain-of-function mutations account for roughly 20% of non–*TP53*-mutant t-MN cases (52) and are driven primarily by platinum-based chemotherapies (38, 52–54). Interestingly, *PPM1D*-mutant HSPCs harbor gain-of-function truncating mutations at exon 6 that induce constitutive PPM1D protein expression, desensitizing these mutant HSPCs to DDR-induced apoptosis (52–54). Crosstalk occurs between PPM1D and p53, in which *PPM1D* is transcriptionally upregulated by p53. PPM1D in turn suppresses various DDR proteins, including p53 (55, 56). A recent murine study revealed the importance of this synergy in myeloid malignancy, as resistance to PPM1D inhibitors is driven by p53 inactivation (57). Moreover, genetic ablation of *Ppm1d* reduced HSC competition and serial replating capacity, suggesting its involvement in promoting HSC fitness (57). While its role in normal HSCs could portend toxicity issues, ablating *Ppm1d* sensitized *MLL-AF9*–expressing leukemia cells to cisplatin treatment, suggesting its therapeutic relevance in myeloid malignancy
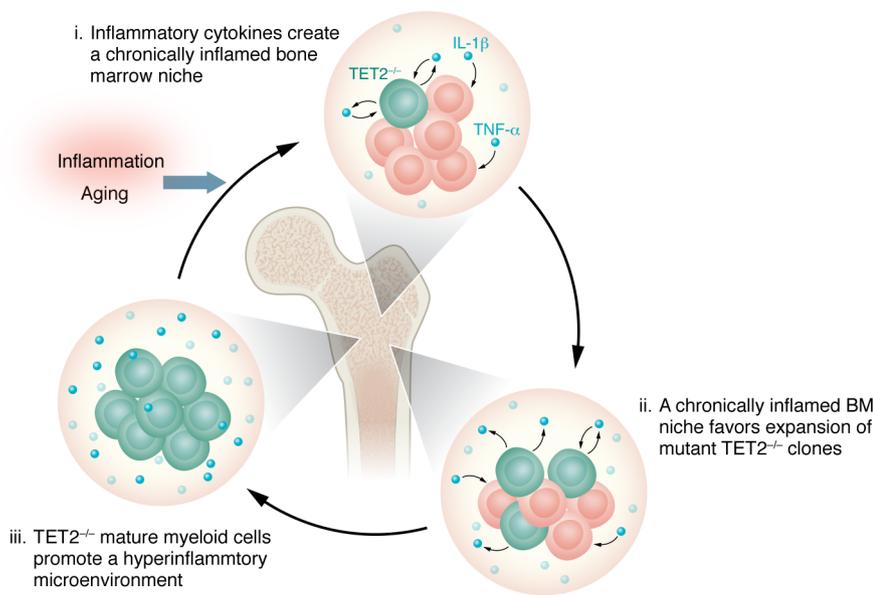
Figure 2. A model of an inflammatory feed-forward cycle in CHIP. *Tet2* deficiency leads to myeloid skewing and an increase in the number of mature myeloid cells carrying the mutation, in the BM and elsewhere. Because TET2 regulates inflammatory gene expression, its loss in myeloid cells leads to a hyperinflammatory BM niche, driven by elevated IL-1 and TNF-α signaling. This, in turn, has been shown to further promote *Tet2*⁻/⁻ clonal expansion. Thus, *Tet2*-mutant HSPCs may establish conditions in the BM that favor their own expansion, effectively creating a feed-forward loop. This model may be relevant to other common CHIP mutations that demonstrate selective advantages under inflammatory stress.

(57). The role of *Ppm1d* mutations in AML development was further corroborated in vivo. While a single dose of γ radiation or two doses of 5-fluorouracil (5-FU) delivered over two weeks failed to initiate leukemia development in *Ppm1d* mutant mice, sequential treatment with four doses of γ radiation over eight weeks induced eventual AML transformation in a proportion of *Ppm1d*-mutant mice (58). These data suggest that malignant transformation depends on cumulative exposures to genotoxic stressors. Furthermore, chemotherapeutic agents, specifically those with neurotoxic properties such as cisplatin, can damage the sympathetic nervous system in the BM, impairing regeneration of both HSPCs and stromal constituents of the niche. In this setting, induction of nerve growth factor or deletion of *Tp53* in sympathetic nerves rescued BM regeneration after a seven-week course of cisplatin (59). One may speculate that mutations in *Ppm1d* or *Tp53* could reduce the dependence of HSPCs on BM sympathetic innervations for their regenerative potential, thereby allowing them to outcompete normal HSPCs during hematopoietic recovery in a chemotherapy-damaged BM niche. Collectively, these studies show that chemotherapeutic agents constitute a potent mechanism for mutant HSPC selection, with impaired BM niche function as a potential contributing factor.

Inflammatory signaling. Inflammation is a complex biological response to harmful stimuli, e.g., pathogens or tissue damage, that involves a coordinated series of events including cytokine/chemokine signaling, activation and recruitment of innate immune cells, and ideally, resolution of the inciting stimulus (60, 61). While inflammation is a critical defense mechanism against infection and injury, dysregulated and/or chronic inflammation can contribute to various disease pathogeneses. Thus, a key area of interest is understanding how acute and chronic inflammation affect HSPC proliferation, differentiation, and self-renewal in normal and malignant hematopoiesis. Although this topic has been comprehensively reviewed elsewhere (62–65), several recent studies have considerably advanced our understanding of the role of inflammation in promoting CHIP initiation or progression, while also uncovering new questions.

Previous work revealed synergy between inflammation and selective expansion of certain mutant HSPC clones. Notably, *Tet2*-mutant HSPCs were shown to selectively expand in response to TNF-α (in vitro) and LPS (in vivo, for four weeks) stimulation (66, 67). This activity has been mechanistically linked to the STAT3/IL-6 signaling axis (67, 68). Moreover, recent work has reinforced IL-1 signaling as a driver of *Tet2*-deficient CHIP (69–71). IL-1 signaling is necessary and sufficient for *Tet2*-deficient clonal expansion, as stimulating mice with IL-1α or IL-1β for at least two weeks accelerated *Tet2*-mutant HSPC expansion, while genetic ablation or pharmacologic inhibition of the IL-1 receptor normalized *Tet2*-mutant HSPC expansion (69, 70). Mechanistically, *Tet2*-deficient HSPCs resisted IL-1–mediated depletion via DNA hypermethylation at prodifferentiation enhancer regions, which epigenetically primed them to favor self-renewal. While IL-1β stimulus promoted demethylation at these enhancer regions in WT HSPCs, resulting in myeloproliferative gene upregulation and subsequent differentiation, *Tet2*-deficient HSPCs maintained sufficient methylation at these regions to prevent their differentiation, thus mediating their expansion over their WT counterparts under chronic inflammatory stress (70), mirroring previous work demonstrating IL-1β–mediated selection for HSPCs with *Cebpa* loss (72).

