p53 involvement in clonal hematopoiesis of indeterminate potential

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ABSTRACT

Purpose of review

Clonal hematopoiesis of indeterminate potential (CHIP) increases with age and occurs when a single mutant hematopoietic stem cell (HSC) contributes to a significant clonal proportion of mature blood lineages. Somatic mutations in the *TP53* gene, which encodes the tumor suppressor protein p53, rank in the top five among genes that were mutated in CHIP. This review focuses on mechanisms by which mutant p53 promotes CHIP progression and drives the pathogenesis of hematological malignancies, including myelodysplastic syndromes (MDS), and acute myeloid leukemia (AML).

Recent findings

TP53 was frequently mutated in individuals with CHIP. While clinical studies suggest that expansion of HSCs with *TP53* mutations predisposes the elderly to hematological neoplasms, there is a significant gap in knowledge regarding the mechanisms by which *TP53* mutations promote HSC expansion. Recent findings suggest that several cellular stressors, including hematopoietic transplantation, genotoxic stress, and inflammation, promote the expansion of HSCs with *TP53* mutations. Further, *TP53* mutations identified in CHIP cooperate with genetic and/or epigenetic changes in leukemogenesis.

Summary

TP53 mutations identified in CHIP are associated with increased risks of *de novo* and therapy-related hematological neoplasms. Thus, targeting mutant p53 and related pathways

holds great potential in preventing CHIP progression and treating hematological malignancies.

Keywords

clonal hematopoiesis of indeterminate potential, age-related clonal hematopoiesis, *TP53*, p53, myelodysplastic syndromes, and acute myeloid leukemia

KEY POINTS

Tumor suppressor gene *TP53* was frequently mutated in individuals with clonal hematopoiesis of indeterminate potential (CHIP).

Several cellular stressors, including transplantation, genotoxic stress, and inflammation, promote the expansion of hematopoietic stem cells (HSCs) with *TP53* mutations.

TP53 mutations identified in CHIP cooperate with genetic and/or epigenetic changes in leukemogenesis.

Targeting mutant p53 and related pathways holds great potential in preventing CHIP progression and treating hematological malignancies.

INTRODUCTION

Human aging is associated with an exponential increase in the occurrence of clonal hematopoiesis of indeterminate potential (CHIP) in aged individuals. CHIP occurs when a single mutant hematopoietic stem cell (HSC) contributes to a significant, measurable clonal proportion of mature blood lineages [1, 2■■, 3]. CHIP is also known as age-related clonal hematopoiesis (ARCH) [4■■]. CHIP is associated with an increased risk of hematological malignancies, such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), as well as a higher incidence of other age-related pathological conditions such as cardiovascular disease (CVD) [5-10,11■]. Given that CHIP is an age-dependent risk factor for MDS, AML, and CVD, preventing CHIP progression may prove to be beneficial for human health. However, mechanisms by which somatic mutations in blood cells contribute to the pathogenesis of age-related diseases are largely unknown. The vast majority of the mutations identified in CHIP are dispersed across the genome. However, five genes, including *DNMT3A, TET2, ASXL1, JAK2* and *TP53*, have disproportionately high numbers of somatic mutations [5-7]. *TP53* ranks in the top five among genes that were mutated in CHIP and the frequency of *TP53* mutations increases with age [5-9, 12■■,13■■]. *TP53* gene encodes the tumor suppressor p53 protein [14]. This review will focus on the involvement of p53 in CHIP progression and pathogenesis of hematological malignancies, including MDS and AML.

p53 in clonal hematopoiesis of indeterminate potential (CHIP)

p53 is a transcription factor that regulates a large number of genes in response to a variety of cellular insults, including oncogene activation, DNA damage, and inflammation. These stressors activate p53 through post-translational modifications that result in augmented levels of p53 protein and transactivation activity [14-15]. Activated p53 induces growth arrest,

apoptosis, DNA repair, and differentiation in damaged cells to suppress cellular transformation [14-15]. p53 is a critical regulator of hematopoietic stem cell behavior and we discovered that p53 maintains HSC quiescence and regulates DNA damage response [16-17]. p53 activates the transcription of target genes to mediate DNA damage repair, growth arrest or apoptosis [14, 18]. We have identified both *Necdin* and *Gfi1* as p53 target genes in HSCs [16-17].

