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Lundgren, Sofie

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Somatic compensation of inherited bone marrow failure

Sofie Lundgren[a,b], Mikko Keränen[a,c], Ulla Wartiovaara-Kautto[c], Mikko Myllymäki[a,b,c,*]

[a] University of Helsinki and Helsinki University Hospital Comprehensive Cancer Center, Hematology Research Unit Helsinki, Helsinki, Uusimaa, Finland
[b] Department of Clinical Chemistry and Hematology, Translational Immunology Research program, University of Helsinki, Helsinki, Uusimaa, Finland
[c] Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Uusimaa, Finland

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ABSTRACT

Inherited bone marrow failure syndromes (IBMFS) are a heterogeneous group of genetic disorders characterized by insufficient blood cell production and increased risk of transformation to myeloid malignancies. While genetically diverse, IBMFS are collectively defined by a cell-intrinsic hematopoietic stem cell (HSC) fitness defect that impairs HSC self-renewal and hematopoietic differentiation. In IBMFS, HSCs frequently acquire mutations that improve cell fitness, a phenomenon known as somatic compensation. Somatic compensation can occur via distinct genetic processes such as loss of the germline mutation or somatic alterations in pathways affected by the disease-causing gene. While the clinical implications of somatic compensation in IBMFS remain to be fully discovered, understanding these mutational processes can help understand disease pathophysiology and may inform future diagnostic and therapeutic approaches. In this review, we highlight current understanding about somatic compensation in IBMFS.

Introduction

Hematopoiesis within the bone marrow continuously produces blood cells in a highly regulated manner [1,2]. The inability of hematopoietic stem cells (HSCs) to maintain adequate blood cell production due to qualitative or quantitative HSC defects is referred to as bone marrow failure (BMF) [3].

Inherited bone marrow failure syndromes (IBMFS) are genetic disorders caused by constitutional defects in stem cell differentiation and maintenance leading to BMF, syndrome-specific non-hematological manifestations, and risk of transformation to hematological malignancies [4,5]. The majority of IBMFS described to date are monogenic disorders caused by genetic variation in a single gene, with germline mutations influencing several biological processes, including ribosome maturation, DNA repair, telomere maintenance, and neutrophil maturation [6]. The extramedullary manifestations of IBMFS have been reviewed elsewhere [7].

Clonal hematopoiesis (CH) refers to increased proportion of blood cells derived from a single hematopoietic stem cell (HSC) clone. Somatic mutations that lead to HSC fitness advantage and drive CH can be detected in peripheral blood using next-generation sequencing technologies [8]. Cell-intrinsic and cell-extrinsic fitness constraints can influence the spectrum of somatic mutations. In IBMFS, context-dependent acquired genetic alterations can improve HSC fitness and restore normal hematopoietic output, and we refer to this phenomenon as somatic compensation (Fig. 1). Mechanisms of somatic compensation in acquired BMF have been summarized elsewhere [9].

Germline mutations in IBMFS result in cell-intrinsic HSC fitness defects, which can be compensated by various genetic mechanisms. In this review, we highlight 3 concepts of somatic genetic compensation observed in IBMFS: (1) gene-specific, and (2) pathway-specific somatic genetic alterations, as well as (3) pathway-independent alterations affecting cell survival (Fig. 1). Several compensatory mechanisms may exist in each IBMFS with potentially variable impact on disease phenotypes [10–12]; however, the clinical implications of detecting somatic compensation in IBMFS is largely unknown. Understanding somatic compensation specific to IBMFS may help elucidate disease pathophysiology in these syndromes, help guide diagnostic testing and surveillance strategies, as well as facilitate syndrome-specific drug development in the future. In this review, we highlight contemporary understanding on the syndrome-specific mechanisms of somatic compensation in IBMFS.

* Corresponding author. Mikko Myllymäki, MD, PhD, Hematology Research Unit Helsinki, University of Helsinki and Helsinki University Hospital Comprehensive Cancer Center, Haartmaninkatu 8, P.O. Box 700, FIN-00290, Helsinki, Finland. Tel.: +358405862516, Fax: +358-9-471-71897.
E-mail address: mikko.myllymaki@helsinki.fi (M. Myllymäki).