While HSPC competitiveness is at least partially defined by how well mutant HSPCs resist chronic stress–induced BM depletion and terminal differentiation (73), mutation-specific phenotypes also contribute to a competitive advantage. Previous work comparing *Dnmt3a*- and *Tet2*-knockout models revealed that *Tet2*-deficient HSCs exhausted at the same rate as their WT counterparts, but loss of *Dnmt3a* effectively immortalized HSCs (74, 75). Other studies showed that loss of *Tet2* favored myeloid lineage bias in HSPCs (69, 70), suggesting a divergent model in which *Dnmt3a*-deficient CHIP is primarily driven by HSCs, while *Tet2*-deficient CHIP is driven primarily by multipotent progenitors (74). Similarly, mutant HSPC competitiveness may also depend on the inflammatory stimulus. While *Tet2*-deficient HSPCs preferentially expand in response to LPS and IL-1, as discussed above

(66, 67, 69–71), *Dnmt3a*-knockout HSPCs expand under chronic (four weeks) IFN-γ stimulation in vivo and, to a lesser extent, IL-1β stimulation (76, 77). On the other hand, four weeks of stimulation with LPS, TNF-α, and poly I:poly C (pIpC) failed to promote selective expansion of *Dnmt3a*-knockout HSCs in this model (76, 77). In contrast, endogenous TNF-α signaling facilitated selective expansion of HSPCs carrying a heterozygous *Dnmt3a^R878H* mutation (which recapitulates the human *DNMT3A^R882H* mutation), suggesting potential differences in response to TNF-α stimulation between genetic knockouts and point mutations in *Dnmt3a*. (76, 77). In this latter study, the aging-associated fitness advantage of *Dnmt3a*-deficient HSCs required TNF-α/TNFR1 signaling, loss of which normalized HSC fitness without affecting lineage output. However, genetically ablating TNFR2 resulted in myeloid lineage bias without affecting HSC fitness (77). While TNFR signaling has not been studied in vivo in *Tet2*-deficient mouse models, in vitro data suggest that loss of *Tet2* and *Dnmt3a* both endow HSPCs with enhanced survival and/or clonogenic activity in response to TNF-α signaling (66, 67). Whether differential expression and/or signaling via TNFR1 or -2 underlies the differences in self-renewal activity between *Tet2*- and *Dnmt3a*-deficient HSCs remains an open question.

Finally, these recent studies provide rationale for an interesting hypothesis related to *Tet2*-mutant clonal selection. Loss of *Tet2* promotes myeloid skewing (78), increasing peripheral mature myeloid cells, such as macrophages and neutrophils (79), that similarly carry this mutation. As *Tet2* regulates inflammatory gene expression (80), its loss in myeloid cells promotes a hyperinflammatory phenotype that can further shape the hematopoietic niche, impairing normal hematopoiesis (81, 82). This hyperinflammation also promoted *Tet2*-deficient clonal expansion via IL-1 (69, 70) and TNF-α signaling (66), thus creating an effective feed-forward loop (Figure 2) by which *Tet2*-deficient myeloid cells shape a niche that favors *Tet2*-deficient HSPC expansion (69, 70, 83). The extent to which such myeloid:HSC feed-forward loops drive selection in other CHIP mutant contexts remains largely an open question.

Beyond epigenetic modifiers, HSPCs harboring the *JAK2^V617F* mutation also preferentially expand in BM under inflammatory conditions. Previous work established that *JAK2^V617F* HSPCs expand at the expense of HSC self-renewal (84), and other work shows that treating mice harboring *JAK2^V617F* HSPCs with IFN-γ, TNF-α, and/or TGF-β enhances *JAK2^V617F* HSPC expansion in a DUSP1-dependent manner (85). Recent work also revealed a role for IL-1β in promoting MPN disease initiation in *JAK2^V617F* HSCs by enhancing their early expansion in the BM (86), mirroring a previous study in which *JAK2^V617F* hematopoietic cells exhibited increased IL-1β secretion, contributing to sympathetic nerve damage and subsequent MSC attrition in the BM niche (86, 87). Indeed, a chronic inflammatory state is a key feature of many MPNs (88), which are often characterized by clonal expansion of HSPCs with gain-of-function mutations in JAK2/STAT3/STAT5 pathways (89). However, it is unclear whether increased IL-1β secretion of *JAK2^V617F* hematopoietic cells directly influences the dynamics of parental HSCs through paracrine or autocrine signaling (90).

Collectively, these studies suggest that inflammation plays a critical role in establishing conditions in the BM niche that select for mutant HSPCs through a combination of cell-intrinsic and -extrinsic mechanisms. However, while these studies conceptually illustrate the role of inflammation as a selection mechanism, caveats and limitations remain to be addressed. The extent to which treatment with single inflammatory mediators recapitulates selection for CHIP mutations is not clear, as physiological inflammation typically involves multiple inflammatory signals. Likewise, few studies have provided direct comparisons between inflammatory factors to assess which ones play a greater or lesser role in selecting for specific mutations. Coordinated studies that facilitate direct comparisons of inflammatory mediators, combined with the use of aging and chronic disease models in mice with targeted knockouts of key inflammatory pathway components, may offer an opportunity to clarify the role(s) of individual factors.

Finally, direct evidence for the role of inflammatory signaling as a driver of CHIP in humans remains relatively limited, though its roles in CHIP-related morbidities such as cardiovascular disease (CVD) are more clearly delineated in clinical studies (91). Analysis for CHIP mutations in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) clinical trial cohort (ClinicalTrials.gov NCT01327846), in which canakinumab (anti–IL-1β antibody) was administered to patients with prior myocardial infarction, revealed decreased subsequent major adverse cardiovascular events (MACEs) in subjects with *TET2* mutations relative to those without CHIP (91). Furthermore, new clinical trials are investigating the efficacy of canakinumab in preventing evolution to malignancy in individuals with clonal cytopenia of undetermined significance (CCUS) (NCT05641831) as well as MDS (NCT04239157). Recent CANTOS data have also shown improvement in anemia and inflammatory marker levels following canakinumab treatment among individuals with CHIP (92). Multiple biologics and antibodies that block cytokines such as TNF-α and IL-6 are in clinical use, typically for rheumatoid diseases (93, 94). These could be efficacious in limiting further selection for specific CHIP mutations and/or CHIP-associated diseases, though safety concerns associated with risk for severe infection have been previously noted (95).

Psychosocial stressors: the Sirens' wail

Odysseus chose to hear the Sirens' song while lashed to his ship's mast. However, psychosocial stressors are a generally unavoidable feature of modern society and include stresses associated with interpersonal conflict and social competition as well as job-related stressors related to achievement of goals and real or perceived impacts on social status (96). Although psychosocial stress responses (akin to the "fight or flight" response) likely evolved to prepare the body to respond to immediate threats of injury, persistent activation of these responses can become maladaptive and negatively affect health (97). However, the impact of psychosocial stress on the hematopoietic niche and its relationship to CHIP remain unknown, despite links to CHIP-associated diseases such as CVD (98). Notably, a study using a mouse model of intruder-mediated social defeat reveals HSPC mobilization from the BM and increased extramedullary monocyte, neutrophil, and erythrocyte production up to 24 days after stress cessation (99). However, whether these hematopoietic changes promote CHIP is unknown and may represent a critical area for future study given the relative ubiquity of social stressors in modern society. More-

over, while long-duration exposure to night-shift work, which disrupts the circadian biological clock (100), is inconclusively linked to hematopoietic cancers (101), its link to nonmalignant CHIP-associated morbidities such as CVD is more evident (102). Below, we offer rationales for investigating potential mechanisms that link impacts on HSPCs caused by circadian rhythm disruption with somatic evolution in the BM, leading to CHIP and its sequelae.