Like solid tumors, p53 function is always compromised in hematological malignancies, usually as a result of somatic mutations and deletions [14-15, 19-23]. *TP53* ranks in the top five among genes that were mutated in CHIP (Fig. 1). The majority of *TP53* mutations in CHIP are missense mutations. The remainder of the *TP53* mutations are nonsense, frameshift, and splice site mutations [5-7,12■■,13■■]. *TP53* mutation spectrums in CHIP are similar to hematological malignancies, including MDS and AML [19-23]. While clinical studies suggest that expansion of HSCs with *TP53* mutations predisposes the elderly to hematological neoplasms [5-7, 12■■,13■■], the mechanisms by which *TP53* mutations promote HSC expansion during aging are largely unknown. We discovered that *TP53* mutations identified in CHIP enhances the repopulating potential of HSCs, thereby conferring a competitive advantage to HSCs following transplantation stress [24■■]. Hematopoietic transplantation also expanded p53 mutant clones in patients with hematological malignancies [13■■].

Modulation of gene transcription is an important mechanism for mutant p53 in cancer development [15]; however, how mutant p53 regulates gene expression in HSCs is largely unknown. Loss of epigenetic regulation of gene expression in aged HSCs contributes to aging phenotypes and dysregulated epigenetic control has been implicated in the

pathogenesis of hematological malignancies [20-21, 25-26]. Indeed, recent studies revealed that some mutant p53 proteins increase the expression of epigenetic factors, including MLL1, MLL2, and MOZ, in human cancer cells [27]. However, we found that the expression of *Mll1*, *Mll2*, and *Moz* is comparable in p53 wild-type and mutant HSCs (S.C. and Y.L., unpublished data). As mutant p53 proteins have been shown to play context dependent roles in human cancer [15], it is possible that mutant p53 proteins may utilize different mechanisms to modulate gene expression in HSCs. We found that mutant p53 interacts with epigenetic regulator EZH2. EZH2, a key component of Polycomb repressive complex 2 (PRC2), catalyzes the trimethylation of lysine 27 of histone H3 (H3K27me3) in cells [28]. Hematopoietic-specific deletion of Ezh2 impairs hematopoietic stem cell self-renewal and terminal differentiation [29]. We discovered that mutant p53 enhanced the association of EZH2 with the chromatin and increased the levels of H3K27m3 in genes regulating HSC self-renewal and differentiation (S.C. and Y.L., unpublished data). Thus, we have uncovered a novel mechanism by which mutant p53 drives clonal hematopoiesis. Since common mutations identified in CHIP affect epigenetic modulators, including DNMT3A, TET2, and ASXL1 [5-7], our findings that mutant p53 modulates EZH2 activity and increases the levels of H3K27m3 in HSCs underscore the importance of dysregulated epigenetic control in CHIP development.

Most of *TP53* mutations in human cancer lost their tumor suppressor function [15]. However, mounting evidence suggests that some mutant p53 proteins not only lose their

tumor suppressor function, but also acquire new oncogenic properties that are independent of wild-type p53, known as gain-of-function (GOF) properties [15]. To ascertain the oncogenic effects of GOF *TP53* mutations, $p53^{R248W}$ and $p53^{R273H}$ mutant were engineered into the endogenous *Trp53* locus in mice [30]. Homozygous $p53^{R248W/R428W}$ and $p53^{R273H/R273H}$ mice developed novel tumors compared to $p53^{-/-}$ mice [30]. Thus, GOF mutant p53 proteins have enhanced oncogenic potential beyond the simple loss of *p53* function. Since EZH2 interacts with mutant p53 but not wild-type p53, our findings suggest that some *TP53* mutations identified in CHIP may have GOF properties.

In transplantation assays, p53 mutant hematopoietic cells always outcompeted wild-type competitor cells and became clonal dominance [13■■, 24■■]. While we have identified a cell autonomous mechanism by which mutant p53 drives clonal hematopoiesis, recent studies indicate that mutations identified in CHIP may utilize cell non-autonomous mechanisms to promote clonal hematopoiesis [11■, 31■■]. For example, mutant hematopoietic cells displayed increased secretion of pro-inflammatory cytokines, including IL-1β and IL-6 [11■, 31■■]. We found that inhibition of inflammatory signaling in Tet2 mutant preleukemic cells mitigates clonal hematopoiesis [31■■]. RNA-seq analysis revealed that inflammatory response genes are enriched in p53 mutant HSCs (S.C. and Y.L., unpublished data), suggesting that mutant p53 may drive clonal hematopoiesis through activating pro-inflammatory pathways. The potential cell non-autonomous mechanisms by which mutant p53 promotes HSC expansion during aging await future investigation.

