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Significance of clonal mutations in bone marrow failure and inherited MDS/AML predisposition syndromes

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Synopsis

Clonal hematopoiesis as a hallmark of myelodysplastic syndrome (MDS) is mediated by the selective advantage of clonal hematopoietic stem cells in a context-specific manner. While primary MDS emerges without known predisposing cause and is associated with advanced age, secondary MDS may develop in younger patients with bone marrow failure syndromes or after exposure to chemotherapy, respectively. This article discusses recent advances in our understanding of context-dependent clonal hematopoiesis in MDS with focus on clonal evolution in inherited and acquired bone marrow failure syndromes.

Keywords

Myelodysplastic syndrome; Bone marrow failure syndromes; Genetic predisposition; Clonal hematopoiesis

Introduction

MDS pathogenesis

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematopoietic disorders characterized by dysfunctional hematopoiesis, bone marrow dysplasia and an increased risk of development of acute myeloid leukemia (AML)[1]. Although MDS is most common in older patients (> 70 years) it can occur in all age groups, including children and young adults. Primary MDS emerges without known predisposing cause and is associated with advanced age, while secondary and therapy-related MDS (t-MDS) are proportionally more common in younger MDS patients and develop in the context of inherited or acquired bone marrow failure or after exposure to chemotherapy, respectively.

Genetic studies have demonstrated that MDS molecular alterations are closely associated with clinical outcomes and disease characteristics[2,3]. Indeed, the spectrum of genetic

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alterations in young MDS patients is different than that of older MDS patients, consistent with the distinct age-associated mechanisms of MDS pathogenesis[2]. Whereas older patients more frequently harbor somatic mutations in genes encoding epigenetic modifiers (*TET2* and *DNMT3A*) or RNA splicing (*SRSF2* and *SF3B1*), younger patients have much higher frequency of genes associated with germline conditions (*GATA2* and *SBDS*) and acquired predispositions (*PIGA*). Mutations in other genes, such as *TP53*, *RUNX1*, or *RAS* are common across all age groups[2].

Clonal hematopoiesis and aging

Advancing age is the most established risk factor for developing clonally-restricted hematopoiesis. During normal aging, individual hematopoietic stem cells (HSCs) steadily accumulate somatic mutations. By age 60, it is estimated that each HSC harbors eight mutations affecting its coding genome[4]. While most of these mutations do not measurably alter stem cell function, some confer a competitive advantage over normal HSCs and cause preferential contribution to mature hematopoietic cells. This phenomenon, when occurring in otherwise healthy individuals, is termed Clonal Hematopoiesis of Indeterminate Potential (CHIP), which has several key properties:

1. a strong association with advancing age,
2. an increased risk of developing frank hematologic malignancy (overall risk = 1% per year), and
3. an increase in all-cause mortality related to an elevated risk of cardiovascular events[5].

The age-dependent accumulation of somatic mutations may underlie the increasing prevalence of MDS among older individuals; the median age at MDS diagnosis is 71–76 years[6]. The close genetic and epidemiologic concordance between CHIP and primary MDS has engendered a model whereby clinically unapparent clonal HSC expansion is caused by an initiating mutation affecting particular genes, such as *DNMT3A*, *TET2* and *ASXL1*, while transformation to frank myeloid malignancy is mediated by subsequent stepwise acquisition of additional myeloid driver mutations[3,5]. The factors that influence the frequency, genetic spectrum, and clinical implications of CHIP remain incompletely understood.

Extrinsic selection and clonal hematopoiesis: CHIP and t-MDS

Changes in cell extrinsic selection pressures due to specific therapeutic exposures or disease characteristics may influence the development and clinical implications of clonal hematopoiesis. For example, CHIP is present in about 30% of patients with non-Hodgkin lymphoma who undergo autologous stem cell transplantation, reflecting a rate more than 5 times higher than healthy adults of similar age spectrum[7]. Similarly, clonal hematopoiesis is common among patients with non-hematologic cancers[8]. The genetic spectrum of CHIP that arises in the context of therapeutic exposure is distinct, showing an enrichment of mutations affecting *TP53* and *PPM1D*, genes that are important for the cellular stress response. Mutations in *TP53* and *PPM1D* are also highly associated with t-MDS, compared to primary

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MDS, suggesting a mechanistic link between CHIP arising in the context of exposure and the subsequent development of t-MDS[2].

