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Environmental Influences on Clonal Hematopoiesis

Katherine Y. King[1,2], **Yun Huang**[3], **Daisuke Nakada**[1,4], **Margaret A. Goodell**[1,2,4,5]

[1]Stem Cells and Regenerative Medicine Center, Baylor College of Medicine

[2]Department of Pediatrics, Section of Infectious Diseases, Baylor College of Medicine

[3]Institute of Biosciences and Technology, Texas A&M University, Houston, Texas

[4]Department of Molecular and Human Genetics, Baylor College of Medicine

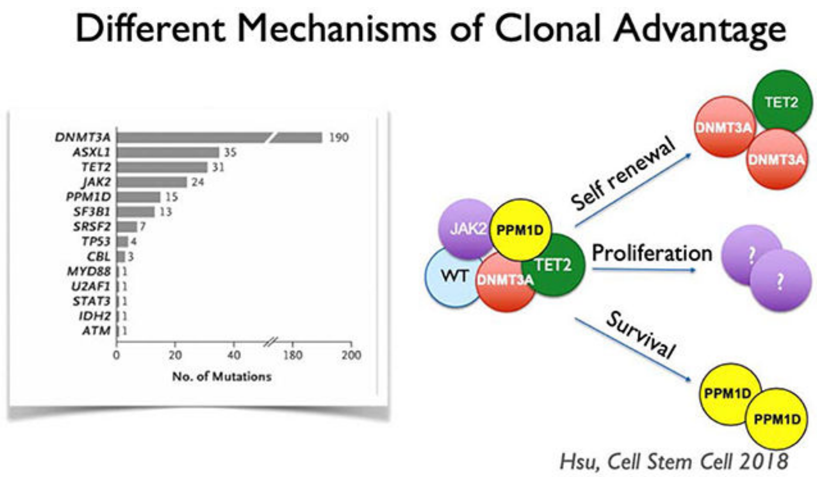
[5]Department of Molecular and Cell Biology, Baylor College of Medicine, Houston, Texas 77030 USA

Abstract

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

Graphical Abstract

Correspondence: Katherine Y. King MD PhD, Associate Professor, Department of Pediatrics, Section of Infectious Diseases, 1102 Bates Street, Houston, TX 77030 USA, (832)824-4330, kyk@bcm.edu.



Introduction

Clonal hematopoiesis (CH) is a condition in which one or a few individual hematopoietic stem cells (HSCs) contribute disproportionately to peripheral blood production (Genovese et al., 2014; Jaiswal et al., 2014; Xie et al., 2014). Not only are individuals with CH at significantly greater risk of developing hematologic malignancies compared to their non-CH counterparts, but importantly they have greater all-cause mortality largely from heart disease and stroke (Jaiswal et al., 2014; Jaiswal et al., 2017). The prevalence of clonal hematopoiesis increases with age and is thought to occur at some level in virtually all people (Young et al., 2016), such that around 20% of individuals above the age of 70 have at least one HSC clone that is contributing to around 20% of their blood and that fraction increases steadily in each decade of life (Genovese et al., 2014; Jaiswal et al., 2014). Though it is believed that the vast majority of 50-year-olds harbor clones with mutations in the genes most commonly associated with CH, only a fraction of these individuals goes on to develop CH. Thus, while CH is clearly associated with mortality, the interaction between environmental and genetic factors that drive its emergence remains unclear (Bowman et al., 2018; Steensma, 2018).

Heterozygous somatic mutations in about 20 genes are recurrently associated with CH, and some of these mutations are associated with cancer development (Steensma, 2018). Of the most frequent mutations, a few are known to confer a growth or self-renewal advantage to HSCs, enabling those mutant clones to attain numerical advantage (Figure 1). However, CH is unlikely to be driven by genetics alone (Loh et al., 2018). The pace at which CH emerges in individuals with known mutations may differ by decades, suggesting that environmental conditions are a critical driver of CH. Indeed, environmental conditions may provide the necessary backdrop for a survival advantage for certain mutant clones.