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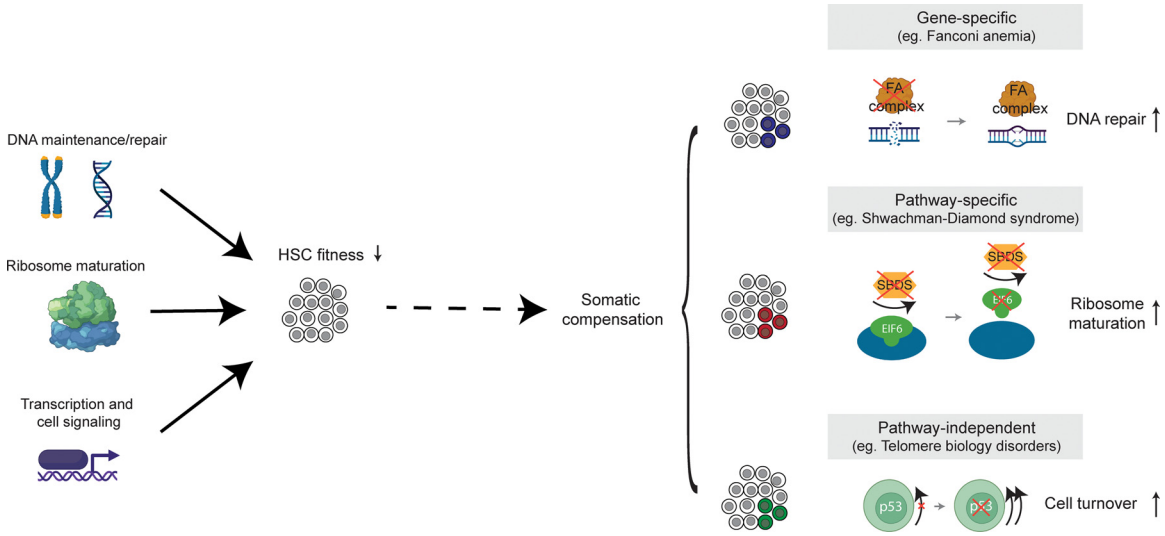

Fig. 1. Fitness constraints and somatic genetic compensation in inherited bone marrow failure syndromes. In IBMFS, constitutional defects lead to decreased HSC fitness and decreased hematopoietic output, sometimes manifesting as bone marrow failure. Germline mutations affect DNA maintenance (eg, Fanconi anemia), ribosome maturation (eg, Shwachman-Diamond syndrome) or cell signaling (eg, severe congenital neutropenia). In some cases, acquired somatic alterations may improve cell fitness and lead to expansion of a mutated clone. Somatic compensation may influence the disease-causing germline gene (gene-specific) or pathway (pathway-specific). Pathway-independent somatic compensatory mechanisms restore cell fitness without influencing the germline-mutated pathway. HSC = hematopoietic stem cell.

Table 1
Gene-specific somatic compensation in inherited bone marrow failure syndromes.

Mechanism of somatic compensation	IBMFS	Germline gene	Somatic alteration	References
Somatic reversion through back mutation or CN-LOH	Fanconi anemia	*FANCA, FANCB, FANCT, FANCD2*	SNV, Indel	[18–23]
	Telomere biology disorder	*DKC1, TERC, RPA1*	SNV, UPD3q, UPD17p	[11,16,17]
	MYSM1	*MYSM1*	SNV	[32]
	Diamond-Blackfan anemia	*RPS26*	UPD12q	[31]
	SAMD9	*SAMD9*	UPD7q	[25]
	SAMD9L	*SAMD9L*	UPD7q	[25–30]
Somatic reversion through Intragenic recombination	Fanconi anemia	*FANCC, FANCD2, FANCN*	Dinucleotide substitution, Del	[22,30]
Non-WT mutation	Fanconi anemia	*FANCA*	Ins	[34]
	GATA2 deficiency	*GATA2*	SNV	[35]
Chromosomal alterations	SAMD9	*SAMD9*	Del7q, monosomy 7	[25,27,28,36,64,65]
	SAMD9L	*SAMD9L*	Del7q, monosomy 7	[26–30]
Second-site mutation	Fanconi anemia	*FANCA, FANCC, FANCD2*	SNV, Indel	[22,30]
	Telomere biology disorder	*TERT, RPA1*	SNV, Del	[11,45
	SAMD9	*SAMD9*	SNV, Del	[30,36,65,77]
	SAMD9L	*SAMD9L*	SNV, Del	[26–30]