Clonal hematopoiesis in inherited bone marrow failure and familial MDS/AML predisposition syndromes

The ability of a cell to persist within a specific selective environment defines its "fitness" and reflects aggregate characteristics of cell survival, differentiation and proliferation. Importantly, cellular fitness is functionally defined only relative to surrounding cells. In healthy individuals, clonal hematopoiesis and MDS arise in the competitive backdrop of normal hematopoiesis. In this context, clonal expansion is based on a gain of fitness relative to otherwise fit cells. By contrast, bone marrow failure syndromes can display subtle or profound alterations of HSC function and microenvironment. Therefore, even mutations that cause modest enhancement of fitness may manifest as clonal hematopoiesis or drive myeloid transformation. Moreover, disease-specific cellular defects (Fig. 1) may create context-dependent selective environments that result in distinct opportunities for somatic genetic cooperation (Fig. 2). Below, the authors discuss how inherited bone marrow failure syndromes and MDS/AML predisposition syndromes may exert an influence on the incidence and genetic spectrum of clonal hematopoiesis and myeloid transformation. Further, the authors consider how disease-specific selective pressures, driven by diverse underlying pathogenetic mechanisms, may define distinct selective pressures that are intrinsic and extrinsic to the HSC.

Shwachman-Diamond Syndrome

Shwachman-Diamond Syndrome (SDS) is an autosomal recessive bone marrow failure syndrome that is caused by biallelic inactivating mutations in the *SBDS* gene on chromosome 7 (q11.21) and associated with short stature, exocrine pancreatic dysfunction and a strong predisposition to MDS/AML transformation[9]. In a cohort of 55 SDS patients, 36% of patients developed MDS or AML by the age of 30 years[10]. Cellular deficiency of the SBDS protein results in ribosomal dysfunction and translational inefficiency, which is linked to Fas ligand-induced apoptosis and induction of TP53-mediated cellular senescence pathways[11,12].

Recurrent clonal cytogenetic alterations are commonly identified in the bone marrow of SDS patients, including isochromosome 7 (i7(q10)), monosomy 7, and del(20q). While monosomy 7 is associated with rapid clonal progression, del(20q) and i7(q10) correlate with a benign clinical course[13,14], suggesting that development of clonal hematopoiesis with somatic genetic alterations may not be deterministic of leukemic transformation.

In SDS patients with compound heterozygosity for the 2 most common SBDS mutations, the presence of i(7)(q10) favored the allele with c.258+2T>C (a splice site mutation causing decreased SBDS levels) over the c.183_184TA>CT allele (a nonsense mutation causing complete SBDS loss). As such, i(7)(q10) may cause a relative increase of SBDS protein, thereby improving the underlying cellular dysfunction and driving a selective clonal advantage[14]. Similarly, the minimally deleted region of del(20q) involves the *EIF6* gene locus. It has been hypothesized that EIF6 haploinsufficiency promotes partial rescue of

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impaired ribosome biogenesis in SDS cells by favoring ejection of EIF6 from the nascent 60S ribosome[13,15]. In each of these scenarios, the selective fitness of somatically mutated clones may be driven by functional complementation of underlying cellular defects, rather than by alteration of pathways directly involved in biological transformation[13,15]. Consistent with this model, neither i(7)(q10) nor del(20q) alterations are associated with an increased risk of leukemic transformation.

In our genetic analysis of samples obtained before transplantation from 1514 patients with MDS, we identified 7 patients with canonical biallelic *SBDS* mutations[2]. These SDS patients were significantly younger than other MDS patients (median age 25.1 years) and had poor clinical outcomes (median survival of 1.2 years) compared to other young patients (median survival not reached). Consistent with their poor survival, all patients with biallelic *SBDS* mutations had at least one somatic *TP53* mutation. Moreover, *TP53* mutations were significantly more frequent in patients with biallelic *SBDS* mutations than in patients without *SBDS* mutations. The high frequency of *TP53* mutations in this cohort suggests that there may be a specific cooperative effect between SBDS deficiency and *TP53* alterations that mediates clinical progression to MDS.

