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Recent insights into inherited bone marrow failure syndromes

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Abstract

Purpose of the review—Inherited bone marrow failure syndromes (IBMFS) are a diverse set of genetic disorders characterized by the inability of the bone marrow to produce sufficient circulating blood cells. The purpose of this review is to highlight novel findings in the last years and their impact into the understanding of IBMFS.

Recent Findings—Mutations in over 80 different genes have been associated with the development of bone marrow failure (BMF). The products of the genes mutated in IBMFS frequently participate in housekeeping pathways, which are important for cell growth and division rather than being specific for hematopoiesis. The common theme of these pathways, when disturbed, is the activation of p53, leading to cell cycle arrest, senescence, and cell death. With continued improvement in therapy for IBMFS, late complications, such as development of malignancies, are seen more frequently. This highlights the importance of understanding the affected pathways and their roles in cancer development.

Summary—The recent advancement of our understanding of IBMFS has come largely through the identification of the genetic lesions responsible for disease and the investigations of their pathways. Applied in clinical practice, these findings make it possible to unambiguously identify mutation carriers even before the development of BMF and exclude or confirm a suspected clinical diagnosis for many of the more common IBMFS. The further characterization of the pathways leading to IBMFS are likely to reveal novel targets for screening tests, prognostic biomarkers, and improved and specific therapeutics.

Keywords

Inherited bone marrow failure syndromes; Fanconi Anemia; Dyskeratosis Congenita; Diamond-Blackfan Anemia; Shwachman Diamond Syndrome; Congenital Neutropenia

Introduction

The inherited bone marrow failure syndromes (IBMFS) are a diverse set of genetic disorders characterized by insufficient blood cell production. Bone marrow failure (BMF) can affect all blood cell lineages causing clinical symptoms similar to aplastic anemia, or be restricted

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to one or two blood cell lineages with symptoms specific to the affected cell lineage. Early and correct disease recognition is important, as there are implications for management and for surveillance of long-term sequelae of the disease. Furthermore, as these conditions are often heritable, other family members and future generations may be affected, requiring insightful genetic counseling.

Current advances in the field of IBMFS have come largely through the rapid identification of new genes, that when mutated, cause or predispose to the development of BMF, and through the investigation of the pathways in which the genes' products are involved. The discovery of new genes currently is driven by the sequencing of candidate genes in pathways identified to be impaired in IBMFS. In the future, development of high-throughput gene sequence technologies is likely to lead to a flood of new genes that are potentially associated with BMF. Understanding the pathways responsible for the development of BMF will be important for determining the clinical significance of newly identified genes, for the development of new screening strategies, and for the identification of potential therapeutic targets.

Excellent reviews in the general field of IBMFS have recently been published. [1–4] In this review we will refer to these reviews and focus on the most recent discoveries, how they advance our understanding in the disease pathophysiology, and their possible implication to clinical practice.

Recent developments in Fanconi Anemia (FA)

Fanconi anemia (FA, MIM #227650) is characterized by progressive bone-marrow failure, congenital abnormalities, and a pronounced susceptibility for malignancy including myelodysplastic syndrome (MDS), leukemia (especially acute myeloblastic leukemia, AML) and solid tumors (particularly carcinoma of the oropharynx and skin) [5]. Cells from FA patients exhibit a characteristic hypersensitivity to DNA interstrand cross-linking agents such as mitomycin C. Mutations in 15 different genes (*FANC* genes) (Table 1) have been identified, the products of which all participate in the sensing, responding, and resolving of DNA interstrand cross-links during replication (Figure 1) [6, 7]. With the exception of X-linked recessive *FANCB,* FA genes are inherited in an autosomal recessive pattern. [6, 8]