Circadian rhythms, which are the body's internal clock, regulate physiological processes, including sleep-wake patterns, hormone regulation, body temperature, and systemic metabolism over an approximately 24-hour period. HSPC proliferation dynamics are dictated by circadian rhythms through sympathetic innervations that regulate hematopoietic and nonhematopoietic cells within the BM niche (103). These sympathetic innervations influence overlapping cycles of HSPC proliferation and DNA synthesis (104), circadian changes in CXCL12 secretion from the niche that regulate HSPC BM egress (105, 106), and rhythmic changes to vascular permeability driven by noradrenaline release in concert with bipotent bursts of TNF-α (107). Interestingly, recent work revealed that sleep interruption exerts lasting epigenetic changes that skew HSPCs toward myeloid lineage bias (108). Similarly, a separate study, which developed a novel murine model of prolonged sleep deprivation (up to 4 days), revealed increased accumulation of neutrophils and multiple proinflammatory cytokines in the peripheral blood, including IL-6, IL-17, and TNF-α, within 24 hours of sleep deprivation (109). Finally, a longitudinal study of 130,343 women aged 50–79 years found that those with higher sleep disturbances were at 22% higher risk of leukemia, particularly myeloid leukemia (110). Altogether, circadian rhythm disruption can profoundly alter hematopoietic homeostasis via systemic increases in proinflammatory cytokines, reduction of key chemokine cues that regulate neutrophil-recycling processes, and lasting epigenetic changes in HSPCs (108, 109, 111) that could select for HSCs with CHIP mutations. Intriguingly, a recent murine study utilized sleep fragmentation (112) throughout an 80-day competitive transplant experiment between WT and *Tet2*-deficient BM. This work showed that sleep disruption accelerates *Tet2*-mutant cell expansion in peripheral blood (113). However, more work using these novel paradigms is necessary to directly investigate how circadian rhythm disruption influences CHIP.

Diet and exercise: whither the Lotus-Eaters?
While the vegetarian diet on the island of the Lotus-Eaters would presumably be healthy, the direct impact of diet on CHIP development or progression is largely unknown. A recent retrospective cohort study of 44,111 participants (mean age = 56.3 years) from the UK Biobank reported that CHIP was present in 162 of 2,271 (7.1%) participants with an unhealthy diet, 2,177 of 38,552 (5.7%) participants with an intermediate diet, and 168 of 3,288 (5.1%) participants with a healthy diet; dietary metrics were scored by weekly frequency of intake of fruits and vegetables versus processed and unprocessed meat. While no statistically significant differences were observed between the distribution of CHIP mutations across dietary classes, the majority (58.6%) of participants with CHIP that had an unhealthy diet had *DNMT3A* mutations, while 16% of participants had *TET2* mutations and 6.2% had *ASXL1* mutations (114). Direct observations using murine

models of *Tet2*-deficient CHIP and an obesogenic diet (high fat and sucrose content) showed clonal expansion similar to that seen with aging (13); however, these experiments did not include direct comparisons of CHIP mutation–bearing mice between regular and obesogenic diets. Interestingly, diabetes-induced hyperglycemic stress can progress *Tet2* CHIP to a full-blown MPN in mice (68). Congruent with other studies, poor diet and obesity may exacerbate CHIP progression through increased inflammatory signaling (13, 68, 115). While others have established inflammation as a driver of mutant HSPC expansion (66, 69, 71, 76, 77, 85–87, 116), these studies also implicate the sufficiency of an obesity-induced inflammatory state in promoting mutant HSPC clonal expansion.

Indeed, previous studies have linked poor diet to systemic inflammation (117). Of note, a high-fat diet increases gut permeability and subsequently upregulates expression of proinflammatory cytokines (118, 119). Conversely, dietary restriction can normalize some aging-associated HSC phenotypes, such as increased leukocyte number, myeloid lineage bias, and decreased quiescence due to suppression of IGF1 and IL-6 signaling (120, 121). Similarly, short-term fasting and refeeding induced autophagy in HSCs, which in turn normalized glucose uptake and glycolytic flux of aged HSCs, improving their regenerative potential (122). These studies point to an exciting unanswered question in the field: can CHIP be mitigated by dietary intervention? Inferential evidence from an analysis of 8,709 women with a mean age of 66.5 years found that, while diet quality and physical activity had no association with CHIP prevalence, maintaining a normal BMI (18.5–25 kg/m²) was strongly associated with lower CHIP prevalence (123). Moreover, dietary restriction increased CXCL12/CXCR4 activity (124), which mitigates age-related HSC dysfunction and maintains normal ROS levels (125–127), constituting a potential avenue for mitigating CHIP clone expansion.

Exercise. In addition to dietary habits, regular exercise is crucial to maintaining a healthy body weight and fosters myriad other benefits (128, 129). However, whether exercise can mitigate CHIP clone expansion has not been investigated beyond an ongoing clinical trial (NCT03996239) studying the impact of aerobic exercise on CHIP progression. Of note, while the capacity of exercise to reduce adipose tissue deposits in humans is well known (130), a murine study showed that aerobic exercise can also decrease dietary-induced BM adipose tissue accumulation (131). Aging and obesity increased BM adipose tissue, which altered HSC polarization, diminished granulocyte and erythroid differentiation (132), reduced bone density, and profoundly remodeled the hematopoietic niche by altering expression of extracellular matrix signaling pathways associated with proliferation and differentiation (133). In this mouse study, a 12-week treadmill regimen delayed high-fat diet–induced obesity, increased trabecular bone mass, and improved the BM microenvironment by partially inhibiting adipokine signaling (131). Moreover, exercise diminished adipocyte leptin production, which in turn augmented production of quiescence-promoting factors secreted from LepR⁺ MSCs in the BM. Notably, while exercise in this study reduced chronic leukocytosis, emergency myelopoiesis was not compromised (131). Moreover, exercise-trained mice had higher BM reconstitution after irradiated transplant even when fed a high-fat diet, suggestive of improved BM niche function. Thus, while exercise could mitigate

CHIP through balancing the inflammatory milieu and partially correcting the adverse composition of the damaged niche, such benefits have not been evaluated in the setting of CHIP, leaving a critical open question in the field.

Aging: the end or beginning of the odyssey?

While Homer's protagonist spent a decade escaping many perils, he did not escape the passage of time. Likewise, the only truly inescapable alteration to the niche, and the most dominant determinant of who develops CHIP, is aging. Our species' evolution has favored tissue maintenance to maximize reproductive output. As this maintenance wanes in postreproductive periods, so does the integrity of the HSC niche, and in combination with a lifetime of insults, comes the inevitable decline in our soma associated with old age (134). It is possible to mitigate these insults by maintaining proper diet, sleep, and exercise routines, reducing chronic stress, and managing inflammatory states. However, aging poses a unique challenge for the BM niche that incorporates many features of the insults outlined above. It is associated with (a) lower bone mineral density, (b) stiffening of the BM matrix, (c) increased inflammation (termed "inflammaging"), and (d) various changes in MSCs (135). These changes can collaborate with cell-intrinsic features of HSC aging (136–138), including proliferative attrition and replicative stress, to profoundly impair hematopoietic fitness and promote mutant clonal selection (Figure 1).

Reduced bone mineral density of older mice diminishes MSC proliferation and response to osteogenic growth factors (139), resulting in decreased niche factors such as Netrin 1 (140) and POT1A (141), leading in turn to DDR defects, BM ROS, and adipose tissue accumulation (141), which can alter HSC polarization, differentiation (132), and long-term function (133). Furthermore, aging increases central marrow LepR$^+$ MSC, which, in addition to having a deleterious effect on the sinusoidal vasculature, is associated with decreased osteoprogenitor function (142). The resultant degraded and inflamed BM niche may parallel developmental HSC/eMPP extinguishment (29, 30), which suggests a potential concomitance between myeloid-skewing extrinsic cues from the niche and lymphoid attrition with age.