IBMFS = inherited bone marrow failure syndrome, CN-LOH = copy neutral loss of heterozygosity, WT = wild type, SNV = single nucleotide variant, Indel = insertion/deletion, UPD = uniparental disomy, Ins = insertion, Del = deletion

Gene-specific somatic compensation

Gene-specific somatic compensation refers to acquired genetic alterations in the disease-causing gene that either partially or fully restore function of the gene product. Several distinct mutational processes can lead to gene-specific somatic compensation: (1) site-specific alterations, (2) second-site mutations, and (3) interstitial or chromosomal rearrangements [13] (Fig. 2). Multiple HSC clones with distinct gene-specific compensatory mechanisms can sometimes be detected even within individual IBMFS patients [10–12]. IBMFS with gene-specific somatic compensation are summarized in Table 1.

Alterations affecting the disease-causing locus (site-specific alterations)

Somatic alterations observed in the disease-causing germline locus include a) somatic reversion to restore wild-type genotype through back mutation, copy neutral loss of heterozygosity (CN-LOH), or intragenic recombination, and (b) site-specific non-wild-type mutations in the affected germline locus, mitigating the detrimental effect of the disease-causing mutation on HSC function (Fig. 2).

Somatic reversion leads to correction of the disease-causing allele to wild-type genotype (Fig. 2). The simplest mechanism of somatic reversion is site-specific back mutation where an acquired single nucleotide variant (SNV) or small indel restores the wild-type sequence. In germline heterozygous diseases, somatic reversion can also occur through CN-LOH, where paternal or maternal allele is lost due to either loss of one allele followed by duplication of the remaining homologue, or a somatic recombination event [14,15]. Somatic reversion has been observed in various IBMFS, including telomere biology disorders [11,16,17], Fanconi anemia [18–24], SAMD9/9L syndromes [25–30], Diamond Blackfan anemia [31], and in patients with *MYSM1* mutations [32]. In autosomal recessive disorders, correction of only one allele may be sufficient to