FANCO and FANCP – new disease-causing members in the FA pathway

Vaz et al [9]** identified biallelic mutations in *RAD51C*, a member of the *RAD51*-like family that is essential for *RAD51*-mediated homologous recombination (HR) in a family with "FA-like" phenotypes. The two affected siblings carrying biallelic *RAD51C* mutations died at a very young age, with multiple congenital abnormalities. Their lymphocytes showed an increased sensitivity to DNA cross-linking agents, characteristic for genes of the FA pathway. The only surviving patient exhibited many characteristic FA phenotypes, including increased sensitivity to DNA cross-linking agents and pronounced cell cycle arrest at G2/M which were rescued by exogenous *RAD51C* cDNA expression, suggesting that *RAD51C* is an FA gene (*FANCO*). At the time of diagnosis none of the affected individuals showed signs of BMF. However the onset of BMF may vary in FA patients.[9]**

SLX4 is the most recent member of the FANC protein family. SLX4 forms a complex with multiple other nucleases that all are required to prevent sensitivity to DNA cross-linking agents. Biallelic *SLX4* mutations were identified in two individuals with typical clinical features of Fanconi anemia and the cellular defects were rescued by wildtype *SLX4*, defining *SLX4* as a new FANC protein, *FANCP*. [10]**

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Preventing nonhomologous end joining suppresses DNA repair defects of Fanconi anemia

The FA pathway promotes HR mediated repair and inhibits the error prone repair by non-homologous end joining (NHEJ) of DNA interstrand crosslinks. Thus FA cells have an increased use of the NHEJ repair mechanism, which in part accounts for cell toxicity in FA. Interestingly, recent reports have shown that the inhibition of the NHEJ pathway in cell lines derived from patients with FA can reduce the toxicity of interstrand crosslinks inducing drugs, thereby identifying an exciting and new drug target for the possible treatment of FA. [11]*

Progression MDS and Leukemia in patients with FA

Patients with FA have an increased risk of myelodysplastic syndrome (MDS) and acute leukemia, typically AML. Recent studies of the FA patient cohort of the National Cancer Institute determined a cumulative incidence of 40% for MDS and of 10% for AML in patients with FA by the age of 50 years[12]*.

Recent studies of disease progression have found that MDS and AML in FA are associated with a specific pattern of acquired genomic abnormalities[13–15]. Transformation to MDS in FA was found to be associated with a pattern of recurrent chromosomal abnormalities, such as monosomy 7 (−7), deletion of the long arm of chromosome 7 (7q-), gain of chromosome 3q (+3q), and gain of chromosome 1q (+1q). Cryptic chromosome 21 abnormalities, including the *RUNX1* gene mutations, were seen in about 20% of FA patients with MDS. Chromosome 7 and 3q abnormalities had a poor prognostic value, whereas an isolated +1q was observed before the development of dysplasia and was not predictive for the development of AML[13]**.

Recent Developments in Dyskeratosis Congenita (DC)

Dyskeratosis congenita (DC, MIM 305000, 127550, 224230) classically presents with skin pigmentation changes, leukoplakia, and nail dystrophy. BMF develops in about 80% of patients by the age of 20 years old. Patients with DC have increased risk of MDS, AML and solid tumors with a cumulative incidence of 30%, 10% and 20–30%, respectively[12]*. There are mutations found in 7 genes, which are all involved in telomere maintenance (Table 1) [16].

Telomeres are at the ends of linear chromosomes. In vertebrates, they are composed of many tandem repeats of a hexanucleotide—TTAGGG—and associated proteins, collectively termed the shelterin complex [17]. Telomeres shorten with cell replication. The telomerase enzyme, a ribonucleoprotein complex, is responsible for the elongation of telomeres by adding telomeric repeats to the end of telomeres in early progenitor cells. Six of the DC genes encode proteins that are part of the telomerase complex, whereas the seventh, *TINF2*, encodes the TIN2 protein, which is part of the shelterin complex (Figure 2). No mutations were identified in the 5 other proteins of the shelterin complex in patients with DC [18]. The clinical symptoms caused by mutations in DC genes vary with the gene, the mutation, and the age of onset of disease. [19, 20]* [21]

Telomere length measurement in peripheral blood mononuclear cells or lymphocytes is a sensitive screening test for patients presenting with BMF. The presence of short telomeres in peripheral blood lymphocytes is suggestive for DC to be the cause of BMF but not necessarily specific as only the demonstration of a pathogenic DC gene mutation can confirm the diagnosis. [22–24].