In contrast to CHIP's low prevalence, defined by a 2% variant allele frequency threshold in nonelderly, rare clones harboring CHIP mutations are present in most people before age 70 when analyzed by error-corrected sequencing methods (26). This suggests that before old age, most CHIP clones either do not expand or expand very slowly, and the altered BM microenvironment associated with aging might be responsible for the emergence of CHIP at clinically relevant rates.

However, there is a paucity of studies directly investigating the aging-specific changes that contribute to CHIP clone selection in humans. Mouse models provide some evidence that aging, primarily through inflammatory signaling, favors certain mutant HSCs. Indeed, age-associated "inflammaging" (143, 144) can drive rapid myelopoiesis and IL-1β production, impairing BM niche function (142). A recent mouse study showed that *Dnmt3a*^{R878H} BM cells expanded faster when transplanted into older recipient mice, due to their reduced sensitivity to LPS- and TNF-induced necroptosis in the aged setting (145). Recent work revealed increased expansion of *Tet2*-deficient HSPCs starting 7 months after selective,

inducible *Tet2* deletion. Intriguingly, IL-1α correlated with the rate of expansion, and deleting the IL-1 receptor in *Tet2*-deficient HSPCs prevented their expansion (69). Additionally, gut microbiome changes in aged mice were associated with increased IL-1α and IL-1β in the BM, reducing engraftment potential and increasing myeloid bias of HSCs (146). As IL-1β promotes expansion of *Tet2*-deficient HSPCs (70), an aged microbiome may promote *Tet2*-deficient HSPC expansion; however, this hypothesis remains untested. In addition to these cell-extrinsic cues, several cell-intrinsic changes have been described in aged HSCs (147). Aged HSCs showed altered heterochromatin landscapes associated with increased aberrant expression of repetitive elements, such as endogenous retroviral sequences that induce interferon-regulated genes. Deleting *Tet2* in aged cells partially mitigated these heterochromatin changes, leading to a more youthful transcriptomic profile. Moreover, reverse transcriptase inhibitors reduced the amount of cytosolic DNA in old WT HSCs, rescuing their fitness compared with old *Tet2*-deficient HSCs in vitro, although whether this approach can abrogate *Tet2*-deficient HSPC expansion in vivo is unknown (83). Notably, others have suggested implementing reverse transcriptase inhibitors as rejuvenating treatments to correct aberrant expression of repetitive elements as well (148).

Finally, impaired glucose metabolism (122) and hyperglycemia are known features of inflammaging, and introduction of *Tet2* mutations into hyperglycemic *Ins2*$^{Akita/+}$ mice triggered age-dependent increases in mortality, hyperactive inflammation, and progression to an MPN/AML phenotype (68), demonstrating key links between inflammation and aging-associated metabolic phenotypes that may promote CHIP. Moreover, the preferential expansion of mutant *Asxl1* HSCs in aged mice also relied on a cell-intrinsic mechanism involving Akt/mTOR activation (149), which can regulate multiple cellular metabolic pathways (150). However, as in the case of *Tet2*-deficient HSPC expansion described above (69), selection was only evident several months after induction. Furthermore, this process may be partially driven by attenuated responses to inflammatory factors in *Asxl1* mutant HSPCs, as shown in zebrafish models (151). In addition to aging-dependent cell-intrinsic and -extrinsic changes, mutant clone evolution due to secondary genetic and epigenetic events could augment their fitness. *Tet2*-deficient differentiated cells expressed higher levels of inflammatory cytokines, such as IL-6 (152) and IL-1 (153, 154), suggesting that *Tet2*-mutant cells can alter the microenvironment to fuel their own expansion in a positive feedback loop (Figure 2). Disentangling these effects from those derived from aging will require careful experimental design.

Conclusions and discussion

Here we have consolidated seminal and recent works that shape our current understanding of CHIP development and progression as a product of cell competition, in which changes in the BM niche dictate genotype-dependent HSC fitness (155). However, as we have alluded to throughout our discussion, much work is still needed to rigorously characterize driving factors of CHIP.

While novel analysis of MPN patient sequencing data reveals crucial insight into the potential origins of CHIP mutations (33), it is unknown which, if any, CHIP mutations occur during fetal development. However, as we and others (155) have pointed out,
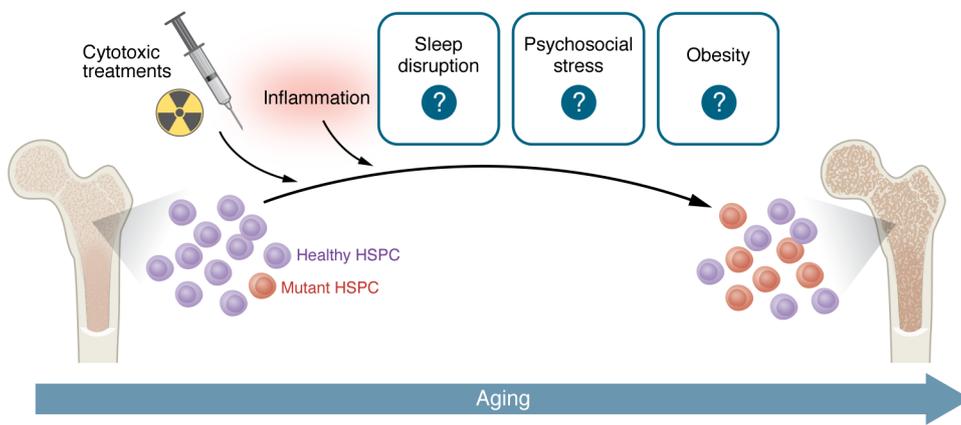
Figure 3. Summary. Aging is a known driver of CHIP. Recent work has further cemented our mechanistic understanding of genotoxic insults and inflammation as drivers of mutant HSPC expansion. However, how lifestyle factors, such as circadian rhythm disruption, psychosocial stress, and dietary/exercise habits, contribute to CHIP progression or development remains largely unknown. These factors constitute likely areas for future investigation, from both the standpoint of clinical intervention and from the basic science standpoint of establishing mechanistic understanding of somatic evolution of the BM and other tissues with age.

the occurrence of the mutation may matter less than the changing microenvironment that dictates clonal fitness. Many studies have elucidated key mechanisms driving mutant HSPC expansion, including cytotoxic stress, inflammation, and aging. Of note, recent murine studies have demonstrated inflammaging as a clear driver of *Tet2*-deficient HSPC expansion. These studies also paint an interesting picture, echoed among other CHIP models, in which mutant HSPCs that selectively expand under inflammatory conditions can promote an inflammatory state via overproduction of dysregulated, hyperinflammatory myeloid progeny (Figure 2). This feed-forward pattern may be a mechanistic basis for CHIP and/or its progression to malignancy in some individuals (156). Moreover, lifestyle factors, such as circadian rhythm disruption, poor diet, and lack of exercise, can have profound impacts on normal hematopoiesis (13, 68, 108, 109, 111, 115, 131, 157), with a common role for increasing systemic inflammation. However, there are few studies that directly investigate how social stress affects the hematopoietic system and no studies that have investigated social stressors as a driver of CHIP. While clinical data and current clinical trials have revealed novel associations between some lifestyle factors and CHIP incidence (110, 114, 123), whether and how these lifestyle factors contribute to CHIP remain unknown (Figure 3).