Age is the strongest epidemiologic predictor of clonal hematopoiesis, and increased inflammation is a common driver of many of the pathologies of older age, frequently termed “inflammaging” (Franceschi et al., 2007). Inflammatory stress may thus be a critical driver of CH. Indeed, a recent study showed that intestinal permeability and elevated inflammatory signaling are necessary for CH in a mouse model of somatic *Tet2* mutation, demonstrating that interactions between genes and environment drive CH (Jaiswal et al., 2017; Meisel et al., 2018). On the other hand, not all environmental conditions affect genetically variant HSC clones the same way, and environmental drivers may be quite specific to certain CH clones. For example, PPM1D-mutant stem cells have been shown to have a clonal advantage only in the setting of chemotoxic stress (Figure 1) (Hsu et al., 2018). Thus, investigating potential environmental drivers of CH is likely to shed light on the role of certain driver mutations in HSC biology and provide insight into individual variation in CH emergence.

Aside from age, other environmental factors including former tobacco use or diseases that are linked to tobacco use such as lung cancer and chronic obstructive pulmonary disease are strongly associated with CH (Coombs et al., 2017), as is radiation exposure (Boucai et al., 2018). However, the full range of epidemiologic factors associated with CH is not known. The impact of these mutations on CH emergence likely depends on specific mutations and the mechanisms by which the two interact biologically.

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

Inflammation as a driver of clonal hematopoiesis

The strong epidemiologic association of CH with age contributes to speculation that inflammation is a critical driver of this process. Inflammation increases with age, and is attributable to decayed regulatory mechanisms (Rea et al., 2018). For example, a recent study suggests that derepression of retrotransposable elements with age triggers interferon (IFN) responses that drive inflammation (De Cecco et al., 2019). These factors contribute to a wide variety of age-associated diseases including diabetes, Alzheimer’s, cardiovascular disease, and cancer.

In the blood system, genetic variants associated with pleiotropic peripheral blood counts are also associated with inflammatory and autoimmune conditions (Tajuddin et al., 2016). Inflammatory and autoimmune conditions are present in up to 25% of myelodysplastic syndrome (MDS) patients (Wolach and Stone, 2016), and a subset of MDS patients are highly sensitive to immunomodulatory medication (Glenthoj et al., 2016). Thus, inflammation is a well-known contributor to age-associated disease processes including in the hematopoietic system.

A significant and growing body of literature provides a conceptual understanding for how inflammation may contribute to clonal hematopoiesis. Infections are a common hematologic stress that generate inflammatory cytokines that impact bone marrow function and demand increased production of blood and immune cells. Numerous studies have demonstrated that infections promote HSC division and impair self-renewal. Increased stem cell division and hematopoietic progenitor prevalence have been recorded in the setting of a variety of infections including viruses such as lymphochoriomeningitis virus and cytomegalovirus, bacteria including mycobacteria, Ehrlichia (Baldridge et al., 2010; Smith et al., 2018), and parasites such as Plasmodium, which causes malaria (Vainieri et al., 2016). Infections may affect hematopoietic progenitors through pathogen-associated molecular patterns (PAMPs) such as LPS or TLR2 agonist (Herman et al., 2016; Takizawa et al., 2017) or cytokines induced during the infection, as previously reviewed (King and Goodell, 2011). Indeed, several studies have shown that cell division and differentiation programs in HSCs can be activated by inflammatory cytokines, including IFNα, IFNγ, IL1β, IL6, and TNFα (Essers et al., 2009; Pietras et al., 2016; Schürch et al., 2014; Yamashita and Passegue, 2019). Since infections naturally occur over the course of life, it is reasonable to view aging as a state of survival past an increasing number of infections.