p53 in therapy-related CHIP

TP53 mutations are commonly found in therapy related CHIP as well as in secondary MDS and AML [12■■,13■■, 24■■, 32]. Indeed, somatic *TP53* mutations are present in 5 to 10% of MDS cases and in 30% of secondary MDS patients arising after exposure to radiation or chemotherapy [20-21]. *TP53* mutations in CHIP are associated with prior exposure to chemotherapy or radiotherapy [12■■,13■■]. Chemotherapy treatment resulted in expansion of both $p53^{+/-}$ and $p53^{R28W/+}$ HSCs [13■■, 24■■, 32]. $p53^{-/-}$ HSCs are resistant to radiation [16] and we observed that *TP53* mutations identified in CHIP confer radiation resistance, leading to selective expansion of *TP53*-mutant HSPCs (S.C. and Y.L., unpublished data). *TP53* mutations in therapy-related CHIP are also associated with smoking [12■■], suggesting that smoking-induced DNA damage may promote the expansion of hematopoietic clones with *TP53* mutations.

Mutations in protein phosphatase $Mg2^{+}$/$Mn2^{+}$ 1D (*PPM1D*) have been identified in CHIP and myeloid neoplasms, with a enrichment in patients previously exposed to chemotherapy [5-7, 12■■,13■■, 33■■,34■■]. PPM1D negatively regulates p53 and several proteins involved in the DNA damage response [35-36]. *PPM1D* mutations confer chemotherapy resistance, resulting in the selective expansion of *PPM1D*-mutant hematopoietic cells [33■■,34■■]. However, PPM1D mutants lack an advantage under bone marrow transplantation stress [13■■, 33■■,34■■]. Thus, mutant p53 appears to play distinct roles in driving clonal hematopoiesis compared to PPM1D mutants.

p53 in the pathogenesis of hematological malignancies

The frequency of *TP53* mutations in AML is approximately 10% [22]. However, in AML with complex karyotype, the frequency of p53 mutations and/or deletions is almost 70% [23]. p53 mutations and/or deletions were thought to be secondary events that occur during leukemic transformation [37-39]. However, an aged individual with *TP53* mutation in hematopoietic cells developed AML after acquiring additional chromosomal changes [5]. Interestingly, Li-Fraumeni syndrome (LFS), a rare, autosomal dominant disease, predisposes individuals to hereditary cancer linked to *TP53* germline mutations, and some LFS patients develop MDS and AML as they age [15, 40], suggesting that *TP53* mutations may be early events in leukemia development.

Most homozygous p53 knockout and mutant mice develop spontaneous tumors, including lymphoma and sarcoma, and die within 3 to 6 months after birth [30]. Since MDS is an age-related hematological disorder [20-21], we reasoned that heterozygous p53 mutant mice may develop myeloid malignancies with age. We maintained $p53^{+/+}$ and $p53^{R248W/+}$ mice for more than a year and monitored tumor development. We found that some $p53^{R248W/+}$ mice developed MDS with age based upon pathological analysis of BM and peripheral blood. Other $p53^{R248W/+}$ mice developed lymphoma and sarcoma (S.C. and Y.L., unpublished data). Thus, we demonstrated that mutant p53 drives MDS in mice with age.

While coexisting mutations with *TP53* mutations in AML are limited, previous studies indicate that *TP53* mutations do co-occur with AML driver mutations in oncogenic signaling molecules such as NRAS and FMS-like tyrosine kinase receptor-3 (FLT3) [41■■, 42, 43■■]. Loss of p53 has been shown to cooperate with *Nras* mutations in AML development in mice. Mechanistically, $p53^{-/-}$ synergizes with enhanced oncogenic $Nras^{G12D}$ signaling to transform megakaryocyte-erythroid progenitors (MEPs) into leukemia-initiating cells (LICs) thereby

driving AML development [43■■]. We found that mutant p53 cooperates with FLT3-ITD in chronic myeloid leukemia (CML) development in mice. Further, we found that mutant p53 enhanced the self-renewal potential of FLT3-ITD$^+$ leukemia-initiating cells [44■■]. Given that *TP53* mutations are present in both chronic and blast crisis phases of CML [45], our studies underscore the importance of mutant p53 in CML pathogenesis.