A subsequent study of 27 patients used a barcoded sequencing approach to confirm that somatic *TP53* mutations are highly recurrent in SDS, affecting 48% of patients[16]. The incidence of *TP53* mutations in this SDS cohort correlated with increased age, and several patients harbored multiple *TP53* mutations. Importantly, the authors identified *TP53* mutations even among patients without clinical or morphologic evidence of transformation, and the presence of *TP53* mutations was not associated with worse hematologic function. *TP53* mutations were not detected in SCN and cyclic neutropenia patients[16], suggesting that *TP53* mutations are not broadly associated with neutropenic conditions, but rather may be specifically linked to SDS biology.

TP53 is a central effector of the cellular response to ribosomal dysfunction[17]. Indeed, TP53 overexpression is observed in bone marrow biopsies from SDS patients[12] and Sbds deficiency in mice was shown to induce Tp53 dependent apoptosis in myeloid cells[18], suggesting that ribosomal dysfunction and translational inefficiency in SDS patients induce TP53 dependent cellular senescence. Consistent with the role of TP53 in mediating the SDS phenotype, genetic ablation of Trp53 in mice attenuates the atrophy seen in Sbds deficient pancreatic acinar cells[11]. It is possible that somatic acquisition of *TP53* mutations in SBDS-deficient hematopoietic cells similarly rescues inefficient hematopoiesis, resulting in selection and clonal expansion of mutated cells.

Diamond-Blackfan Anemia

Diamond-Blackfan Anemia (DBA) is characterized by red blood cell aplasia and is associated with infantile onset of isolated, severe, macrocytic anemia, as well as short stature and congenital anomalies[9]. DBA is inherited in an autosomal dominant pattern and is most frequently caused by mutations affecting genes that encode ribosomal proteins which are important for 18S or 28S rRNA maturation and small or large ribosomal subunit synthesis, respectively[9]. Approximately 25% of DBA patients have a mutation in *RPS19*, although

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more than 10 causative genes have been identified[9]. The Diamond Blackfan Anemia Registry reports that DBA patients have a cumulative incidence for AML of 5% by the age of 46 years[19].

In our MDS transplant cohort, only one patient had DBA (defined by the presence of a heterozygous frameshift mutation in the *RPS17* gene)[2]. In this case, we identified 6 distinct somatic mutations involving *TP53* and *PPM1D*, which encodes a serine-threonine protein phosphatase that regulates TP53 and the cellular stress response. This observation is consistent with a mechanistic link between ribosomal dysfunction and *TP53* dependent transformation that has been observed in SDS patients that develop MDS.

In bone marrow specimens from DBA patients without transformation, TP53 has been shown to accumulate in erythroid progenitor cells, and *TP53* was induced selectively in primary human erythroid progenitor cells after *RPS19* knockdown[20]. Moreover, the erythroid phenotype in mouse models of DBA is rescued by concomitant inactivation of *Tp53*[21]. Mutations in the TP53 pathway may thus drive clonal expansion by attenuating DBA-related erythroid apoptosis[20,22]. However, specific characteristics of clonal evolution in DBA patients and mechanistic links between DBA-related ribosomal dysfunction and TP53-dependent myeloid transformation remain to be elucidated.

Severe Congenital Neutropenia

Severe Congenital Neutropenia (SCN) is most commonly caused by germline mutations in *ELANE* or *HAX1* and leads to promyelocytic maturation arrest, dysfunctional production of neutrophils in the bone marrow, and a heighted risk of life-threatening infections[9]. Supportive therapy involves administration of G-CSF which results in most cases in significant improvement of neutrophil counts[23]. The risk of myeloid transformation is high, with a cumulative incidence of 22% after 15 years of G-CSF treatment, and correlates with a poor response to G-CSF therapy[23].