The long-term consequences of infection and inflammatory signaling on HSCs can be severe. Indeed, excessive IFNγ has long been recognized to be an etiologic driver of acquired aplastic anemia (Nisticò and Young, 1994) whereas increased inflammation is also significantly associated with MDS (Barreyro et al., 2018). Where HSC activation and bone marrow dysfunction may at first appear contradictory, it is now recognized that stem cell divisions are often associated with a loss of self-renewal (Esplin et al., 2011). Indeed, an increase in the differentiation rate of HSCs leads to a loss of HSC reserves. Using a mouse model, we demonstrated that chronic infection depletes HSCs via excessive terminal differentiation (Matatall et al., 2016). Increased stress-induced apoptosis may also contribute to HSC loss (Pietras et al., 2014), whereas HSCs that survive long term inflammatory stress must do so by downregulating their responses to stress (Pietras et al., 2014). Whereas Rantes and CCL5 were previously reported to strongly influence HSC skewing with age (Ergen et al., 2012), the relative importance of various inflammatory cytokines in driving age-associated changes in hematopoiesis has yet to be fully defined (Kovtonyuk et al., 2016).

A variety of studies have demonstrated that individual subclasses of HSCs are differentially affected by inflammatory signaling. We showed that myeloid- versus lymphoid-biased HSCs respond differentially to IFNγ signaling (Matatall et al., 2014). In other studies, IFNα has been shown to preferentially stimulate a stem cell-like megakaryocyte progenitor (Haas et al., 2015), whereas histamine signaling affects a certain subclass of HSCs (Chen et al., 2017). Furthermore, a subclass of HSCs marked by CCR2 is activated to divide after the stress of myocardial infarction (Dutta et al., 2015). Collectively these studies indicate that not all HSCs are equally responsive to cytokine stress, leading to the concept that environmental conditions can provide a selection advantage to some subclasses over others. HSCs harboring CH-associated mutations may be considered as competing HSC subclasses, but there are already examples wherein a differential response to inflammation by these genetically variant HSCs leads to CH (Cai et al., 2018; Meisel et al., 2018).

Aside from age, epidemiologic factors associated with CH include smoking, smoking related-diseases, treatment of addiction, psychiatric disease, and chronic pulmonary disease, many or all of which are related to smoking (Zink et al., 2017). Smoking is strongly correlated with inflammation (Kianoush et al., 2017), but it remains to be determined whether smoking and inflammation contribute additively or synergistically to CH, or if they are one and the same.

Environmental stress and TET2 mutations in CH

Environmental impacts on Ten-eleven Translocation 2 (TET2)-mutant CH are particularly well studied. TET2 is an epigenetic modifier that is frequently mutated across myeloid malignancies. In CH, TET2 is the second most-frequently mutated gene, and growing evidence suggests that factors including secondary genetic alterations (Muto et al., 2013; Zhang et al., 2016), inflammation (Cai et al., 2018; Shen et al., 2018; Zhang et al., 2015) and changes in the microbiota (Meisel et al., 2018) may contribute to the clonal expansion and pre-leukemic condition of TET2-mutant hematopoietic stem and progenitor cells (HSPCs). Here, we will discuss the biological studies investigating environmental influences on HSPCs with TET2 loss-of-function (LOF) in CH.

The TET family of dioxygenases are able to successively oxidize 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) in the mammalian genome (He et al., 2011; Ito et al., 2011; Tahiliani et al., 2009). Among the three *TET* genes, somatic mutations of *TET2* are the most frequently observed in individuals with CH (Busque et al., 2012; Jaiswal et al., 2014) and hematological malignancies (Couronne et al., 2012; Delhommeau et al., 2009; Langemeijer et al., 2009). Although TET2 mutations contribute to the selective advantage of HSPCs through increased self-renewal, not all the individuals with somatic *TET2* mutations in HSPCs develop hematological neoplasms. In mouse models, Tet2 ablation leads to variable outcomes. Some studies documented only mild phenotypes with increased HSPC self-renewal and myeloid bias in Tet2 knockout mice (Ko et al., 2011; Moran-Crusio et al., 2011). However, several other groups reported that Tet2-deficient mice displayed hypermutagenicity and developed myeloid or lymphoid malignancies (Li et al., 2011; Pan et al., 2017; Quivoron et al., 2011).