Targeting mutant p53 to prevent CHIP progression and treat hematological malignancies

TP53 is the most frequently mutated gene across all cancer types [14-15, 46■■]. The presence of mutant p53 predisposes to tumor development and is associated with ineffective therapeutic responses and unfavorable prognosis [15, 46■■]. Indeed, somatic *TP53* mutations are associated with advanced disease and poor prognosis in both MDS and AML [19-23]. Despite these effects, no drug that abrogates the oncogenic functions of mutant p53 has yet been approved for the treatment of cancer [46■■]. To date, there are no effective treatment for MDS and AML patients with *TP53* mutations, and most patients die within two years of diagnosis [19-23]. Thus, there is an urgent need to develop therapeutic strategies that can target mutant p53 and related pathways, enhancing our abilities to prevent CHIP progression and treat age-related diseases. While hematopoietic cell transplantation has curative potential, *TP53* mutations are unfavorable prognostic markers for transplantation in MDS patients and negatively affect post-transplant survival [47■■, 48]. While MDS and AML patients with *TP53* mutations have been observed to have favorable clinical response and robust mutation clearance after receiving a 10-day courses of decitabine, the response is not durable [49]. Epigenetic factor EZH2 is rarely mutated in CHIP [5-7] and we found that genetic and pharmacological inhibition of EZH2 decrease the repopulating potential of p53

mutant HSCs (S.C. and Y.L., unpublished data), suggesting that EZH2 may be a novel target for preventing CHIP progression in aged individuals with *TP53* mutations.

CONCLUSION

Tumor suppressor gene *TP53* was frequently mutated in individuals with CHIP and the frequency of *TP53* mutations increases with age [5-9]. Recent findings suggest that several cellular stressors, including hematopoietic transplantation, genotoxic stress, and inflammation, promote the expansion of HSCs with *TP53* mutations [11■, 12■■,13■■, 24■■, 31■■,32]. Further, *TP53* mutations identified in CHIP cooperate with genetic and/or epigenetic changes in leukemogenesis [43■■,44■■] (Fig. 2). Since *TP53* mutations identified in CHIP are associated with increased risks of *de novo* and therapy-related hematological neoplasms [5-9, 12■■,13■■], targeting mutant p53 and related pathways holds great potential in preventing CHIP progression and treating hematological malignancies.

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Conflicts of interest

There are no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Tumor suppressor gene *TP53* ranks in the top five among genes that were mutated in clonal hematopoiesis of indeterminate potential (CHIP).

Figure 2. *TP53* mutations identified in CHIP utilize distinct mechanisms to promote HSC expansion during aging. Expanded mutant HSCs become fully transformed leukemia-initiating cells (LICs) after acquiring additional genetic and/or epigenetic changes.

