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Clonal hematopoiesis driver mutations: molecular mechanisms and clinical implications - inclusive fitness of pre-leukemic hematopoietic stem and progenitor cells through pro-inflammatory features of their progeny

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Abstract

Clonal hematopoiesis (CH) is driven by the age-associated expansion of hematopoietic stem and progenitor cells (HSPCs) that harbor somatic driver mutations; however, the mechanisms underlying their long-term persistence remain incompletely understood. This review frames CH through the lens of inclusive fitness, proposing that mutant pre-leukemic HSPCs enhance their evolutionary success not only through intrinsic self-renewal advantages, but also via indirect effects mediated by their differentiated progeny. We synthesize evidence showing that mutant immune cells promote inflammatory microenvironments that selectively impair wild-type HSCs while reinforcing mutant self-renewal, establishing self-sustaining feedback loops that shape clonal dynamics and systemic disease risk.

Introduction

Long-lived cells inevitably accumulate somatic mutations over time, and counterintuitively, non-replicating cells can accrue more mutations than proliferating ones; for example, cardiomyocytes harbor substantially more somatic single-nucleotide variants than lymphocytes[1]. However, clonal expansion, defined as the proliferation of a single cell into a large population of daughter cells, can only occur in replicating cells and may result from either positive selection or genetic drift. Accordingly, clonal expansions are expected in most renewing human tissues[2]. In this review, we aim to describe the various attributes of clonal hematopoiesis (CH) using terms from evolutionary sciences, with a particular focus on inclusive fitness.

Selection versus drift in clonal hematopoiesis

In clonal hematopoiesis (CH), while some observations are compatible with genetic drift, most evidence suggests that positive selection is the dominant force shaping the somatic evolution of the aging blood system. Drift may occur in the context of a decreased effective population size of hematopoietic stem cells (HSCs). Examples for such occurrences include aplastic anemia, where autoimmunity drastically depletes HSCs, or the small HSC population sizes early in embryogenesis, which could similarly enable stochastic fixation of rare variants to high variant allele frequency (VAF). Evidence for such genetic drift comes from CH cases, which lack recurrent driver mutations and may involve unknown, non-recurrent events[3–5]. Aging is also associated with reduced HSC clonal diversity (reduced effective population size)[6], which may allow fixation of mutations without a fitness advantage. In one extreme example of such clonal restriction, researchers have documented mutational patterns in a single supercentenarian and demonstrated that most blood cells were the descendants of two major clones, which carried somatic mutations that were not predicted to have a functional selective advantage carrying [7]. An alternative explanation for the non-recurrent mutations can be that we still do not understand the selective advantage of many variants and thus term these cases drift by mistake[3]. If one considers all non-recurrent events, as cases of CH the prevalence of clones at more than 1% variant allele fraction (VAF) is universal after age 70, not 10–20% prevalent as previously estimated[3]. The debate between drift and positive selection in CH remains unsettled; however, it remains highly clinically important, as non-recurrent events most probably do not lead to leukemia, but can lead to other pathologies.

Nevertheless, the probability of drift-driven expansion in hematopoiesis is low. The effective population size of HSCs is estimated at ~10,000-100,000 cells[8] and is even larger for downstream progenitors, making stochastic fixation rare among young individuals. Moreover, with age, recurrent mutations in a limited set of genes arise in multiple individuals within the same hematopoietic cell type - i.e. the phenomenon of CH. The extremely low likelihood of these mutations arising independently in multiple individuals strongly indicates that positive selection drives their recurrent occurrence. The observation that identical somatic mutations can be detected across multiple hematopoietic lineages (both myeloid and lymphoid), including both HSCs and mature cells[9], provides evidence that positive selection acts at the level of HSCs. In contrast, observations where variant allele frequencies (VAF) of CH mutations are greater in mature blood cells than in HSCs suggest that positive selection may also act within more differentiated cell compartments. However, clear evidence to support such a claim is still lacking. Overall, most CH cases are likely driven by positive selection operating, at least in part, at the HSC level, resulting in the generation of pre-leukemic hematopoietic stem cells (preL-HSCs)[10,11].