Multiple reports have shown that TET2-deficient HSPCs tend to expand relative to WT HSPCs in response to environmental stress, such as inflammation arising from stress stimulation or pathogenic organisms. In the bone marrow, Tet2-ablated HSPCs exhibited strong proliferation advantages and myeloid bias in response to lipopolysaccharide (LPS)-induced acute inflammation (Cai et al., 2018). Mechanistically, Tet2-deficient HSPCs tend to produce high levels of proinflammatory cytokines, such as interleukin-6 (IL-6), to maintain HSPC survival and suppress apoptosis through the upregulation of a novel anti-apoptotic long non-coding RNA, *Morrbid* during inflammation (Cai et al., 2018). In parallel, the progeny of Tet2-deficient HSPCs, particularly innate myeloid cells, also produce high levels of IL-6 during LPS challenge (Zhang et al., 2015). The upregulation of IL-6 in Tet2 deficient myeloid cells is due to the loss of transcriptional suppression at the Il6 promoter mediated by HDAC2. The up-regulation of IL-6 in Tet2-deficient innate myeloid cells might evoke a positive feedback to HSPCs during infection-induced inflammation and further promote the expansion of HSPCs to cause CH (Figure 2).

Interestingly, increased IL-6 production is also observed in microbiota-dependent inflammation in a Tet2-deficient mouse model. Meisel *et al* showed increased intestinal permeability and spontaneous bacterial translocation (e.g., *Lactobacillus*) into the blood of Tet2-deficient mice, thereby resulting in an increase of plasma and spleen IL-6 levels (Meisel et al., 2018). These studies provide strong evidence to support a positive feedback loop between Tet2-deficient HSPCs and their progeny innate myeloid cells during the response to inflammation-induced cytokine production (Figure 2). Given that myeloid cells derived from Tet2-deficient HSPCs can exert non-cell-autonomous effects on HSPCs, it is interesting to speculate whether such cells could also promote expansion of HSPC clones carrying other mutations. In other words, would presence of a Tet2-deficient clone which produces Tet2-deficient macrophages accelerate the expansion of a Dnmt3a-mutant clone? Since people are likely to harbor a variety of genetically variant HSC clones, such cross-cutting effects may exist.

TET2-mutant HSPCs produce immune cells that contribute to abnormal adaptive and innate immune responses not only in the hematopoietic system, but also in the peripheral tissues. Indeed, it has been reported that Tet2-KO mice displayed worse tissue damage in both lung and gut after immune challenge (Zhang et al., 2015). Furthermore, previous reports point to a strong correlation between TET2 mutations and cardiovascular disease progression (Jaiswal et al., 2017). The causal relationship between Tet2 deletion in HSPCs and the increased risk of cardiovascular diseases has been further demonstrated in animal models (Fuster et al., 2017; Sano et al., 2018). Mechanistically, deletion of Tet2 in HSPCs leads to the upregulation of NLRP3 inflammasome and IL1■ production in myeloid cells, thereby leading to increased plaque sizes and impaired cardiac repair. TET2 mutations are also detected in patients with COPD/asthma and neurodegenerative disorders (Buscarlet et al., 2017; Keogh et al., 2018), but the causal relationship between TET2 mutations and these diseases are yet to be defined.

Clonal hematopoiesis driven by chemotoxic exposures

While epigenetic regulators such as DNMT3A and TET2 sit at the top of the list for genes commonly mutated in clonal hematopoiesis, there are also a number of CH genes that are involved in DNA repair. The selective advantage their mutations impart is likely through entirely different mechanisms. Among this class of genes are *PPM1D* and *TP53* (Coombs et al., 2017). PPM1D mutations are among the top ten CH mutations in individuals with an identified driver, representing on the order of 5% of CH cases. PPM1D mutations have recently been studied in some depth and likely represent a paradigm for this class of mutations.