Most of the studies discussed here are limited to "paradigmatic" CHIP mutations such as *TET2* or *DNMT3A*, whereas mechanisms promoting clonal selection for other mutations remain somewhat understudied. For instance, mutations in the SFs *SF3B1*, *SRSF2*, and *U2AF1* perturb hematopoiesis via several mechanisms, including myeloid skewing, impairment of the DDR, and exacerbated inflammatory responses (158–160). However, the extent to which these mechanisms contribute to selection remains unknown. This lack of information creates potential hazards in drawing inductive conclusions from limited data sets regarding the mechanism(s) driving selection for different CHIP mutations. CHIP mutations are often segregated into low-risk (*DNMT3A*, *TET2*, *ASXL1*) and high-risk (*SRSF2*, *SF3B1*, *JAK2*,

RUNX1, *IDH2*, *TP53*) groups, where risk is defined as having increased incidence of myeloid neoplasms (161). However, while *TET2* may be considered low risk with respect to myeloid malignancy, it is high risk in the context of atherosclerosis (14, 162). These data suggest there are likely unique courses of somatic evolution for each mutation, which in turn may exacerbate specific clinical risks. Thus, determining the extent to which a changing BM niche (Figure 1) or activity of inflammatory feed-forward loops (Figure 2) favors one mutation or another will require tailored studies. For many of these mutations, further investigation is needed to evaluate whether CHIP-promoting conditions differ from those that result in a downstream disease phenotype (MDS/AML/CVD).

Finally, although the studies reviewed here highlight the independent impacts of selective factors such as inflammation or altered BM niche composition and function, an integrated view of how various contexts (old age, lifestyles, and exposures) alter the BM niche to differentially influence the fate/fitness of mutant HSPCs that confer different risks for malignant progression will be key to designing interventions that limit these risks. Unraveling these interactions will provide a more nuanced understanding of the mechanisms governing the clonal odyssey in the BM niche across (potentially) a lifetime.

Author contributions

WES, BH, JD, and EMP conceived the project. WES, BH, and MDD wrote the original draft of the manuscript. WES, BH, MDD, JD, and EMP reviewed and edited the manuscript. JD and EMP supervised the project. Order of co–first authors was determined by the senior role of WES in developing the manuscript outline.

Acknowledgments

Address correspondence to: Eric M. Pietras, University of Colorado Anschutz Medical Campus, Mailstop B130, Aurora, Colorado 80045, USA. Phone: 303.724.9657; Email: eric.pietras@cuanschutz.edu. Or to: James DeGregori, University of Colorado Anschutz Medical Campus, Mailstop 8101, Aurora, Colorado 80045, USA. Phone: 303.724.3230; Email: james.degregori@cuanschutz.edu.

1. Kessler MD, et al. Common and rare variant associations with clonal haematopoiesis phenotypes. *Nature*. 2022;612(7939):301–309.

2. Bick AG, et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature*. 2020;586(7831):763–768.

3. Fabre MA, et al. The longitudinal dynamics and natural history of clonal haematopoiesis. *Nature*. 2022;606(7913):335–342.

4. Marnell CS, et al. Clonal hematopoiesis of indeterminate potential (CHIP): Linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease. *J Mol Cell Cardiol*. 2021;161:98–105.

5. Steensma DP, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood*. 2015;126(1):9–16.

6. Franch-Expósito S, et al. Associations between cancer predisposition mutations and clonal hematopoiesis in patients with solid tumors. *JCO Precis Oncol*. 2023;7(7):e2300070.

7. Saygin C, et al. Acute lymphoblastic leukemia with myeloid mutations is a high-risk disease associated with clonal hematopoiesis. *Blood Cancer Discov*. 2024;5(3):164–179.

8. Stonestrom AJ, et al. High risk and silent clonal hematopoietic genotypes in patients with non-hematologic cancer. *Blood Adv*. 2024;8(4):846–856.

9. Liu C, et al. Clonal hematopoiesis of indeterminate potential in chronic thromboembolic pulmonary hypertension: a multicenter study. *Hypertension*. 2024;81(2):372–382.

10. Qiu X, et al. Association between clonal hematopoiesis-related gene mutations and unfavorable functional outcome in patients with large-artery atherosclerotic stroke. *Eur J Med Res*. 2023;28(1):599.

11. Wong WJ, et al. Clonal haematopoiesis and risk of chronic liver disease. *Nature*. 2023;616(7958):747–754.

12. Papa V, et al. Translating evidence from clonal hematopoiesis to cardiovascular disease: a systematic review. *J Clin Med*. 2020;9(8):2480.

13. Fuster JJ, et al. TET2-loss-of-function-driven clonal hematopoiesis exacerbates experimental insulin resistance in aging and obesity. *Cell Rep*. 2020;33(4):108326.

14. Jaiswal S, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med*. 2017;377(2):111–121.

15. Rasheed A. Niche regulation of hematopoiesis: the environment is "micro," but the influence is large. *Arterioscler Thromb Vasc Biol*. 2022;42(6):691–699.

16. Schofield R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. *Blood Cells*. 1978;4(1–2):7–25.

17. Gao X, et al. The hematopoietic stem cell niche: from embryo to adult. *Development*. 2018;145(2):dev139691.

18. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. *Nature*. 2014;505(7483):327–334.

19. Peci F, et al. The cellular composition and function of the bone marrow niche after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2022;57(9):1357–1364.

20. Chen JY, et al. Hoxb5 marks long-term haematopoietic stem cells and reveals a homogenous perivascular niche. *Nature*. 2016;530(7589):223–227.

21. Kunisaki Y, et al. Arteriolar niches maintain haematopoietic stem cell quiescence. *Nature*. 2013;502(7473):637–643.

22. Itkin T, et al. Distinct bone marrow blood vessels differentially regulate haematopoiesis. *Nature*. 2016;532(7599):323–328.

23. Acar M, et al. Deep imaging of bone marrow shows non-dividing stem cells are mainly perisinusoidal. *Nature*. 2015;526(7571):126–130.

24. Comazzetto S, et al. Niches that regulate stem cells and hematopoiesis in adult bone marrow. *Dev Cell*. 2021;56(13):1848–1860.

25. Wei Q, Frenette PS. Niches for hematopoietic stem cells and their progeny. *Immunity*. 2018;48(4):632–648.

26. Young AL, et al. Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. *Nat Commun*. 2016;7(1):12484.

27. Boulais PE, Frenette PS. Making sense of hematopoietic stem cell niches. *Blood*. 2015;125(17):2621–2629.

28. Ivanovs A, et al. Highly potent human hematopoietic stem cells first emerge in the intraembryonic aorta-gonad-mesonephros region. *J Exp Med*. 2011;208(12):2417–2427.

29. Patel SH, et al. Lifelong multilineage contribution by embryonic-born blood progenitors. *Nature*. 2022;606(7915):747–753.

30. Beaudin AE, et al. A transient developmental hematopoietic stem cell gives rise to innate-like B and T cells. *Cell Stem Cell*. 2016;19(6):768–783.

31. Ganuza M, et al. Murine foetal liver supports limited detectable expansion of life-long haematopoietic progenitors. *Nat Cell Biol*. 2022;24(10):1475–1486.

32. Chan CKF, et al. Endochondral ossification is required for haematopoietic stem-cell niche formation. *Nature*. 2009;457(7228):490–494.

33. Williams N, et al. Life histories of myeloproliferative neoplasms inferred from phylogenies. *Nature*. 2022;602(7895):162–168.

34. Schuermans A, et al. Birth weight is associated with clonal hematopoiesis of indeterminate potential and cardiovascular outcomes in adulthood. *J Am Heart Assoc*. 2023;12(13):e030220.