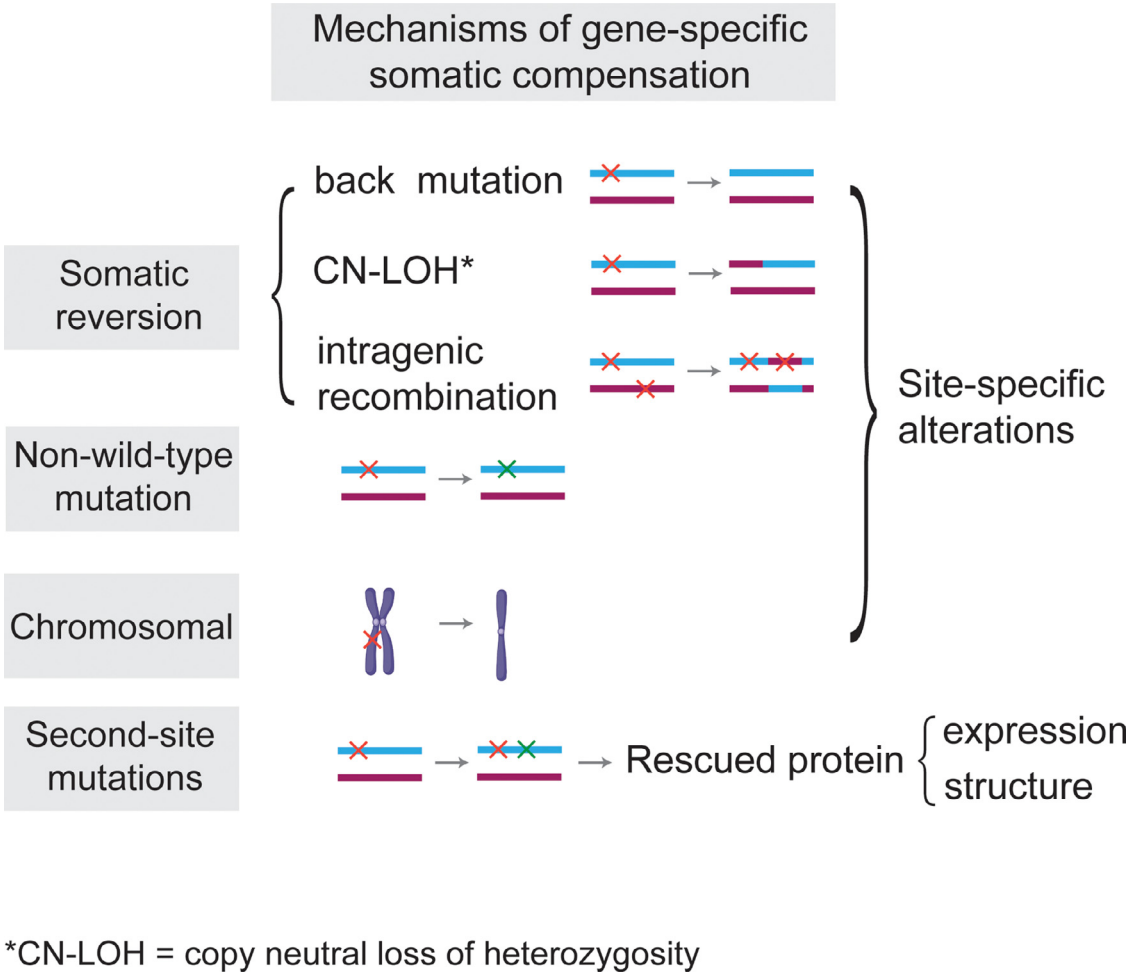

Fig. 2. Mechanisms of gene-specific somatic compensation. Gene-specific somatic compensation can improve HSC fitness by restoring function of the mutated protein. The function can be restored via germline mutation site-specific or second-site somatic alterations. Somatic compensation caused by back mutation, copy-number neutral loss of heterozygosity (CN-LOH) or intragenic recombination results in wild-type protein. In addition, somatic chromosomal alterations can lead to loss of the disease-causing germline allele. On the other hand, non-wild-type site-specific or second-site mutations can improve HSC fitness without reversion to wild-type sequence. HSC = hematopoietic stem cell.

increase HSC fitness. In disorders caused by compound heterozygous mutations (ie, two distinct mutations in different alleles in the disease-causing gene), this can result from somatic reversion originating from intragenic recombination, such as in autosomal recessive forms of Fanconi anemia [18,33] (Fig. 2).

In some IBMFS, somatic alterations in the disease-causing locus may not cause reversion to wild-type sequence but instead lead to non-wild-type mutations in the affected germline locus. In one patient with Fanconi anemia, a somatic missense mutation (c.2546C>T; p.S848F) replaced the germline frameshift deletion (c.2546delC; p.S849fs) at the germline mutation locus in myeloid lineage cells [34]. In another study, the germline truncating *GATA2* mutation (c.216C>A; p.Y72*) was replaced by a non-wild-type SNV leading to a synonymous variant (c.216C>T; p.Y72Y) in 93% of peripheral blood leukocytes in 1 family member [35].

Second-site mutations

Gene-specific somatic compensation does not necessarily influence the same locus as the original disease-causing mutation in IBMFS. Somatic second-site mutations can rescue either the expression level or protein structure of the mutated gene product to restore HSC fitness. In the contexts of germline heterozygous gain-of-function mutations in IBMFS, truncating somatic second-site mutations in the same allele (ie, in *cis*) may inactivate mutant protein function and lead to somatic compensation. For example, in a patient with germline gain-of-function *RPA1* mutation leading to telomere biology disorder, normalization of blood counts co-occurred with genetic somatic rescue in two HSC clones, one with a truncating *RPA1* mutation in *cis* with the germline mutation [11]. In addition, multiple HSC clones with distinct compensatory mechanisms were found to be present simultaneously in patients with SAMD9/SAMD9L syndromes, including inactivating somatic second-site mutations in *cis* with the germline alteration [12,36]. Furthermore, restoration of protein structure and function by somatic second-site mutations has been described in Fanconi anemia [22,37].

Interstitial or chromosomal rearrangements

Somatic chromosomal abnormalities are common in IBMFS patients, and can lead to loss or duplication of the disease-causing allele if they encompass the locus with germline mutation. *SAMD9* and *SAMD9L* genes are located in chromosome 7q. Monosomy 7 and loss of chromosome 7q are recurrent chromosomal alterations in SAMD9/SAMD9L syndromes, leading to somatic compensation via loss of germline mutated alleles [12,36].