PPM1D had not been described as a major participant in hematopoiesis previously so its frequent mutation in CH was of particular interest. PPM1D is a protein phosphatase that acts to down-modulate the DNA damage response by de-phosphorylating p53, ATM, CHEK1 and other damage response proteins(Le Guezennec and Bulavin, 2010). PPM1D mutations are typically clustered in the C-terminus of the protein and result in a truncated and highly stabilized protein. This stabilized protein results in an enhanced phosphatase activity that constitutively reduces the stress response. Normally, cells exposed to chemotoxic stress will pause to allow DNA repair to occur, with many cells undergoing apoptosis. However, cells with the PPM1D mutations are less sensitive to stress, and exhibit a lower rate of apoptosis(Hsu et al., 2018; Kahn et al., 2018). The net result of their stress resistance is that HSCs bearing a PPM1D mutation are more resistant to chemotherapeutic insults than WT cells. While chemotoxic treatment results in apoptosis in both WT and mutant cells, the rate of cell death in mutant cells is lower. At the end of each round of chemotherapy, a greater proportion of mutant cells have survived compared to WT cells. We found that this larger number of surviving cells, even if relatively small, was sufficient to give a competitive advantage to the mutant cells in the context of repeated rounds of chemotherapy.

In mice, when *Ppm1d*-mutant stem cells were transplanted in competition with WT cells, they were able to engraft and contribute to blood production with equivalent efficiency. However, when mice were exposed to DNA damaging agents, the mutant cells quickly out-competed their WT counterparts, and affect that was maintained for months after cessation of chemotherapy treatment. However, not all types of stress gave the PPM1D mutant cells a selective advantage; DNA damaging agents were the most powerful, while stress such as serial transplantation did not offer any advantage to the mutant cells. While PPM1D mutant cells may exhibit a slight proliferative advantage (Kahn et al., 2018), a moderate difference in apoptosis can explain most of the differential expansion of PPM1D mutant cells in the blood.

These data can be extrapolated to explain at least some of the presence of PPM1D mutations in individuals with CH. In patients who have previously undergone chemotherapy for solid tumors, CH with PPM1D mutations is much more prevalent than without such exposures (Coombs et al.). Similarly, in therapy-related AML patients who have been exposed to DNA damaging agents, PPM1D mutations are particularly common (Hsu et al., 2018). Notably, PPM1D mutations do show up in the general population with CH (Genovese et al., 2014). It is possible that these individuals represent those in the general population who have been exposed to chemotherapy or other stresses, or that PPM1D mutations offer advantages in some additional contexts that are yet to be identified.

Diet, metabolism, and clonal hematopoiesis

While the effects of diet or metabolic milieu on CH remain to be studied, obesity and metabolic syndromes are known to influence the fate of HSPCs. Specifically, obesity and metabolic syndromes enhance myelopoiesis. Both hyperglycemia in type 1 diabetes models and obesity caused by high-fat diet increase myeloid progenitors and myelopoiesis (Lee et al., 2018; Luo et al., 2015; Nagareddy et al., 2013; Singer et al., 2014). These metabolic disorders affect myelopoiesis largely through cell extrinsic mechanisms involving the HSC niche or by causing an inflammatory state.

HSCs reside in the bone marrow niche consisting of several cell types such as endothelial cells and bone marrow mesenchymal stromal cells (BMSCs), which have the capacity to differentiate into adipocytes, osteoblast, and chondrocytes (Morrison and Scadden, 2014). Obesity not only expands subcutaneous and visceral fat mass, it also promotes differentiation of BMSCs into adipocytes (Ambrosi et al., 2017). Increased marrow adipocytes, in turn, reduce the number of HSCs (Ambrosi et al., 2017; Hu et al., 2019; Naveiras et al., 2009). In contrast, a recent study suggests that exercise reduces leptin, a hormone that governs energy expenditure, and reduction of leptin instructs BMSCs to express HSC niche factors to promote HSC quiescence (Frodermann et al., 2019). These studies illuminate the links between metabolic and physical conditions to the bone marrow microenvironment to support HSCs, with obesity and exercise negatively and positively affecting HSCs, respectively.