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TCAB1, a new disease-causing member in the DC pathway

WDR79/TCAB1 (WRAP53) binds the telomerase RNA *TERC* and is required for the trafficking of the telomerase complex to the Cajal bodies, which is essential for telomerase function[25, 26]. Mutations in the TERC/TCAB1 binding domain (CAB domain) or the loss of TCAB1 results in the mislocalization of the telomerase RNA *TERC* and telomere shortening. Biallelic missense mutations in these genes have been identified in 2 patients with the classic presentation of DC, including BMF and shortened telomeres. The heterozygous parents and siblings demonstrated no clinical manifestations and had a telomere length within the normal distribution.

Clericuzio-type Poikiloderma with Neutropenia - a disease with clinical similarities but normal telomeres

Neutropenia and poikiloderma (Clericuzio-type Poikiloderma with Neutropenia, CPN, MIM # 604173) is an autosomal recessive disease with clinical features that share similarities to those of classic DC, including hyperpigmenation of the skin, nail changes, marrow failure with a propensity to develop MDS and AML[16]. Recently, biallelic mutations in the *C16orf57* gene had been identified in patients with CPN. However, in contrast to all other forms of DC, telomere lengths are normal in peripheral blood cells of these individuals. As the exact function of the C16orf57 protein remains unknown, it remains to be determined whether the gene product shares or overlaps with pathways of other DC genes.

Recent developments in Diamond Blackfan Anemia

Diamond–Blackfan anemia (DBA, MIM 105650) is an inherited form of pure red cell aplasia. DBA was the first human disease that was directly linked to a defect in ribosome biogenesis, with the discovery of the ribosomal protein (RP) S19 mutation. Despite this discovery, it took several years before DBA was recognized as a disease of impaired ribosome biogenesis (Figure 3). There was an initial disbelief that a disorder that primarily affects erythropoiesis may be caused by a defect in a housekeeping pathway essential for every dividing cell. Now, mutations in 9 proteins of the large and small ribosomal subunits have been identified as accounting for about half of DBA cases (Table 1 and DBA mutation Database http://www.dbagenes.unito.it). Haploinsufficiency in RPs is thought to be responsible for disease. [27]

RP S7, S15, S26, S27A, L11, L5, and *L36*, - new disease causing genes in the DBA pathway

Mutations in *RP S19*, *S24*, *S17*, and *L35A* have been identified in approximately one-third of patients with DBA. *RP L5* and *L11* were found to be mutated in an additional 11.4% of patients[28]. A large-scale screen of additional 45 RP genes in a large DBA cohort revealed pathogenic mutations in *S7*, *S15*, *S27A*, *S10*, *S26*, and *L36*. [29–31]. Together, mutations in 9 of these RPs account for about 53% of patients with DBA (Table 1). This screen did not include the looking for intragenic or large gene deletions, which may account for possibly another 20–30% of patients. Interestingly, mutations have been found only in some RPs and some are more frequently mutated in patients with DBA than others. A possible explanation is that there is a delicate balance in the synthesis of functional RPs and that haploinsuffciency of specific RPs is compatible with life and leads to the DBA specific red cell aplasia.

RPs are important in the processing of the ribosomal RNA (rRNA). Defects in RPs often lead to the accumulation normal and abnormal rRNA precursors. Quantitation of rRNA precursors in immortalized lymphoblastoid cell lines has been suggested as a screening test for DBA. In addition, it is thought that quantitation of rRNA precursors may indicate the RP

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that is affected. However, the changes in the accumulation of the rRNA precursors are very subtle and are shared between RPs. Therefore, results would have to be carefully interpreted.

Genotype-phenotype correlations

While the phenotype of DBA is highly variable, recent studies suggested some genotype-phenotype correlations. Mutations in L5 were associated with a higher frequency of physical abnormalities, including cleft lip and/or palate, whereas mutations in L11 had more isolated thumb abnormalities compared with patients with mutations in S19.[28, 32]

p53 activation as a result of ribosome dysfunction

There is experimental evidence through a variety of animal and cellular disease models that impairment of ribosome biosynthesis causes the activation of p53. The p53 protein and RNA interacts with a several RPs on different levels. An area of major regulation occurs through MDM2 binding to L11 and L5 [33].