35. Florez MA, et al. Clonal hematopoiesis: Mutation-specific adaptation to environmental change. *Cell Stem Cell*. 2022;29(6):882–904.

36. Krisl JC, Doan VP. Chemotherapy and transplantation: the role of immunosuppression in malignancy and a review of antineoplastic agents in solid organ transplant recipients. *Am J Transplant*. 2017;17(8):1974–1991.

37. Khaddour K, et al. Hematopoietic Stem Cell Transplantation. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; May 6, 2023.

38. Bolton KL, et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. *Nat Genet*. 2020;52(11):1219–1226.

39. Wong TN, et al. Cellular stressors contribute to the expansion of hematopoietic clones of varying leukemic potential. *Nat Commun*. 2018;9(1):455.

40. Mohrin M, et al. Hematopoietic stem cell quiescence promotes error-prone DNA repair and mutagenesis. *Cell Stem Cell*. 2010;7(2):174–185.

41. Stoddart A, et al. Cytotoxic therapy-induced effects on both hematopoietic and marrow stromal cells promotes therapy-related myeloid neoplasms. *Blood Cancer Discov*. 2020;1(1):32–47.

42. Shao L, et al. Hematopoietic stem cell senescence and cancer therapy-induced long-term bone marrow injury. *Transl Cancer Res*. 2013;2(5):397–411.

43. Wong TN, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. *Nature*. 2015;518(7540):552–555.

44. Ok CY, et al. TP53 mutation characteristics in therapy-related myelodysplastic syndromes and acute myeloid leukemia is similar to de novo diseases. *J Hematol Oncol*. 2015;8(1):45.

45. Coombs CC, 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(3):374–382.

46. Sano S, et al. TP53-mediated therapy-related clonal hematopoiesis contributes to doxorubicin-induced cardiomyopathy by augmenting a neutrophil-mediated cytotoxic response. *JCI Insight*. 2021;6(13):e146076.

47. Marusyk A, et al. Irradiation selects for p53-deficient hematopoietic progenitors. *PLoS Biol*. 2010;8(3):e1000324.

48. Lotem J, Sachs L. Hematopoietic cells from mice deficient in wild-type p53 are more resistant to induction of apoptosis by some agents. *Blood*. 1993;82(4):1092–1096.

49. Bondar T, Medzhitov R. p53-mediated hematopoietic stem and progenitor cell competition. *Cell Stem Cell*. 2010;6(4):309–322.

50. Wu W-S, et al. Slug antagonizes p53-mediated apoptosis of hematopoietic progenitors by repressing puma. *Cell*. 2005;123(4):641–653.

51. Liu Y, et al. p53 regulates hematopoietic stem cell quiescence. *Cell Stem Cell*. 2009;4(1):37–48.

52. Hsu JI, et al. PPM1D mutations drive clonal hematopoiesis in response to cytotoxic chemotherapy. *Cell Stem Cell*. 2018;23(5):700–713.

53. Kim B, et al. Somatic mosaic truncating mutations of PPM1D in blood can result from expansion of a mutant clone under selective pressure of chemotherapy. *PLoS One*. 2019;14(6):e0217521.

54. Kahn JD, et al. *PPM1D*-truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. *Blood*. 2018;132(11):1095–1105.

55. Fiscella M, et al. Wip1, a novel human protein phosphatase that is induced in response to ionizing radiation in a p53-dependent manner. *Proc Natl Acad Sci U S A*. 1997;94(12):6048–6053.

56. Lu X, et al. The type 2C phosphatase Wip1: an oncogenic regulator of tumor suppressor and DNA damage response pathways. *Cancer Metastasis Rev*. 2008;27(2):123–135.

57. Miller PG, et al. PPM1D modulates hematopoietic cell fitness and response to DNA damage and is a therapeutic target in myeloid malignancy. *Blood*. 2023;142(24):2079–2091.

58. Buroczziova M, et al. Ppm1d truncating mutations promote the development of genotoxic stress-induced AML. *Leukemia*. 2023;37(11):2209–2220.

59. Lucas D, et al. Chemotherapy-induced bone marrow nerve injury impairs hematopoietic regeneration. *Nat Med*. 2013;19(6):695–703.

60. Dinarello CA. Immunological and inflammatory

functions of the interleukin-1 family. *Annu Rev Immunol*. 2009;27(1):519–550.

61. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunol Rev*. 2018;281(1):8–27.

62. Pietras EM. Inflammation: a key regulator of hematopoietic stem cell fate in health and disease. *Blood*. 2017;130(15):1693–1698.

63. Caiado F, et al. Inflammation as a regulator of hematopoietic stem cell function in disease, aging, and clonal selection. *J Exp Med*. 2021;218(7):e20201541.

64. Takizawa H, et al. Demand-adapted regulation of early hematopoiesis in infection and inflammation. *Blood*. 2012;119(13):2991–3002.

65. Li J, et al. Chronic inflammation can transform the fate of normal and mutant hematopoietic stem cells. *Exp Hematol*. 2023;127:8–13.

66. Abegunde SO, et al. An inflammatory environment containing TNFα favors Tet2-mutant clonal hematopoiesis. *Exp Hematol*. 2018;59:60–65.

67. Cai Z, et al. Inhibition of inflammatory signaling in Tet2 mutant preleukemic cells mitigates stress-induced abnormalities and clonal hematopoiesis. *Cell Stem Cell*. 2018;23(6):833–849.

68. Cai Z, et al. Hyperglycemia cooperates with *Tet2* heterozygosity to induce leukemia driven by proinflammatory cytokine–induced lncRNA *Morrbid*. *J Clin Invest*. 2021;131(1):e140707.

69. Caiado F, et al. Aging drives Tet2+/- clonal hematopoiesis via IL-1 signaling. *Blood*. 2023;141(8):886–903.

70. McClatchy J, et al. Clonal hematopoiesis related TET2 loss-of-function impedes IL1β-mediated epigenetic reprogramming in hematopoietic stem and progenitor cells. *Nat Commun*. 2023;14(1):8102.

71. Burns SS, et al. Il-1r1 drives leukemogenesis induced by Tet2 loss. *Leukemia*. 2022;36(10):2531–2534.

72. Higa KC, et al. Chronic interleukin-1 exposure triggers selection for Cebpa-knockout multipotent hematopoietic progenitors. *J Exp Med*. 2021;218(6):e20200560.

73. Matatall KA, et al. Chronic infection depletes hematopoietic stem cells through stress-induced terminal differentiation. *Cell Rep*. 2016;17(10):2584–2595.

74. Ostrander EL, et al. Divergent effects of Dnmt3a and Tet2 mutations on hematopoietic progenitor cell fitness. *Stem Cell Reports*. 2020;14(4):551–560.

75. Jeong M, et al. Loss of Dnmt3a immortalizes hematopoietic stem cells in vivo. *Cell Rep*. 2018;23(1):1–10.

76. Hormaechea-Agulla D, et al. Chronic infection drives Dnmt3a-loss-of-function clonal hematopoiesis via IFNγ signaling. *Cell Stem Cell*. 2021;28(8):1428–1442.

77. SanMiguel JM, et al. Distinct tumor necrosis factor alpha receptors dictate stem cell fitness versus lineage output in Dnmt3a-mutant clonal hematopoiesis. *Cancer Discov*. 2022;12(12):2763–2773.

78. Kunimoto H, Nakajima H. TET2: A cornerstone in normal and malignant hematopoiesis. *Cancer Sci*. 2021;112(1):31–40.

79. Huerga Encabo H, et al. Loss of TET2 in human hematopoietic stem cells alters the development and function of neutrophils. *Cell Stem Cell*.