Obesity-induced changes in the microbiome have also been shown to alter the HSC niche and promote myelopoiesis (Luo et al., 2015; Yan et al., 2018). Whether these changes in the microbiome are responsible for age-related changes in HSCs and their niche, leading to the emergence of CH, remains to be tested. Thus, whether by regulation of adipocytes or through microbiome-related changes, the net effect of obesity is to reduce the HSC population. It is therefore tempting to speculate that some CH mutations confer mutant HSCs with resistance against the negative pressure imposed by fatty marrow in obese or aged populations.

Additionally, metabolic syndromes may promote CH indirectly by causing chronic inflammation. Obesity is a state of chronic inflammation characterized by expansion of proinflammatory immune cells in adipose tissues (Reilly and Saltiel, 2017). Adipocytes themselves also regulate inflammation by secreting a proinflammatory cytokine leptin and an anti-inflammatory cytokine adiponectin, the expression of which are increased and decreased in adipocytes of obese subjects, respectively. Obesity has been shown to increase intestinal permeability, causing a systemic endotoxemia state (Cani et al., 2008). Additionally, hyperglycemia in a mouse model of type 1 diabetes caused neutrophils to produce a sterile inflammatory signal S100A8/S100A9, which then instructed myeloid progenitor cells to secrete myelopoietic cytokines such as M-CSF (Nagareddy et al., 2013).The resulting pro-inflammatory state was characterized by increased secretion of cytokines such as TGFβ, IL-1, and IFNS, all of which act on HSPCs as discussed above.

The effects of metabolic syndromes on promoting myelopoiesis parallel the observation that HSCs and myeloid progenitors with CH mutations exhibit preferential expansion compared to lymphocytes (Arends et al., 2018). Intriguingly, some individuals with CH show preferential expansion of myeloid progenitors over the more immature HSCs, suggesting that some mutations, environmental selective pressure, or the combination of both may encourage clonal expansion of committed progenitors. It should be noted that neither diet nor metabolic syndromes have been demonstrated to be epidemiological factors associated with CH, and the links remains speculative. Nevertheless, identification of the mutations that allow CH clones to expand in the proinflammatory conditions associated with metabolic syndromes may lead to strategies to assess the risk of developing CH or to prevent the expansion of such clones in people with metabolic syndromes.

Unanswered questions and future directions

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

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Highlights

- Environmental factors influence development of clonal hematopoiesis.
- Inflammation exerts a strong influence on hematopoietic stem cell biology and may serve as a unifying driver of CH.
- Obesity, hyperglycemia, and the microbiome affect hematopoietic stem cell responses and may contribute to CH.