In a study of 148 SCN patients, 13 out of 23 patients (78%) who developed MDS or AML carried somatic activating *CSF3R* receptor mutations[24]. However, disease latency was highly variable and several patients harbored *CSF3R* mutations for many years without evidence of transformation. Similarly, serial analysis of one patient showed that 5 different *CSF3R* mutations were present 15 years prior to transformation, and that eventual development of leukemia was associated with outgrowth of a single clone that had gained additional myeloid driver mutations[25]. Together, these data suggest that *CSF3R* mutations may require cooperating genetic events to cause leukemia.

Most *CSF3R* mutations cause a truncation of the cytoplasmic domain mediating enhanced cell proliferation and survival[26]. By potentiating G-CSF signaling, *CSF3R* mutations may thus result in functional compensation for ELANE and HAX1 related defects in neutrophil production, providing a potential explanation for the high prevalence of *CSF3R* mutations in SCN patients[20,27]. A definite role for *CSF3R* mutations in initiating SCN-related leukemogenesis, independent of enabling adaptive hematopoiesis, and the link to G-CSF therapy, remains to be determined.

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Somatic *RUNX1* mutations were recently identified in 64.5% of SCN patients with MDS or AML, often occurring in clones that had already acquired *CSF3R* mutations[28]. In contrast, no *RUNX1* mutations were seen in a cohort of 40 SCN patients without leukemic transformation[16]. These data strongly support a role for *RUNX1* mutations as a late step in leukemic transformation in the context of SCN. The variable latency between acquisition of somatic *CSF3R* mutations and the development of *RUNX1* mutations suggests that additional cooperating clinical or genetic variables may not yet be identified[25,28].

Fanconi Anemia

Fanconi Anemia (FA) is a disorder of chromosomal instability caused by germline mutations in DNA repair genes of the FA/BRCA pathway[9]. Clinical features can vary widely, with some individuals manifesting bone marrow failure, short statue, skin and upper limb abnormalities, and others (25–40%) having no abnormal physical findings[29]. Patients with FA have elevated cumulative incidence of various cancers by the age of 50 years, including MDS (40%), AML (10%) and solid tumors (20–30%)[30].

Somatic reversion of germline FANC gene mutations in hematopoietic cells has been reported in 15% of FA patients[31]. Cells with one functionally corrected allele may have a selective clonal advantage over cells with two pathogenic alleles, thus causing functional rescue with enhanced contribution to the HSC pool and to hematopoiesis, resulting in stabilization of blood counts[31]. Importantly, reversion events were not detected in FA-related MDS or AML, suggesting that restoration of Fanconi pathway function may drive relative clonal advantage in the context of impaired hematopoiesis, but is biologically distinct from malignant transformation[32].

The frequency of somatic chromosomal gains and losses in 57 FA patients was evaluated using high-density genome-wide CGH/SNP arrays[32]. In this study, alterations were identified in 61% of patients with diverse clinical phenotypes, demonstrating that clonal hematopoiesis is common in FA patients, irrespective of hematologic status. Highly recurrent alterations in this cohort included gains of 1q (45%) and 3q (41%), monosomy 7/del(7q) (17%), 11q- (13.8%) and abnormalities involving *RUNX1* (21%), although the distribution of alterations across hematologic phenotypes was distinct. Whereas clonal hematopoiesis involving somatic genetic reversions of mutated FANC genes or 1q+ were associated with an indolent clinical course, the presence of *RUNX1* lesions, 3q+, or −7/del(7q) were more common in MDS and AML[32–34]. Moreover, the presence of molecular genetic alterations associated with non-FA AML, such as oncogenic *NRAS* mutations, FLT3 internal tandem duplication (FLT3-ITD), or MLL partial tandem duplication (MLL-PTD) were restricted to patients with frank AML[32].