2023;30(6):781–799.

80. Li J, et al. Role of Tet2 in regulating adaptive and innate immunity. *Front Cell Dev Biol*. 2021;9:665897.

81. Lee Y-S, et al. Microbiota-derived lactate promotes hematopoiesis and erythropoiesis by inducing stem cell factor production from leptin receptor+ niche cells. *Exp Mol Med*. 2021;53(9):1319–1331.

82. Kwak H-J, et al. Myeloid cell-derived reactive oxygen species externally regulate the proliferation of myeloid progenitors in emergency granulopoiesis. *Immunity*. 2015;42(1):159–171.

83. Hong T, et al. TET2 modulates spatial relocalization of heterochromatin in aged hematopoietic stem and progenitor cells. *Nat Aging*. 2023;3(11):1387–1400.

84. Kent DG, et al. Self-renewal of single mouse hematopoietic stem cells is reduced by JAK2V617F without compromising progenitor cell expansion. *PLoS Biol*. 2013;11(6):e1001576.

85. Stetka J, et al. Addiction to DUSP1 protects JAK2V617F-driven polycythemia vera progenitors against inflammatory stress and DNA damage, allowing chronic proliferation. *Oncogene*. 2019;38(28):5627–5642.

86. Rai S, et al. IL-1β promotes MPN disease initiation by favoring early clonal expansion of JAK2-mutant hematopoietic stem cells. *Blood Adv*. 2024;8(5):1234–1249.

87. Arranz L, et al. Neuropathy of haematopoietic stem cell niche is essential for myeloproliferative neoplasms. *Nature*. 2014;512(7512):78–81.

88. Tefferi A, et al. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *J Clin Oncol*. 2011;29(10):1356–1363.

89. Kralovics R, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med*. 2005;352(17):1779–1790.

90. Heaton WL, et al. Autocrine Tnf signaling favors malignant cells in myelofibrosis in a Tnfr2-dependent fashion. *Leukemia*. 2018;32(11):2399–2411.

91. Svensson EC, et al. TET2-driven clonal hematopoiesis and response to canakinumab: an exploratory analysis of the CANTOS randomized clinical trial. *JAMA Cardiol*. 2022;7(5):521–528.

92. Woo J, et al. Effects of IL-1β inhibition on anemia and clonal hematopoiesis in the randomized CANTOS trial. *Blood Adv*. 2023;7(24):7471–7484.

93. Fox DA. Cytokine blockade as a new strategy to treat rheumatoid arthritis: inhibition of tumor necrosis factor. *Arch Intern Med*. 2000;160(4):437–444.

94. Jarlborg M, Gabay C. Systemic effects of IL-6 blockade in rheumatoid arthritis beyond the joints. *Cytokine*. 2022;149:155742.

95. Ridker PM, et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390(10105):1833–1842.

96. Dhabhar FS. The short-term stress response – mother nature's mechanism for enhancing protection and performance under conditions of threat, challenge, and opportunity. *Front Neuroendocrinol*. 2018;49:175–192.

97. Dhabhar FS. A hassle a day may keep the pathogens away: The fight-or-flight stress response and the augmentation of immune function. *Integr Comp Biol*. 2009;49(3):215–236.

98. Cohen S, et al. Psychological stress and disease. *JAMA*. 2007;298(14):1685–1687.

99. McKim DB, et al. Social stress mobilizes hematopoietic stem cells to establish persistent splenic myelopoiesis. *Cell Rep*. 2018;25(9):2552–2562.

100. Stevens RG, et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med*. 2011;68(2):154–162.

101. Zhang Y, et al. Rotating nightshift work and hematopoietic cancer risk in US female nurses. *JNCI Cancer Spectr*. 2020;4(2):pkz106.

102. Torquati L, et al. Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose-response relationship. *Scand J Work Environ Health*. 2018;44(3):229–238.

103. Stenzinger M, et al. Hematopoietic-extrinsic cues dictate circadian redistribution of mature and immature hematopoietic cells in blood and spleen. *Cells*. 2019;8(9):1033.

104. Méndez-Ferrer S, et al. Circadian rhythms influence hematopoietic stem cells. *Curr Opin Hematol*. 2009;16(4):235–242.

105. Méndez-Ferrer S, et al. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature*. 2008;452(7186):442–447.

106. García-García A, et al. Dual cholinergic signals regulate daily migration of hematopoietic stem cells and leukocytes. *Blood*. 2019;133(3):224–236.

107. Golan K, et al. Daily onset of light and darkness differentially controls hematopoietic stem cell differentiation and maintenance. *Cell Stem Cell*. 2018;23(4):572–585.

108. McAlpine CS, et al. Sleep exerts lasting effects on hematopoietic stem cell function and diversity. *J Exp Med*. 2022;219(11):e20220081.

109. Sang D, et al. Prolonged sleep deprivation induces a cytokine-storm-like syndrome in mammals. *Cell*. 2023;186(25):5500–5516.

110. Shang H, et al. A longitudinal study of sleep habits and leukemia incidence among postmenopausal women. *Am J Epidemiol*. 2023;192(8):1315–1325.

111. Casanova-Acebes M, et al. Rhythmic modulation of the hematopoietic niche through neutrophil clearance. *Cell*. 2013;153(5):1025–1035.

112. McAlpine CS, et al. Sleep modulates haematopoiesis and protects against atherosclerosis. *Nature*. 2019;566(7744):383–387.

113. Heyde A, et al. Increased stem cell proliferation in atherosclerosis accelerates clonal hematopoiesis. *Cell*. 2021;184(5):1348–1361.

114. Bhattacharya R, et al. Association of diet quality with prevalence of clonal hematopoiesis and adverse cardiovascular events. *JAMA Cardiol*. 2021;6(9):1069–1077.

115. Pasupuleti SK, et al. Obesity-induced inflammation exacerbates clonal hematopoiesis. *J Clin Invest*. 2023;133(11):e163968.

116. Schwartz LS, et al. Transcriptional and functional consequences of Oncostatin M signaling on young Dnmt3a-mutant hematopoietic stem cells. *Exp Hematol*. 2023;130:104131.

117. Duan Y, et al. Inflammatory links between high fat diets and diseases. *Front Immunol*. 2018;9:2649.

118. Kim K-A, et al. High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. *PLoS One*. 2012;7(10):e47713.

119. Laurans L, et al. An obesogenic diet increases atherosclerosis through promoting microbiota dysbiosis-induced gut lymphocyte trafficking into the periphery. *Cell Rep*. 2023;42(11):113350.

120. Tang D, et al. Dietary restriction improves repopulation but impairs lymphoid differentiation capacity of hematopoietic stem cells in early aging. *J Exp Med*. 2016;213(4):535–553.

121. Young K, et al. Decline in IGF1 in the bone marrow microenvironment initiates hematopoietic stem cell aging. *Cell Stem Cell*. 2021;28(8):1473–1482.

122. Dellorusso PV, et al. Autophagy counters inflammation-driven glycolytic impairment in aging hematopoietic stem cells [preprint]. https://doi.org/10.1101/2023.08.17.553736. Posted on bioRxiv August 19, 2023.

123. Haring B, et al. Healthy lifestyle and clonal hematopoiesis of indeterminate potential: results from the Women's Health Initiative. *J Am Heart Assoc*. 2021;10(5):e018789.

124. Collins N, et al. The bone marrow protects and optimizes immunological memory during dietary restriction. *Cell*. 2019;178(5):1088–1101.