Table 2
Pathway-specific and pathway-independent somatic compensation in inherited bone marrow failure syndromes.

Type of somatic compensation	IBMFS	Mechanism of somatic compensation	Genes affected by somatic compensation	Somatic alteration	References
Pathway-specific	Shwachman-Diamond syndrome	Rescue of ribosome maturation	*EIF6*	SNV, Indel, Del20q	[10,50,51]
	Telomere biology disorder	Rescue of telomere maintenance	*TERT* (promoter), *POT1*, *TERF2IP*	SNV	[45–47]
	Severe congenital neutropenia	Increased growth factor signaling	*CSF3R*	SNV	[53–55]
Pathway-independent	Several IBMFS eg, Shwachman-Diamond syndrome and telomere biology disorders	Escape from cell senescence caused by eg, telomere and ribosomal stress	*TP53*	SNV/indel/chromosomal	[10]
	Several IBMFS, eg, GATA2 deficiency and telomere biology disorders	Unknown	Candidate genes: *SAMD9*, *SAMD9L*, *EZH2*, *MLL3*, and *CUX1*	Monosomy 7	[66–69]

IBMFS = inherited bone marrow failure syndrome, SNV = single nucleotide variant, Indel = insertion/deletion, UPD = uniparental disomy, Ins = insertion, Del = deletion

Another example of gene-specific somatic compensation due to chromosomal alterations is isochromosome i7q10, which is a rare in myeloid malignancies but recurrent in compound heterozygous forms of Shwachman-Diamond syndrome [38–40]. Over 90% of Shwachman-Diamond syndrome patients have biallelic germline loss-of-function mutations in the *SBDS* gene [41]. Isochromosome i7q10 leads to duplication of one allele, resulting in three copies of *SBDS*. The duplicated allele in isochromosome i7q10 typically includes the c.258+2T>C splicing mutation of *SBDS* [39], which allows the production of low levels of normal SBDS protein [42]; therefore, duplication of this allele may partially rescue SBDS deficiency in HSC, resulting in somatic compensation.

Pathway-specific somatic compensation

In contrast to gene-specific somatic compensatory mechanisms, pathway-specific compensation restores HSC fitness via genetic alterations in other genes involved in the constitutionally perturbed pathways (Table 2). For example, somatic activating *TERT* promoter mutations [43,44] are not only seen in patients with germline *TERT* mutations, where they occur predominantly in *trans* (ie, in different allele) with the germline mutation to increase expression of the wild-type protein [45], but also in telomere biology disorder patients with genetic defects in other telomere maintenance genes, such as *PARN* [45,46] and *TERC* [47], likely to increase telomerase activity and promote telomere maintenance in HSCs. In addition to *TERT* promoter mutations, telomere biology disorder patients have pathway-specific somatic compensation in other genes related to telomere maintenance: Schratz and colleagues found that 13% of 56 telomere biology disorder patients had somatic mutations in telomere maintenance genes *POT1* or *TERF2IP* [46]. Acquired *POT1* mutations showed a loss-of-function phenotype, potentially facilitating telomere elongation by improving telomerase processivity [46].

Pathway-specific somatic compensation is also recurrently observed in Shwachman-Diamond syndrome, which is characterized by defective ribosomal maturation and reduced protein translation [48], typically resulting from loss-of-function mutations in *SBDS* gene [41]. In normal cells, SBDS removes EIF6 protein from the ribosomal subunit, allowing formation of mature ribosomes [49]. Kennedy and colleagues found recurrent loss of EIF6 (either due to point mutations in *EIF6* gene or interstitial deletions in chromosome 20q) in the majority of Shwachman-Diamond syndrome patients [10]. Loss-of-function *EIF6* mutations mitigate the ribosomal maturation defect incurred by germline *SBDS* mutations and improve protein translation, leading to clonal fitness advantage of the mutated clone without conferring increased risk of transformation to myeloid malignancies [10,50,51].