Gains of 1q and 3q are specifically enriched in FA patients, suggesting that they may confer a distinct clonal advantage in the context of impaired FA/BRCA pathways[32]. Moreover, 1q+ can be observed in FA patients with clonal hematopoiesis with and without myeloid transformation and could reflect an uncharacterized mechanism of functional complementation of Fanconi abnormalities in HSCs. Conversely, gain of 3q is highly

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associated with malignant transformation, possibly due to the amplification of the leukemogenic oncogene EVI1[32,35].

Dyskeratosis Congenita

Dyskeratosis Congenita (DC) is caused by germline mutations in a set of genes involved in telomere maintenance including *TINF2* (12%), *TERT* (5%), *TERC* (5%), *RTEL1* (2%) and *DKC1* (25%)[9]. Characteristic clinical features include abnormal skin pigmentation, oral leukoplakia and nail dystrophy, hypoplastic bone marrow, pulmonary fibrosis, and liver disease[9]. DC patients have a high risk of developing hematologic complications such as aplastic anemia, MDS and AML, as well as solid tumors[9].

The role of acquired somatic genetic alterations in myeloid transformation in DC patients has not been systematically characterized. In 16 DC patients analyzed using a combination of X-inactivation analyses, comparative whole exome sequencing (WES) and single nucleotide polymorphism arrays (SNP-A), 8 out of 9 female patients showed skewed X-inactivation, suggesting that clonal hematopoiesis is common[36]. Among 6 patients evaluated by whole exome sequencing, no somatic mutations affecting recurrently mutated genes associated with hematologic cancers were identified. Importantly, one patient showed somatic reversion in *DKC1*, suggesting that restoration of normal telomere length maintenance affords a selective advantage in hematopoietic cells[36]. None of the patients in this study had clinical or morphologic evidence of myeloid transformation.

In our analysis of MDS patients receiving allogeneic transplantation, 1% of adults harbored pathogenic germline mutations affecting genes involved in telomere maintenance, including *TERT*, *TERC*, or *DKC1*, while at least another 2% of cases had rare variants of uncertain biological significance[2]. Among 11 adult patients with germline *TERT* or *TERC* mutations, 8 (73%) had somatic mutations in established myeloid driver genes, including 7 with mutations affecting *TP53* or *PPM1D*. TP53 plays a critical role in enforcing senescence and apoptotic responses to telomere dysfunction, while PPM1D is a serine-threonine protein phosphatase that negatively regulates the DNA damage response via dephosphorylation of specific residues on ATM, CHK1, and TP53[37]. Mutations in *PPM1D* are localized to exon 6, and cause C-terminal truncations that may cause an increase in phosphatase activity that aberrantly inhibits checkpoint and DNA damage response (DDR) pathways[38]. Similar to SDS and DBA, where the mechanism of bone marrow failure drives activation of TP53 activity, our data suggest that severe telomere attrition may select for somatic clones with genetic inactivation of *TP53*.

GATA2 Deficiency

Germline mutations of *GATA2* cause a spectrum of clinical phenotypes defined by GATA2 haploinsufficiency with autosomal dominant inheritance. GATA2 regulates HSC function in a dose dependent manner, and mutations lead to inactivation via truncation or impairment of functional DNA-binding[39]. Patients with GATA2 haploinsufficiency have a 70% risk of progression to early-onset myeloid malignancies along with immune deficiencies and variable systemic features[40].

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Myeloid transformation in GATA2 deficiency syndromes is associated with somatic mutations in typical myeloid driver genes, including chromosomal abnormalities, such as monosomy 7 and trisomy 8[41]. Among young MDS patients, the association between monosomy 7 and germline *GATA2* mutations is particularly striking: 70% of adolescent patients with monosomy 7 have an underlying GATA2 deficiency[42]. *ASXL1* mutations are most common, identified in 14 out of 48 patients (29%) in one study, and associated with monosomy 7 and trisomy 8, young age, female gender and poor survival[41]. Other smaller studies have seen similar association with *ASXL1* mutations, as well as recurrent mutations affecting other hematologic driver genes including *SETBP1*, *RUNX1*, *NRAS*, and *STAG2*[43–45].