Haploinsufficiency of S19 caused selective activation of the p53 pathway in erythroid progenitor cells compared with cells from other hematopoietic lineages[34]* suggesting that terminal erythroid differentiation is particularly sensitive to reduced expression levels of RPs. Decreased expression of p53 was shown to rescue the red cell phenotype. Unfortunately the lack of p53 is also associated with leukemia transformation in patients with 5q-, a form of MDS that is associated with red cell aplasia due to the deletion of S14. [35]

Dexamethasone and lenalidomide have distinct functional effects on erythropoiesis

The efficacy of lenalidomide in 5q- MDS has raised the possibility that lenalidomide might have therapeutic utility in DBA. While dexamethasone increases selectively the number of burst-forming units-erythroid (BFU-E), lenalidomide was found to specifically increase colony-forming units-erythroid (CFU-E). Use of the drugs in combination demonstrated that their effects are not overlapping.[36]* However the long-term effects of lenalidomide, particularly an increased risk of developing MDS/AML is a concern, as DBA with current treatment has a low incidence of transformation to MDS/AML.

Recent developments in Shwachman Diamond Syndrome

Shwachman–Diamond syndrome (SDS, MIM 260400) is an autosomal recessive multisystem disorder characterized by bone-marrow failure, pancreatic insufficiency, and skeletal abnormalities. Biallelic *SBDS* gene mutations inherited in an autosomal recessive fashion is causative of the disease (Table 1). In over 90% of patients diagnosed with SDS, the most common mutations are 258+2T>C, followed by 183−184TA>CT. Compound heterozygote mutations at 183−184TA>CT and 258+2T>C account for approximately 81% of patients with SDS. Patients with SDS have an increased propensity for MDS and leukemia of about 30–40% by the age of 30 years old. [37]

Multifunctional role for the SBDS protein

The SBDS protein is localized throughout the cell and shuttles in and out of the nucleolus, the major cellular site of ribosome biosynthesis. Mammalian SBDS binds to the 60S large ribosomal subunit. While involvement of SBDS in ribosome biogenesis had long been suspected, other possible functions of the SBDS protein, including chemotaxis and mitotic spindle destabilization, have been postulated. Recent data using slime mold as a disease model showed that SBDS-depleted cells had a defect in ribosome subunit joining.[38] A recent study also showed that SBDS evicted eIF6 from interaction with the 60S subunit. eIF6 is a translation initiation factor that binds to the 60S subunit in the nucleolus and

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inhibits subunit joining. Defective ribosomal subunit joining was also demonstrated in lymphoblasts from SDS patients.[38]* This work supports the idea that SDS is a ribosomopathy[29].

Progression to clonal hematopoiesis, MDS, and Leukemia in patients with SDS

Abnormalities of chromosome 7 and 20q deletions are the most frequent chromosomal changes in patients with SDS. If these chromosomal abnormalities are isolated findings without dysplastic changes in the marrow, they may be transient and not necessarily indicative for progression to advanced MDS or AML.

Isochromosome i(7)is the most frequent karyotypic anomaly in patients with SDS. It causes a duplication of the SBDS locus and usually occurs on the allele with some residual SBDS function. Interestingly, this chromosomal abnormality is not found in AML cells arising in SBDS patients suggesting that this karyotypic abnormality does not contribute to leukemia transformation. [39]

Recent developments in Congenital Neutropenia

Congenital neutropenia is genetically and phenotypically heterogeneous. To date several genetic causes associated with neutropenia have been identified (Table 1 and for review, see [40, 41]). There is currently no consensus on the classification of congenital neutropenias. Patients with severe congenial neutropenia (SCN) typically present with recurrent life-threatening infections in the first few moths of life and have neutrophil count of less than 500/ul for at least 3 months. SCN often shows a characteristic a maturation arrest of myeloid precursors at the promyelocyte stage of differentiation. Heterozygous *ELANE* mutations are the most frequent cause of SCN and are found in approximately 30% of patients with SCN.