Combinations of cell-intrinsic and cell-extrinsic factors can drive pathway-specific somatic genetic compensation. Severe congenital neutropenia is commonly caused by germline mutations in *ELANE*, which result in apoptosis of myeloid progenitor cells [52]. Severe congenital neutropenia patients are treated with granulocyte colony-stimulating factor (G-CSF), and multiple reports have shown high incidence of acquired gain-of-function mutations in granulocyte colony-stimulating factor receptor *CSF3R* gene in severe congenital neutropenia [52–55], leading to elevated proliferative response upon stimulation with G-CSF [52]. Similar pathway-specific compensatory mechanisms likely exist also in other IBMFS, but remain to be fully discovered.

Pathway-independent somatic compensation

In IBMFS patients, HSCs may bypass the germline fitness constraints by disrupting cell cycle control without specifically correcting the gene or pathway influenced by the disease-causing germline mutation (Table 2). In some contexts, HSCs with such alterations may confer increased risk of transformation to myeloid malignancies [56]. In this section, we focus on two such compensatory mechanisms that are recurrently observed in IBMFS: loss of *TP53* and monosomy 7.

TP53 is the most frequently mutated gene in human cancer [57]. p53 is activated in response to cellular stimuli such as DNA damage and oxidative stress [58]. *TP53* mutations are recurrently found in Shwachman-Diamond syndrome [10] and in myelodysplastic syndrome (MDS) patients with biallelic *SBDS* mutations [59]. In contrast to *EIF6* loss, loss of *TP53* does not rescue the ribosomal maturation defect in Shwachman-Diamond syndrome [10], highlighting distinct somatic mechanisms to improve HSC fitness in specific IBMFS. Additional insights into the role of *TP53* mutations as a somatic compensatory mechanism can be derived from MDS/acute myeloid leukemia (AML) patients with underlying IBMFS. *TP53* mutations are common and associated with erythroleukemic AML subtype in patients with germline mutations in *ERCC6L2* [60], a IBMFS gene [61]. Also, 25% of MDS/AML patients with underlying telomere biology disorders had mutations in *TP53* [46], suggesting that mutations in DNA damage response pathway genes, including *TP53*, may drive somatic compensation also in telomere biology disorders [62].

Monosomy 7 is a common chromosomal alteration observed in children with myeloid malignancies [63], and is highly recurrent in various IBMFS. In SAMD9/SAMD9L syndrome, monosomy 7 causes deletion of the disease-causing allele [25-28,30,64,65]. Monosomy 7 has also been recurrently observed in *GATA2* deficiency [66], telomere biology disorders [67], Fanconi anemia [68], and severe congenital neutropenia [69]; however, the cellular mechanisms by

which monosomy 7 leads to HSC growth advantage are not well understood in non-SAMD9/SAMD9L IBMFS and in myeloid malignancies [63]. Candidate genes located in chromosome 7 that may be responsible for alleviating HSC fitness constraints in IBMFS include *SAMD9*, *SAMD9L*, *EZH2*, *MLL3*, and *CUX1* [63]. Further studies are warranted to understand which genes and pathways are driving somatic compensation in IBMFS with acquired monosomy 7.

Clinical implications of somatic compensation in IBMFS

Diagnostics

Somatic compensation may pose challenges to diagnostics testing in patients with IBMFS suspicion. Blood-based genetic testing may fail to detect pathogenic germline mutations in the case of somatic reversion; therefore, DNA sequencing from non-hematopoietic tissues such as skin fibroblasts is the clinical standard for germline genetic testing for IBMFS. Functional diagnostic testing may also be affected by somatic compensation. As an example, a patient with recessive form of Fanconi anemia and somatic reversion of one germline allele in blood may appear as only a heterozygous carrier. Additionally, chromosomal breakage testing performed on blood cells in this context may be normal. Therefore, genetic and functional testing on skin fibroblasts is indicated in cases where blood-based testing is negative despite a high clinical suspicion of disease [19].