Familial Platelet Disorder with Predisposition to Acute Myeloid Leukemia

The Familial Platelet Disorder with Predisposition to Acute Myeloid Leukemia (FPD/AML) is an autosomal dominant disease caused by inactivating germline alterations affecting the hematopoietic transcription factor RUNX1. Typical clinical manifestations include thrombocytopenia with defects of platelet function leading to a mild to moderate bleeding tendency and a propensity to develop MDS or AML[46]. In a study of 10 families with 5 pedigrees harboring *RUNX1* germline mutations the median incidence of MDS/AML was 35% [47].

In the context of germline *RUNX1* mutations, acquisition of somatic mutations is a common, if not ubiquitous characteristic of MDS/AML transformation. In focused genetic analyses, acquired mutations in FPD/AML patients have been identified in a typical spectrum of myeloid driver genes, but the most frequent progression mutation affects the second *RUNX1* allele[48,4950]. In a study of 9 asymptomatic individuals with germline *RUNX1* mutations, 6 (67%) had evidence of clonal hematopoiesis, reflected by detectable somatic mutations in the blood or bone marrow[51]. However, only one patient harbored a mutation in a canonical myeloid driver gene, suggesting existence of novel cooperating drivers of clonal hematopoiesis, or other factors that favor development of clonally-restricted hematopoiesis in RUNX1 deficient HSCs. Although these data suggest a high cumulative risk of developing clonal hematopoiesis[51], a direct link between clonal hematopoiesis and development of subsequent myeloid malignancies with recurrent drivers has not been established.

Acquired Aplastic Anemia

Acquired aplastic anemia (AA) is caused by human leukocyte antigen (HLA) restricted destruction of HSCs by autoreactive T cells[52]. Immunosuppression therapy (IST), supportive therapies, and allogeneic HSCT has improved the outcome of the disease. However, even after successful IST, patients remain at high risk of developing clonal disorders such as MDS/AML and PNH, with a 10-year cumulative incidence of 10–15% and 50%, respectively[53,54].

Clonal hematopoiesis in AA patients most frequently involves mutations in *BCOR*, *BCORL1*, *PIGA*, *DNMT3A*, *ASXL1*, *RUNX1* and HLA genes and is often detectable at

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diagnosis and dynamic over time[54–56]. *ASXL1*, *RUNX1* and *DNMT3A* mutations are associated with advanced age, progression to MDS, and an inferior overall survival, while mutations in *PIGA* and *BCOR*/*BCORL1* correlate with a better response to immunosuppressive therapy and a better overall outcome[54,55]. Although clonal dynamics detected in serial samples of 35 AA patients were highly variable, clones harboring PIGA or *BCOR*/*BCORL1* mutations tended to remain stable or to decrease over time, suggesting a specific clonal advantage in the setting of autoimmune destruction which is lost during effective IST[54].

Frequent uniparental disomy (UPD) involving the HLA locus and recurrent loss-of-function HLA mutations support a model where escape from T-cell mediated destruction can drive selective clonal advantage in some AA patients[54,56–58]. However, expansion of HLA mutated clones has not been linked to myeloid transformation, suggesting that immune evasion might drive a biologically distinct pathway of clonal dominance (Fig. 3). Clonal hematopoiesis in AA may thus be driven by a range of selection contexts, including immune evasion, aberrant survival in an altered microenvironment, or stem cell attrition.

Summary

Development of clonal hematopoiesis represents the hallmark initiation of myeloid transformation. However, the timing, genetic spectrum, and clinical implications of clonal hematopoiesis can be influenced by a range of cell-intrinsic and cell-extrinsic factors. Importantly, context-specific variables, such as germline mutations in inherited bone marrow failure or immune mediated cell destruction in AA can exert a strong selection pressure on the development and progression of clonal hematopoiesis. Global hematopoietic dysfunction or bone marrow microenvironmental abnormalities may enable expansion of clones which are better adapted to specific extrinsic or intrinsic selection (Fig. 2, Fig. 3).