Despite the progress in gene discovery an all-encompassing mechanism causing SCN has not yet emerged. Pathways of the unfolded protein response, endoplasmic reticulum stress [42], lysosomal trafficking, mitochondrial dysfunction, and defective glycosylation[43] have all been implicated in the apoptosis of the maturing myeloid cell.

Interestingly many, but not all, forms of SCN are associated with an increased risk transformation to MDS and AML (30% by the age of 40 years in SCN patients with *ELANE* mutations). The development of MDS/AML in SCN patients with *ELANE*, *HAX1*, and activating *WASP* mutations is often preceded by clonal expansion of cells harboring nonsense mutations in the *CSF3R* gene, which results in the expression of truncated CSF3R proteins. These mutations in SCN patients are highly predictive of leukemic transformation [44]. This suggests a common early common pathway of leukemogenesis that is unique for patients with SCN. Chromosome 7 abnormalities, *RUNX1*, *RAS*, and *KIT* gene mutations have also been described in MDS/AML of patients with *ELANE* mediated SCN [45].

Ongoing controversy of G-CSF treatment and leukemic transformation

Patients with severe congenital neutropenia present early in infancy with severe infections. With the introduction of GCSF treatment has significantly improved survival and morbidly for patients with congenital neutropenias, however, there is ongoing concern that the long-term use of G-CSF is associated with the development of MDS/AML. Transformation to MDS/AML is highest for patients with a poor G-CSF response requiring higher doses of G-CSF. Whether this is directly caused by G-CSF or by the underlying condition remains controversial.

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Clinical Impact

What are the insights gained by the recent discoveries and how do they translate to clinical practice? The increasing number of new genes associated with BMF indicates that genetic causes or susceptibly to develop BMF is probably more common than previously thought and that mutations in BMF genes may account for a far broader clinical spectrum than originally anticipated, both in the pediatric and adult patient population. The increasing numbers of genes associated with BMF make genetic testing for a large number of genes prohibitively expensive and impractical at the moment. However in the future, with the development of parallel testing of multiple BMF genes in a single sample using next-generation sequencing, comprehensive genetic testing will be available. The interpretation of comprehensive genetic testing as well as of screening tests however also adds to the complexity of making a clinical diagnosis.

Thus, interpretation should be performed by a specialist or preferably a team of specialists familiar with the clinical presentation of the patient. Family and personal history, physical examination, and laboratory findings may raise the suspicion of an IBMFS. Screening tests, in particular for genetic predisposition that would drastically alter the therapeutic decisions should be performed not only in children but also in the adult patient with BMF. Chromosomal breakage studies or telomere length measurements, for example, should be performed in all patients with BMF for whom HSCT is considered a possible therapy. Figure 4 highlights some of the findings in clinical history, physical exam, family history and suggested laboratory tests that may indicate an IBMFS.

Conclusion

Understanding of the pathophysiology of IBMFS has exploded with the identification of genes. Many of these genes encode proteins involved in cellular housekeeping pathways that, when disturbed, cause cell senescence and apoptosis as well as predispose to malignant transformation (Figure 5). The understanding of the disease causing pathways will allow us to cope with the large number of genes likely to be discovered with the new sequence technologies. It will enable us to develop the appropriate screening tools, discover new prognostic markers, and develop more specific drugs.

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Key Phrases

- IBMFS are a diverse set of genetic disorders characterized by the inability of the bone marrow to produce sufficient blood cells.
- Many of the pathways discovered in IBMFS involve cellular housekeeping pathways, that when disturbed, lead to cellular apoptosis and can predispose to malignant transformation.
- Continued identification of new genes and pathways involved in IBMFS is likely allow for development of new screening tools, discovery of new prognostic markers, and development of new therapeutics.