The incomplete penetrance of CH-related mutations and the transformation to leukemia

While not all pre-L-HSPCs will evolve into leukemia during an individual's lifetime, they have a higher potential for such evolution compared to WT HSCs and are therefore termed pre-L-HSPCs here. The incomplete penetrance of CH-related mutations (some progress to leukemia while others do not) remains largely enigmatic. It is suggested here that the mechanisms of somatic incomplete penetrance will adhere to similar mechanisms in germline-related diseases[12]. One exception will be the age at which the somatic mutation appeared, which might be relevant for somatic incomplete penetrance and not in the germline. While this subject will not be discussed in depth in this review, it is essential to recognize that genotype-phenotype correlations result from the sum of risk alleles and protective alleles and their interplay with variable environments, ultimately determining the phenotype. All such variants can occur at the germline or somatic level. An example of a protective germline variant was recently discovered (in the gene *TCL1A*)[13]. Whether CH develops into leukemia depends on complex evolutionary pressures within blood cells, including the timing of when mutations occur, how cells compete

with each other, and whether protective mechanisms can keep dangerous clones in check. A comprehensive understanding of such clonal dynamics remains to be elucidated.

Clonal dynamics of preL-HSPCs

Clonal dynamics within HSCs provide insights into hematopoietic regeneration and hematological disease development. Advances in sequencing have revealed that mutations driving clonal dominance can emerge early in life and expand gradually over decades[14]. Most clones begin their expansion before the age of 40[3]. This implies that most pre-L-HSPCs spread very slowly, due to a small selective advantage. Outlawyers to this paradigm are the spliceosome mutations in *SRSF2, SF3B1,* and *U2AF1,* which appear most probably at older age[15] and have one of the highest fitness effect scores[11]. Wagner et.al recently calculated the doubling time of preL-HSPCs[16]. They assumed that a human stem cell pool consists of 10,000 (or 100,000) cells, and that a detectable clone will make up 1% of that population. Further assumptions were that this expansion starts from a single mutated cell and takes about 60 years; the doubling time of the relative clone size is estimated to be around 9 years (10,000 HSCs) or 6 years (100 HSCs). This compares well to the clonal growth rates estimated for CH clones in the order of around 10% per year[17,18]. However, most of the current clonal dynamics studies rely on short-term monitoring of individuals with CH using whole exome/genome sequencing approaches [16]. Such studies will face challenges in tracking slowly expanding clones. Extended follow-up periods and improved measurement precision are needed to accurately assess clonal dynamics in clinical and therapeutic contexts[16]. As many aspects of the clonal dynamics of CH have been reviewed extensively, the current review will focus on a specific aspect of CH evolutionary landscape: how preL-HSCs actively shape the environment to promote their own expansion through the influence of their progeny.

Inclusive fitness in CH

The concept of inclusive fitness was first formulated by W.D. Hamilton in 1964[19]. Inclusive fitness comprises both direct fitness (gains from an individual's own reproduction) and indirect fitness (gains via benefits to related individuals). An illustrative example of inclusive fitness is

the extended post-reproductive lifespan of female killer whales, which enhances the survival of offspring -especially older males- thereby increasing the mother's inclusive fitness[20–22].