Figure 1

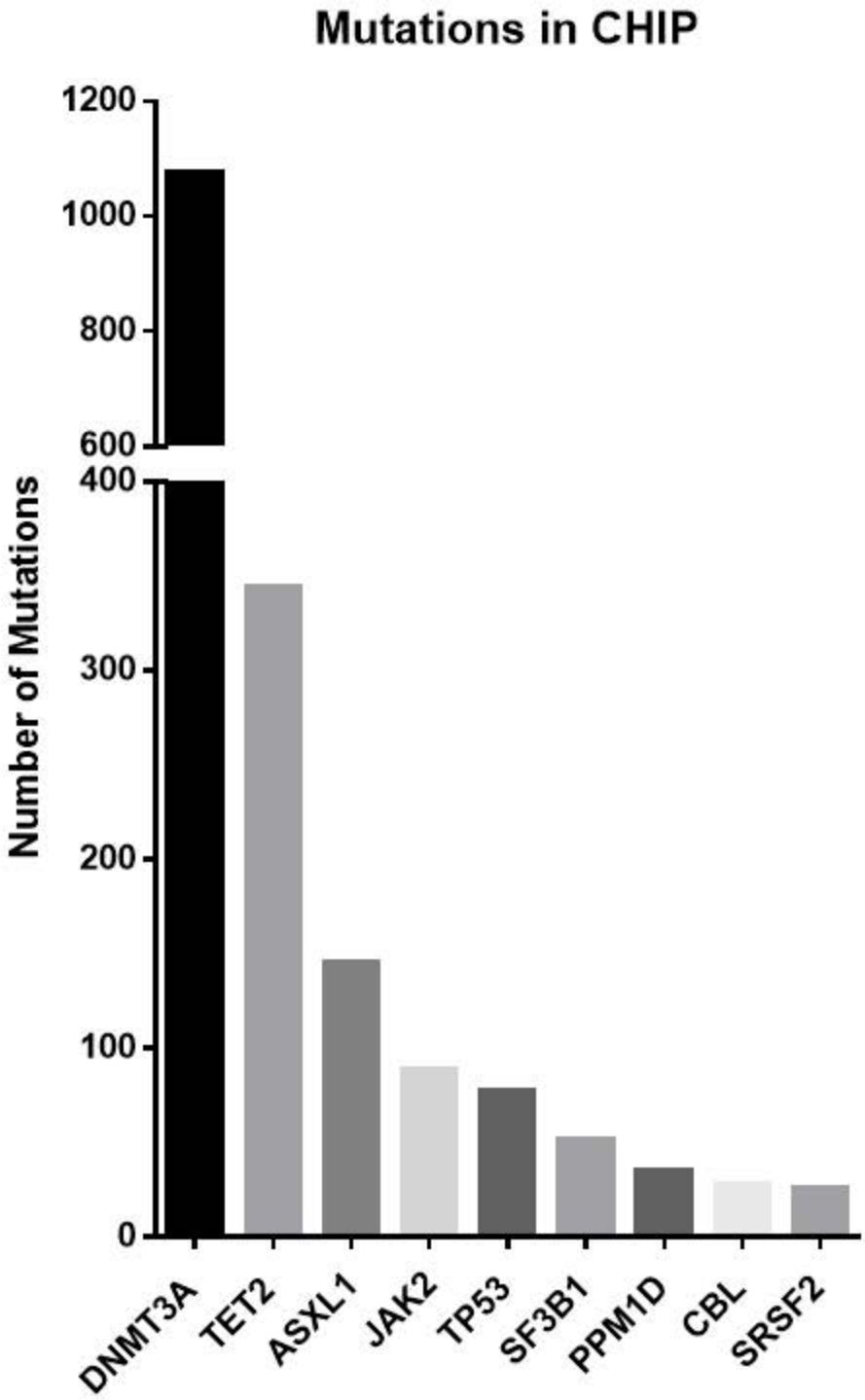
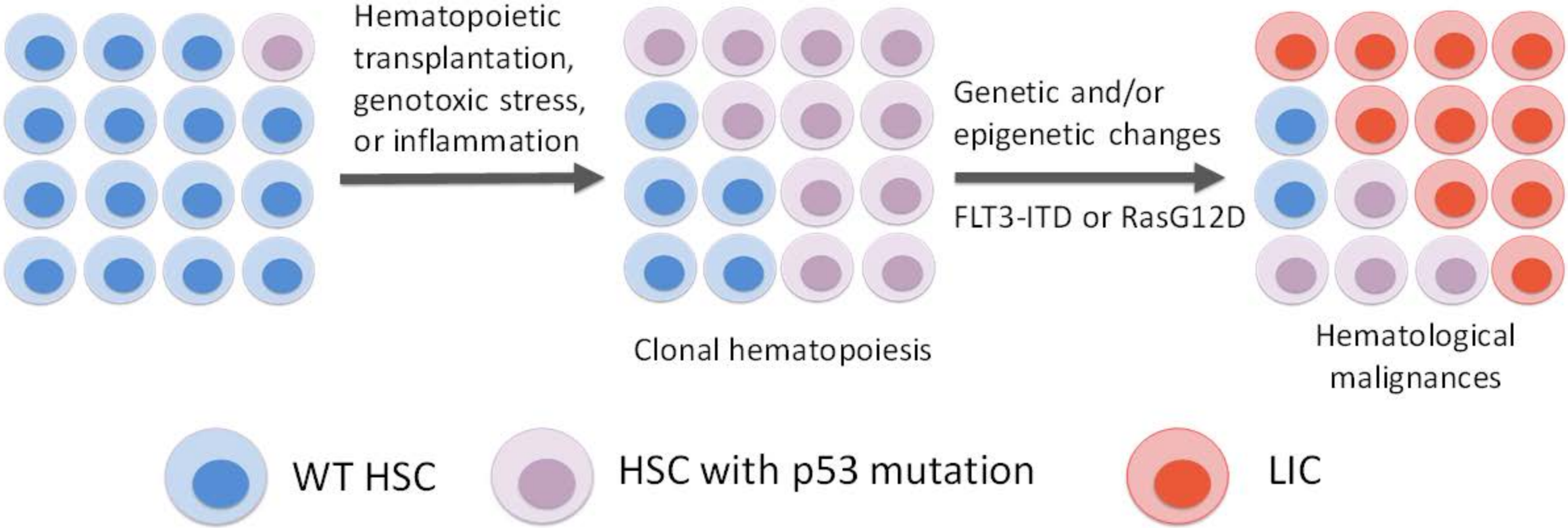

Mutations in CHIP
Number of Mutations
1200
1000
800
600
400
300
200
100
0
DNMT3A
TET2
ASXL1
JAK2
TP53
SF3B1
PPM1D
CBL
SRSF2

Figure 2


Hematopoietic transplantation, genotoxic stress, or inflammation
Genetic and/or epigenetic changes
FLT3-ITD or RasG12D
Clonal hematopoiesis
Hematological malignances
WT HSC
HSC with p53 mutation
LIC