Clinical implications

Based on the genetic data outlined above, several outstanding questions remain to be answered. What clinical or genetic factors mediate myeloid transformation in patients with inherited bone marrow diseases? How can adaptive clonal hematopoiesis best be distinguished from incipient malignant degeneration? Can identification of specific somatic genetic characteristics be integrated prospectively into clinical care of individual patients? Unbiased genetic analysis of patient samples using whole exome or whole genome sequencing approaches, paired with systematic longitudinal analysis of samples obtained from patients at multiple times during the course of life may provide answers to these questions. An improved understanding of the role of acquired somatic mutations in clonal progression of bone marrow failure syndromes has the potential to improve outcomes in this high-risk patient group by identifying novel therapeutic vulnerabilities or enabling improved clinical decision-making based on objectively measurable molecular characteristics.

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Key Points

- Clonal evolution in myelodysplastic syndromes can be driven by specific extrinsic and intrinsic selective pressures.
- Acquired somatic mutations in inherited bone marrow failure syndromes can partially complement underlying cellular defects leading to a selective clonal advantage that might be distinct from myeloid transformation.
- Long-term mutational studies with systematic analysis of serial samples in a larger number of patients are required to define prognostic and therapeutic implications of clonal hematopoiesis in patients with bone marrow failure syndromes.

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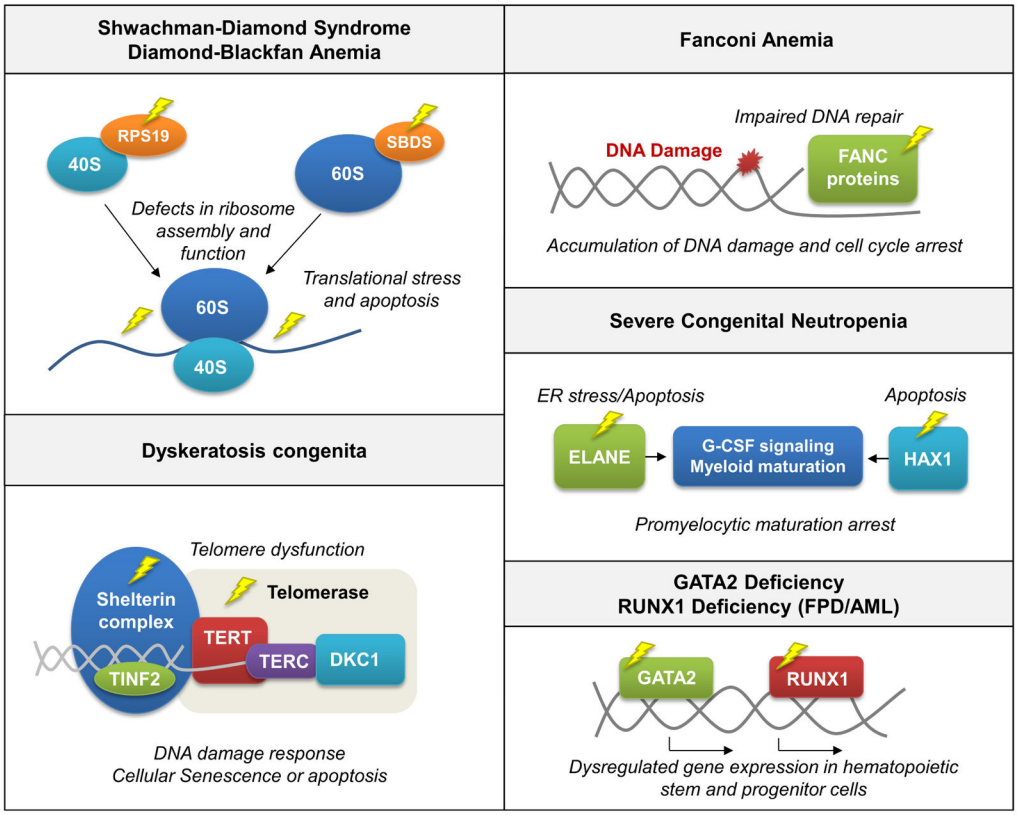

Figure 1.

Pathways affected in inherited bone marrow failure and MDS/AML predisposition syndromes.