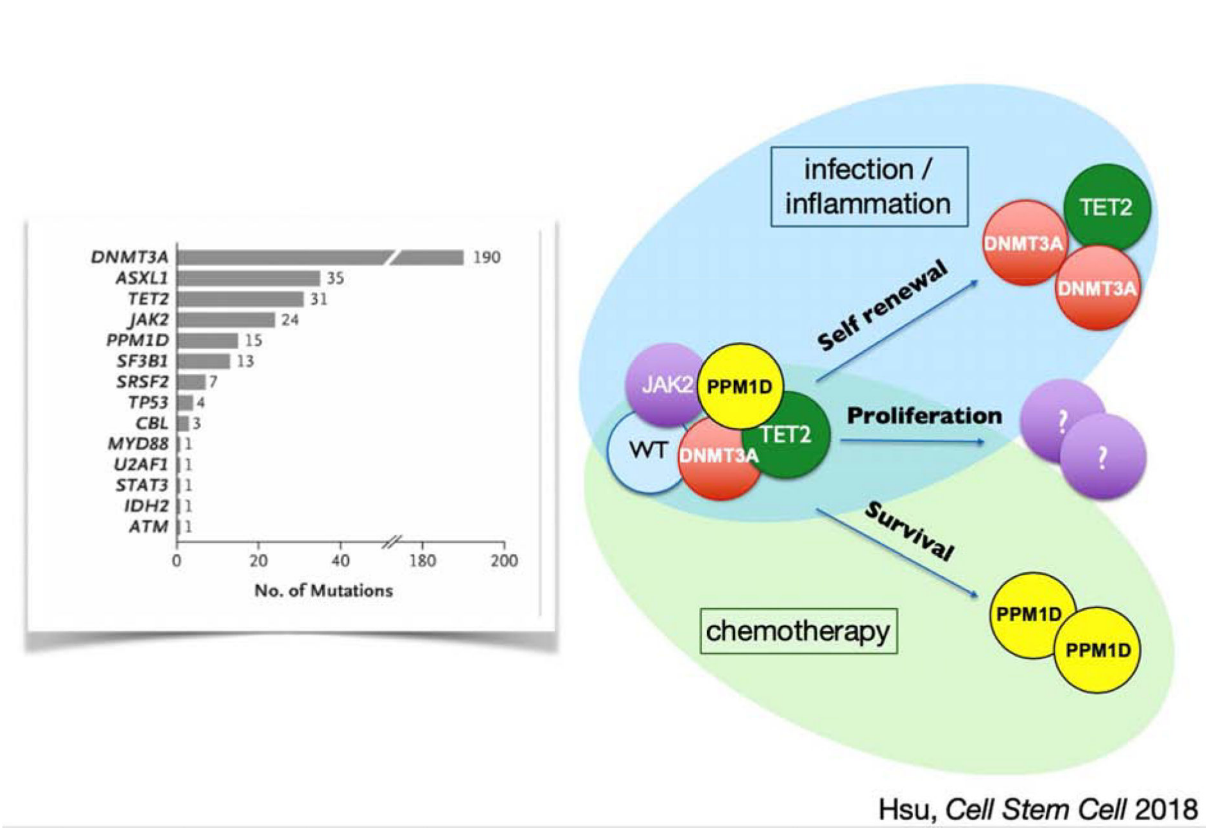

Figure 1.

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

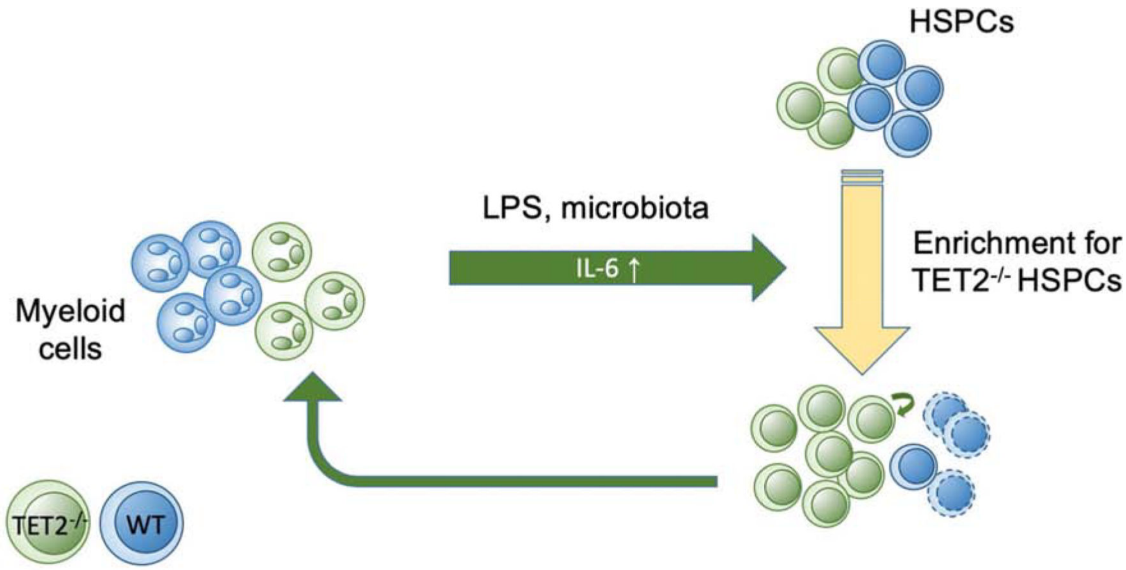

Figure 2.

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