Myeloid transformation

Patients with IBMFS have a markedly increased risk of myeloid malignancies [56,69], which can be considered an extreme consequence of somatic compensation in the hematopoietic system. The clonal processes leading to malignant transformation are variable and depend on the cell-intrinsic HSC fitness constraint [62]. In Shwachman-Diamond syndrome, single-cell DNA sequencing may help identify *TP53* mutated clones with highest potential for myeloid transformation [10]. On the other hand, clones with *EIF6* loss were not associated with transformation risk [10], indicating that distinct somatic compensatory mechanisms have variable impacts on myeloid malignancy risk in IBMFS. Stepwise acquisition of genetic alterations may also drive clonal evolution to myeloid malignancies, such as in severe congenital neutropenia, where *RUNX1* mutations serve as secondary hits in *CSF3R*-mutated clones to drive myeloid transformation [69]. In contrast, there is limited knowledge about the clonal processes that cause transformation to myeloid malignancies in telomere biology disorders. In addition to *TP53* loss [67], other mechanisms may include non-coding genetic alterations together with clonal epigenetic and transcriptional changes to drive clonal evolution in telomere biology disorders as well as in other IBMFS.

Surveillance

Early detection of myeloid transformation poses a major clinical challenge in IBMFS. Routine serial assessment of BM morphology, cytogenetics, and peripheral blood counts remain the golden standards of long-term surveillance of the hematopoietic system. Serial monitoring of HSC clones with next-generation sequencing may allow early detection of impending myeloid transformation in the future, potentially opening a time window for therapeutic interventions to prevent or delay myeloid malignancy onset in IBMFS. However, disease-specific guidelines based on prospective cohort studies are needed to establish surveillance and treatment algorithms before wide-spread incorporation of serial mutational assessment in routine clinical practice.

Therapeutic interventions

Understanding the somatic compensatory mechanisms that circumvent HSC fitness constraints in IBMFS can guide future drug development. For example, pharmacological inhibition of *EIF6* or *POT1* may improve baseline HSC fitness and hematopoietic output in Shwachman-Diamond syndrome [10] and telomere biology disorders [46], respectively, mimicking the somatic compensatory mechanisms observed in sequencing studies. Direct inhibition of the disease-causing mutant proteins such *SAMD9*/*SAMD9L* and *RPA1* may also become suitable therapeutic targets in the future, as somatic genetic loss of mutant proteins were associated with hematopoietic improvements in some patients [11,12].

Gene therapy using *ex vivo* manipulation of HSCs to correct germline defects is emerging as a novel therapeutic approach in inherited disorders [70]. Long-term engraftment of gene-corrected HSCs was confirmed in a recent study of Fanconi anemia patients [71] and similar studies are warranted in other IBMFS [72]. The impact of somatic compensatory alterations on gene therapy outcomes and whether they may serve as targets for gene therapy will be exciting topics for future studies.

Discussion

In this review, we have covered specific genetic compensatory mechanisms contributing to clonal hematopoiesis in inherited bone marrow failure. Whereas accumulation of somatic alterations in HSCs is likely a stochastic process [8], only mutated clones with relative HSC fitness advantage are enriched in the bone marrow. CH characterized by mutations in genes recurrently mutated in myeloid malignancies (such *DNMT3A*, *TET2*, *ASXL1*) becomes nearly ubiquitous with aging in the general population [73,74]. However, the spectrum of genetic alterations in IBMFS is distinct from healthy population, as specific somatic alterations are selected in different IBMFS due to context-dependent HSC fitness constraints.

The prevalence of somatic genetic compensation varies between IBMFS. However, the direct comparison between different syndromes is limited by small cohort sizes, including case reports and small case series, and variable sequencing strategies used in many studies published to date. The highest prevalence of somatic compensation has been reported in SAMD9/9L and Shwachman-Diamond syndromes, where the majority of patients have somatic compensatory mutations [10,12].

Somatic mutations also accumulate in non-hematopoietic tissues as part of normal aging [75,76]. Somatic compensation of germline defects is not only limited to HSCs and has been reported in constitutional disorders affecting skin, muscle and liver [13]. However, whether IBMFS patients have somatic genetic compensation in non-hematopoietic cells and tissues has not been characterized to date.

The clinical consequences of somatic compensation are mostly obscure, and evidence-based recommendations for surveillance and therapeutic interventions based on somatic compensation are lacking in IBMFS. Hence, larger studies using novel approaches such as single-cell sequencing are warranted to further elucidate clonal hierarchies and their associations with clinical phenotypes, including myeloid transformation risk, in IBMFS. Increased understanding of the clinical consequences of somatic compensation in IBMFS may inform clinical decision-making in the future.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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