To be able to apply the design principles of inclusive fitness to the case of CH, the following should be proved: 1) evidence for direct fitness, which was discussed and proved in previous sections of this review, 2) evidence for indirect fitness contributed by the preL-HSPCs progeny, namely mature cells. Here, it is proposed that mutated mature blood cells (from the preL-HSC progeny) can create a microenvironment that favors the self-renewal and persistence of the ancestral preL-HSCs. Such indirect effects can occur in two different ways: 1) The mutated mature immune cells/platelets/progenitors can directly modify the microenvironment. Such changes, particularly those altering the bone marrow stroma or immune microenvironment, can further potentiate clonal expansion in hematopoiesis. This subject was recently reviewed by Ngo et.al[23] and Bachrach[24]. 2) The mutated mature immune cells can directly influence other tissues and modify many different diseases (non-hematologic pathologies), as was also recently reviewed[25]. The disease influenced by CH can, in turn, foster further expansion of the preL-HSPCs. The first evidence for such possible inclusive fitness arises from the observations that **Inflammation leads to decreased self-renewal and increased differentiation in wild-type HSCs and the opposite effect in CH.** In normal hematopoiesis, HSC self-renewal and differentiation are maintained in equilibrium under both homeostatic and stress conditions. Inflammatory conditions disturb this balance in opposite ways for wild-type (WT) and CH-mutated HSCs: inflammation drives terminal differentiation and loss of self-renewal in WT HSCs[26–31], but enhances self-renewal in mutant HSCs[32,33], biasing toward leukemogenesis. Furthermore, mutant HSC progeny can amplify inflammation through cytokine secretion, influence neighboring stromal and mesenchymal cells, and remodel tissue microenvironments. Collectively, these effects establish a self-reinforcing cycle in which preL-HSPCs generate an inflammatory niche that, in turn, supports their continued expansion. Examples for mechanisms of this self-reinforcing cycle will be the focus of this review.

Inflammation increases self-renewal and decreases differentiation in CH-mutated HSCs INF-γ

In contrast to the inflammatory response of WT HSCs, *M. avium* infection in *DNMT3A* KO mice resulted in increased engraftment at both 2- and 12-months post-infection[34]. Following infection, *DNMT3A* KO HSCs exhibited reduced differentiation and lower apoptosis rates upon secondary stress compared with WT HSCs. As in WT mice, the response was IFN-γ–dependent, as the increased engraftment in *DNMT3A* KO mice was abolished in IFNGR1 KO mice[34]. Notably, infected *DNMT3A* KO mice did not show increased numbers of mature myeloid or lymphoid cells, suggesting a block in differentiation[34]. Of note, in human disease, patients with ulcerative colitis harboring *DNMT3A* mutations displayed elevated serum IFN-γ levels, although causality was not established in this setting[35]. While the exact mechanisms of increased serum IFN-γ could not be determined in this study, one can hypothesize that it is related to the DNMT3A mutations and thus provides the first possible example for inclusive fitness. *DNMT3A* mutant pre-L-HSPCs in ulcerative colitis patients produce mature cells that secrete IFN-γ, which provides a selective advantage to their progenitors (the pre-L-HSPCs). Formal evidence to support such a hypothesis is still needed.

Inflammation increases self-renewal and decreases differentiation in CH-mutated HSCs related to Fatty bone marrow and IL-6

In another example in a mouse model of fatty bone marrow (FBM), an age-associated phenomenon, human and murine *DNMT3A*-mutant preL-HSPCs demonstrated increased self-renewal, an effect exacerbated when the mutant cells were derived from aged mice[36]. BM fluid and adipocytes from FBM mice expressed higher IL-6 levels *in vitro*, and neutralization of IL-6 reduced the selective advantage of *DNMT3A*-mutant preL-HSPCs under FBM conditions. These findings suggest that age-related FBM creates a pro-inflammatory marrow microenvironment which, via IL-6 and potentially other mediators, confers a fitness advantage to *DNMT3A*-mutant preL-HSPCs. Interestingly, SRSF2-mutant HSCs did not gain a similar advantage under FBM conditions[36], highlighting mutation-specific interactions between intrinsic cellular programs and extrinsic inflammatory cues. In this example, IL-6 promoted self-renewal of *DNMT3A*-mutant preL-HSPCs. The evidence for *DNMT3A* mutant-related increased secretion of IL-6 comes from in vitro experiments using lipopolysaccharide (LPS)-stimulated Dnmt3aR878H/+ splenic neutrophils and monocytes, which both release higher amounts of IL-1β, IL-6, and TNF than