125. Porto ML, et al. Reactive oxygen species contribute to dysfunction of bone marrow hematopoietic stem cells in aged C57BL/6 J mice. *J Biomed Sci*. 2015;22(1):97.

126. Ludin A, et al. Reactive oxygen species regulate hematopoietic stem cell self-renewal, migration and development, as well as their bone marrow microenvironment. *Antioxid Redox Signal*. 2014;21(11):1605–1619.

127. Zhang Y, et al. CXCR4/CXCL12 axis counteracts hematopoietic stem cell exhaustion through selective protection against oxidative stress. *Sci Rep*. 2016;6(1):37827.

128. Swift DL, et al. The role of exercise and physical activity in weight loss and maintenance. *Prog Cardiovasc Dis*. 2014;56(4):441–447.

129. Warburton DER, et al. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801–809.

130. Stanford KI, Goodyear LJ. Exercise regulation of adipose tissue. *Adipocyte*. 2016;5(2):153–162.

131. Frodermann V, et al. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nat Med*. 2019;25(11):1761–1771.

132. Sarachakov A, et al. Spatial mapping of human hematopoiesis at single cell resolution reveals aging-associated topographic remodeling. *Blood*. 2023;142(26):2282–2295.

133. Shi Z, et al. Exercise promotes bone marrow microenvironment by inhibiting adipsin in diet-induced male obese mice. *Nutrients*. 2022;15(1):19.

134. Marusyk A, DeGregori J. Declining cellular fitness with age promotes cancer initiation by selecting for adaptive oncogenic mutations. *Biochim Biophys Acta*. 2008;1785(1):1–11.

135. Ganguly P, et al. Age-related changes in bone marrow mesenchymal stromal cells: a potential impact on osteoporosis and osteoarthritis development. *Cell Transplant*. 2017;26(9):1520–1529.

136. Bernitz JM, et al. Hematopoietic stem cells count and remember self-renewal divisions. *Cell*. 2016;167(5):1296–1309.

137. Beerman I, et al. Quiescent hematopoietic stem cells accumulate DNA damage during aging that is repaired upon entry into cell cycle. *Cell Stem Cell*. 2014;15(1):37–50.

138. Flach J, et al. Replication stress is a potent driver of functional decline in ageing haematopoietic stem cells. *Nature*. 2014;512(7513):198–202.

139. Marinkovic M, et al. Matrix-bound Cyr61/CCN1 is required to retain the properties of the bone marrow mesenchymal stem cell niche but is depleted with aging. *Matrix Biol*. 2022;111:108–132.

140. Ramalingam P, et al. Restoring bone marrow niche function rejuvenates aged hematopoietic stem cells by reactivating the DNA Damage Response. *Nat Commun*. 2023;14(1):2018.

141. Nakashima K, et al. POT1a deficiency in mesenchymal niches perturbs B-lymphopoiesis. *Commun Biol*. 2023;6(1):996.

142. Mitchell CA, et al. Stromal niche inflammation mediated by IL-1 signalling is a targetable driver of haematopoietic ageing. *Nat Cell Biol*. 2023;25(1):30–41.

143. Ravalet N, et al. Modulation of bone marrow and peripheral blood cytokine levels by age and clonal hematopoiesis in healthy individuals. *Clin Immunol*. 2023;255:109730.

144. Franceschi C, et al. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol*. 2018;14(10):576–590.

145. Liao M, et al. Aging-elevated inflammation promotes DNMT3A R878H-driven clonal hematopoiesis. *Acta Pharm Sin B*. 2022;12(2):678–691.

146. Kovtonyuk LV, et al. IL-1 mediates microbiome-induced inflammaging of hematopoietic stem cells in mice. *Blood*. 2022;139(1):44–58.

147. Mejia-Ramirez E, Florian MC. Understanding intrinsic hematopoietic stem cell aging. *Haematologica*. 2020;105(1):22–37.

148. Brochard T, et al. Repurposing nucleoside reverse transcriptase inhibitors (NRTIs) to slow aging. *Ageing Res Rev*. 2023;92:102132.

149. Fujino T, et al. Mutant ASXL1 induces age-related expansion of phenotypic hematopoietic stem cells through activation of Akt/mTOR pathway. *Nat Commun*. 2021;12(1):1826.

150. Szwed A, et al. Regulation and metabolic functions of mTORC1 and mTORC2. *Physiol Rev*. 2021;101(3):1371–1426.

151. Avagyan S, et al. Resistance to inflammation underlies enhanced fitness in clonal hematopoiesis. *Science*. 2021;374(6568):768–772.

152. Zhang Q, et al. Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. *Nature*. 2015;525(7569):389–393.

153. Sano S, et al. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1β/NLRP3 inflammasome. *J Am Coll Cardiol*. 2018;71(8):875–886.

154. Shin T-H, et al. A macaque clonal hematopoiesis model demonstrates expansion of TET2-disrupted clones and utility for testing interventions. *Blood*. 2022;140(16):1774–1789.

155. King KY, et al. Environmental influences on clonal hematopoiesis. *Exp Hematol*. 2020;83:66–73.

156. Burocziova M, et al. Chronic inflammation promotes cancer progression as a second hit. *Exp Hematol*. 2023;128:30–37.

157. Emmons R, et al. Effects of obesity and exercise on bone marrow progenitor cells after radiation. *Med Sci Sports Exerc*. 2019;51(6):1126–1136.

158. Gurule NJ, et al. Myelodysplastic neoplasm-associated U2AF1 mutations induce host defense defects by compromising neutrophil chemotaxis. *Leukemia*. 2023;37(10):2115–2124.

159. Kim SP, et al. Mutant U2AF1-induced alternative splicing of H2afy (macroH2A1) regulates B-lymphopoiesis in mice. *Cell Rep*. 2021;36(9):109626.

160. Ilagan JO, et al. U2AF1 mutations alter splice site recognition in hematological malignancies. *Genome Res*. 2015;25(1):14–26.

161. Weeks LD, et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. *NEJM Evid*. 2023;2(5):10.1056/evidoa2200310.

162. Abelson S, et al. Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature*. 2018;559(7714):400–404.

163. Chen S, et al. Mutant p53 drives clonal hematopoiesis through modulating epigenetic pathway. *Nat Commun*. 2019;10(1):5649.

164. Yura Y, et al. The cancer therapy-related clonal hematopoiesis driver gene *Ppm1d* promotes inflammation and non-ischemic heart failure in mice. *Circ Res*. 2021;129(6):684–698.

165. Rotunno G, et al. Epidemiology and clinical relevance of mutations in postpolycythemia vera and postessential thrombocythemia myelofibrosis: a study on 359 patients of the AGIMM group. *Am J Hematol*. 2016;91(7):681–686.

166. Agrawal M, et al. TET2-mutant clonal hematopoiesis and risk of gout. *Blood*. 2022;140(10):1094–1103.

167. Graubert TA, et al. Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. *Nat Genet*. 2012;44(1):53–57.

168. Xu JJ, et al. Genome-wide screening identifies cell-cycle control as a synthetic lethal pathway with SRSF2P95H mutation. *Blood Adv*. 2022;6(7):2092–2106.

169. Shirai CL, et al. Mutant U2AF1 expression alters hematopoiesis and pre-mRNA splicing in vivo. *Cancer Cell*. 2015;27(5):631–643.

170. Grockowiak E, et al. Different niches for stem cells carrying the same oncogenic driver affect pathogenesis and therapy response in myeloproliferative neoplasms. *Nat Cancer*. 2023;4(8):1193–1209.