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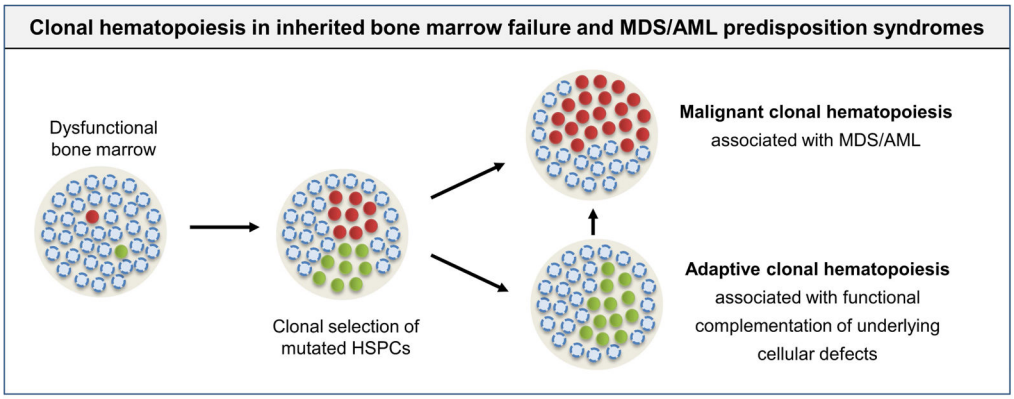

Figure 2. Clonal hematopoiesis in inherited bone marrow failure and MDS/AML predisposition syndromes

Bone marrow failure syndromes are associated with dysfunctional hematopoiesis that may drive a strong selective pressure that favors mutated hematopoietic stem and progenitor cells with enhanced fitness. While some mutations cause leukemic transformation (red circles), others may enable clonal expansion due to functional complementation of disease specific cellular defects (green circles). The latter may involve biological pathways that are distinct from leukemic transformation and not associated with elevated risk of progression to MDS or AML.

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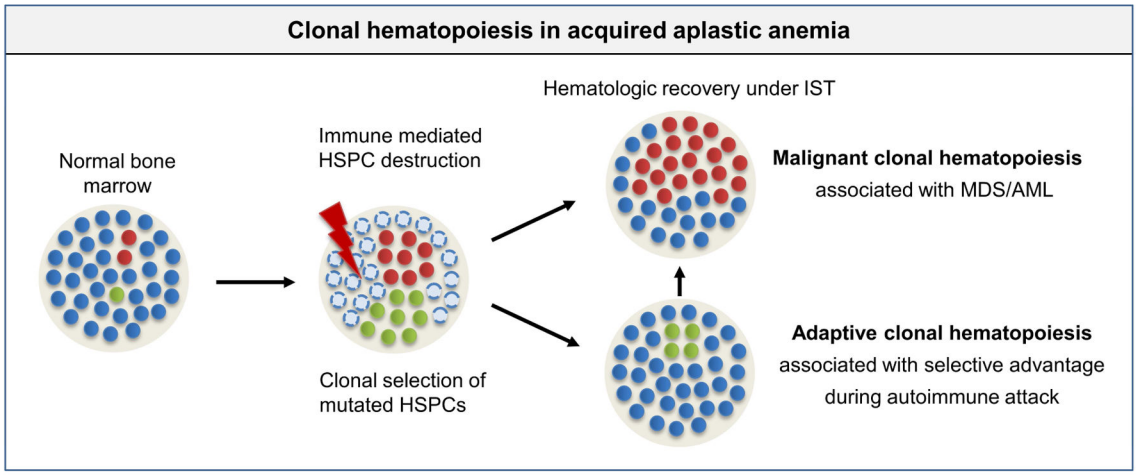

Figure 3. Clonal hematopoiesis in acquired aplastic anemia

Immune mediated selection pressure drives expansion of HSPCs with context-specific growth advantage. Some clones may expand during the initial phase of disease due to a capacity for immune evasion, but may recede after successful immunosuppressive therapy (IST) and hematologic recovery (green circles). Other clones with typical myeloid driver mutations may display more context-independent expansion (red circles).