their respective Dnmt3a+/+ counterparts[37]. In the same study compared with controls, 10% *Dnmt3a*$^{R878H/+}$BMT mice exhibited significantly increased ligature-induced bone loss[37]. Depletion of Ly6g^{+} neutrophils by anti-Ly6g neutralizing antibodies reversed bone height loss and normalized gingival cytokine expression, implicating DNMT3a-mutant neutrophils as drivers of local inflammatory pathology in periodontitis. In human studies, the amount of marrow fat is associated with bone mineral density (BMD). Several studies have reported a significant negative association between marrow fat content and BMD in both healthy and osteoporotic populations[38]. Altogether, it seems like inclusive fitness might explain all these correlations. *DNMT3A*-mutant preL-HSPCs produce IL-6-secreting monocytes and neutrophils, together with increased osteoclasts, which reduce BMD and increase fatty bone marrow, which further secretes IL-6. The dual contribution of IL-6 from mutant monocyte/neutrophils and from the wild type fatty BM promote *DNMT3A*-mutant preL-HSPCs expansion. Again a formal evidence is neede however such theory is supported by the literature.

Inflammation increases self-renewal and decreases differentiation in CH-mutated HSCs the case of *TET2* and and IL-1β.

In an acute inflammation model using LPS treatment, *TET2* KO mice exhibited expansion of HSCs, hematopoietic stem and progenitor cells (HSPCs; LSK cells), and myeloid progenitors (CMPs)[39]. Whereas LPS reduced the engraftment capacity of WT HSCs, *TET2* KO HSC engraftment was increased. TET2 KO LSK cells exhibited resistance to apoptosis following infection and displayed elevated IL-6 expression. IL-6 activated a Shp2/Stat3/Morrbid mediated pro-survival pathway in both WT and TET2 KO Lin- cells, with enhanced activation in KO mice. In transplantation experiments of other mouse models, in which *TET2* KO cells were transplanted into IL-1β-treated recipients without additional inflammatory stimulation, *TET2* KO cells maintained higher engraftment regardless of treatment, while IL-1β markedly increased myeloid output in both genotypes, with a more pronounced effect in *TET2* KO cells[40]. IL-1β also enhanced the self-renewal capacity of *TET2* KO HSCs in serial colony-forming assays. This studies establish the role of IL-1β in TET2 KO increased self-renewal in order to close the inclusive fitness loop. Evidence is needed for increased secretion of IL-1β by *TET2* KO mature cells.

In an atherosclerotic mouse model, TET2 KO HSCs exhibited higher engraftment than WT HSCs which was associated with increased aortic plaque size[41]. Peritoneal *TET2* KO macrophages from these mice, when stimulated with LPS or IFN-γ, demonstrated increased pro-inflammatory gene expression, including IL-6 and IL-1β. Both IL-1β secretion from macrophages and aortic plaque size were reduced upon pharmacologic inhibition of the NLRP3 inflammasome[41], indicating that under inflammatory stress, TET2-deficient macrophages promote a hyper-inflammatory state through the secretion of IL-1β that exacerbates atherosclerosis. A comparable pattern was observed in a myocardial infarction (MI) model induced by left anterior descending (LAD) artery ligation, where TET2 KO mice developed more severe pathology - including worsened systolic dysfunction, increased fibrosis, and cardiac hypertrophy[42]. Myeloid-specific TET2 deletion reproduced these effects, accompanied by elevated IL-1β, IL-6, CCL5, and SELP expression in cardiac tissue and bone marrow–derived macrophages. Inhibition of the inflammasome rescued the impaired cardiac healing phenotype, highlighting a role for TET2-deficient macrophages, via inflammasome activation, in post-MI pathology. TET2 loss in macrophages also aggravated insulin resistance and hyperglycemia in obese and aged mice[43] through IL-1β. Altogether another inclusive fitness cycle of IL-1β (and other cytokines) secreted from mature TET2 mutant macrophages which can promote TET2 KO increased self-renewal.

Inflammation increases self-renewal in JAK2 mutant PreL-HSPCs

In myeloproliferative neoplasm (MPN) patients, IL-1β and IL-1α expression in granulocytes correlated with $JAK2^{V617F}$ variant allele frequency (VAF)[44]. In a mouse model, the combination of the $JAK2^{V617F}$ mutation along with the deletion of the IL1 receptor (IL1R) reversed multiple disease phenotypes seen in $JAK2^{V617F}$ mice, including peripheral blood count abnormalities, myeloid cell expansion in bone marrow and spleen, elevated HSPC levels, increased colony formation (CFU-GM and CFU-MK), splenomegaly, bone marrow fibrosis, and altered HSC

engraftment[44]. These results indicate that IL-1β contributes to both enhanced self-renewal and clinical features of JAK2V617F-driven MPN, and yet another example of inclusive fitness.

The JAK2^{V617F} VAF also correlated with plasma TNF-α levels in MPN patients[45]. TNF-α supplementation reduced CFU-GM colony formation in healthy CD34+ cells but increased colony output from MPN-derived CD34+ cells. Moreover, TNF-α selectively promoted the expansion of mutant colonies at the expense of WT colonies in MPN-derived CD34+ cells[45].

CH mutant immune cells propagate inflammation by affecting neighboring cells in non-cell autonomous mechanisms

WT monocyte-derived macrophages (MDMs) exposed to conditioned media from *DNMT3A*- or *TET2*-deficient MDMs upregulated interferon signaling without changes in their own *DNMT3A* or *TET2* expression[46]. This indicates that CH-mutant myeloid cells can promote inflammation through both cell-autonomous and non-cell-autonomous mechanisms. Similarly, WT CD34^{+} hematopoietic progenitors from myeloproliferative neoplasm (MPN) patients carrying JAK2^{V617F} were more sensitive to TNF-α-mediated suppression of colony formation compared with WT CD34^{+} cells from individuals without the mutation[45], further supporting the role of CH-mutant cells in modulating the inflammatory environment to influence other hematopoietic populations.

In cardiovascular contexts, cardiac fibroblasts treated with supernatant from DNMT3a-KO monocytes upregulated TGF-β and α-smooth muscle actin (α-SMA), a marker of myofibroblast activation[47]. Similarly, treatment of cardiospheres-a 3D cardiac tissue model-with DNMT3a-KO monocyte supernatant impaired contractile function, suggesting that mutant myeloid cells can influence cardiac remodeling and function via secreted factors.

In summary, mutations in DNMT3a and TET2 in myeloid cells enhance inflammatory signaling and promote secretion of cytokines like IL-1β, IL-6, and TNF-α, which contribute to local and systemic inflammation, influence nearby non-hematopoietic cells, and drive pathological tissue remodeling such as fibrosis and cardiac dysfunction.

Conclusion and future directions

This review synthesizes accumulating evidence that clonal hematopoiesis is shaped not only by cell-intrinsic effects of driver mutations in HSPCs, and their interaction with the environment (classic positive selection), but also by non-cell-autonomous mechanisms mediated by their differentiated progeny (inclusive fitness). Across multiple CH-associated mutations—including DNMT3A, TET2, and JAK2—mutant preL-HSPCs display a selective advantage under inflammatory conditions that suppress wild-type stem cell self-renewal while preserving or enhancing mutant stem cell persistence. At the same time, mature mutant immune cells frequently exhibit hyper-inflammatory phenotypes, driven by pathways such as cytokine signaling and innate immune sensing, which remodel local and systemic environments. Together, these observations support a conceptual framework in which CH mutations increase HSPC fitness both directly and indirectly, aligning with the evolutionary principle of inclusive fitness, whereby progeny contribute to the long-term success of their ancestral clone.

Despite strong circumstantial and mechanistic support, key questions remain unresolved and represent important directions for future research. Foremost among these is the need for direct experimental evidence linking specific mutant progeny populations to sustained advantages at the stem cell level in vivo. Dissecting mutation-specific feedback loops, defining the relative contributions of systemic versus bone marrow–restricted inflammation, and determining how age, tissue context, and comorbid disease modify these interactions will be essential. In parallel, longitudinal human studies integrating clonal dynamics, inflammatory states, and clinical outcomes will be critical to distinguish permissive from causative roles of inflammation in disease evolution. Finally, this framework raises the possibility that selectively targeting inflammatory circuits or progeny-derived signals—rather than mutant HSPCs themselves—may represent a therapeutic strategy to limit clonal expansion while preserving normal hematopoiesis. Understanding when and how such interventions could safely disrupt inclusive-fitness–like feedback loops remains a central challenge for the field.

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