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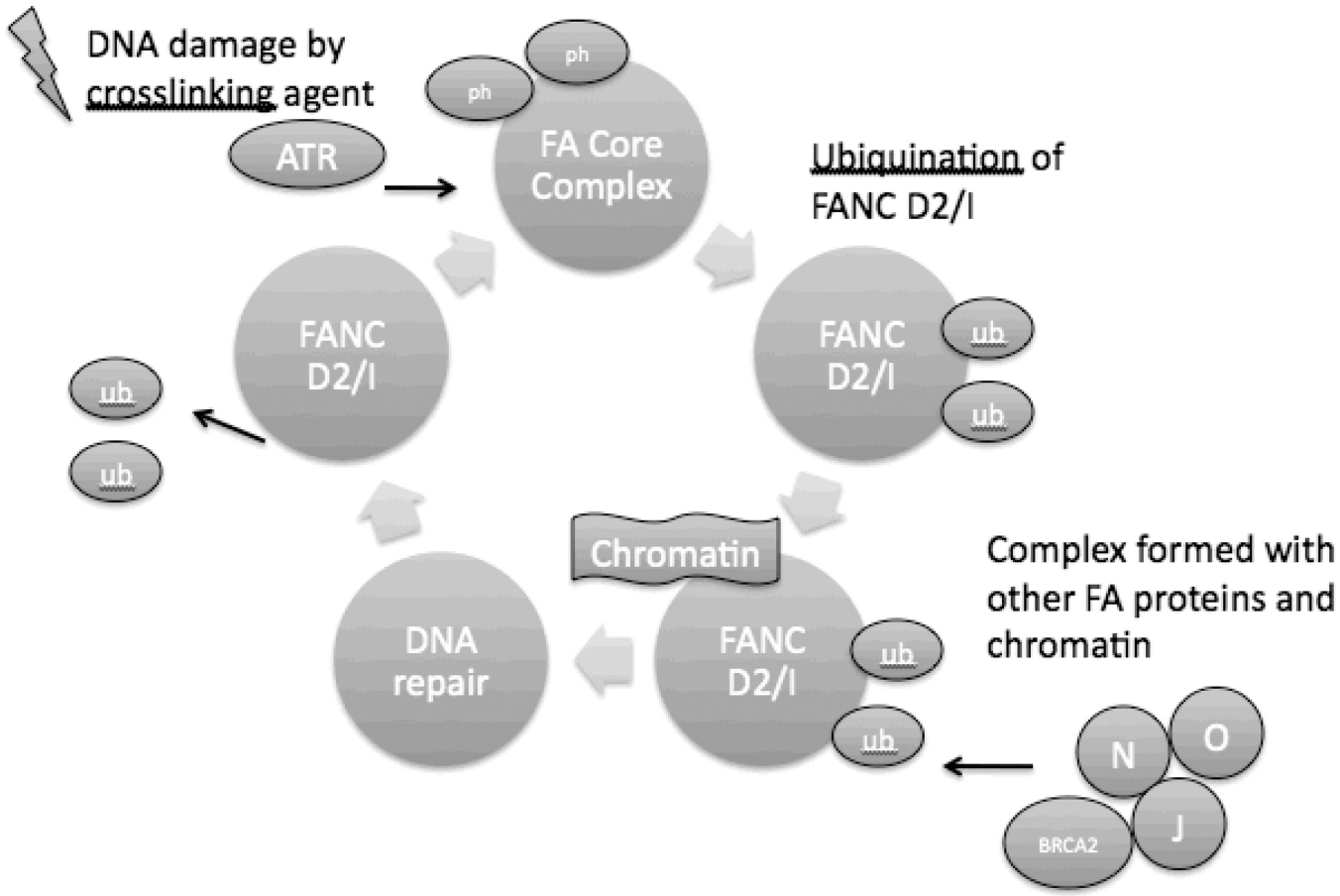

Figure 1. DNA repair and FANC proteins

After DNA damage, the Ataxia Telangiectasia and RAD3-related kinase (ATR) activates the FA core complex (consisting of FANC A/B/C/E/F/G/L/M) by phosphorylation (ph). The core complex then acts as a ubiquitin ligase and monoubiquinates (ub) FANCD2 and FANCI. This monoubiquinated complex then is targeted to chromatin where it forms a complex with additional FA proteins and DNA repair proteins. DNA repair occurs through a variety of mechanisms. FANC D2/I are then deubiquinated, allowing their release from chromatin. Mutations in any of the FANC proteins will lead to defective DNA repair.

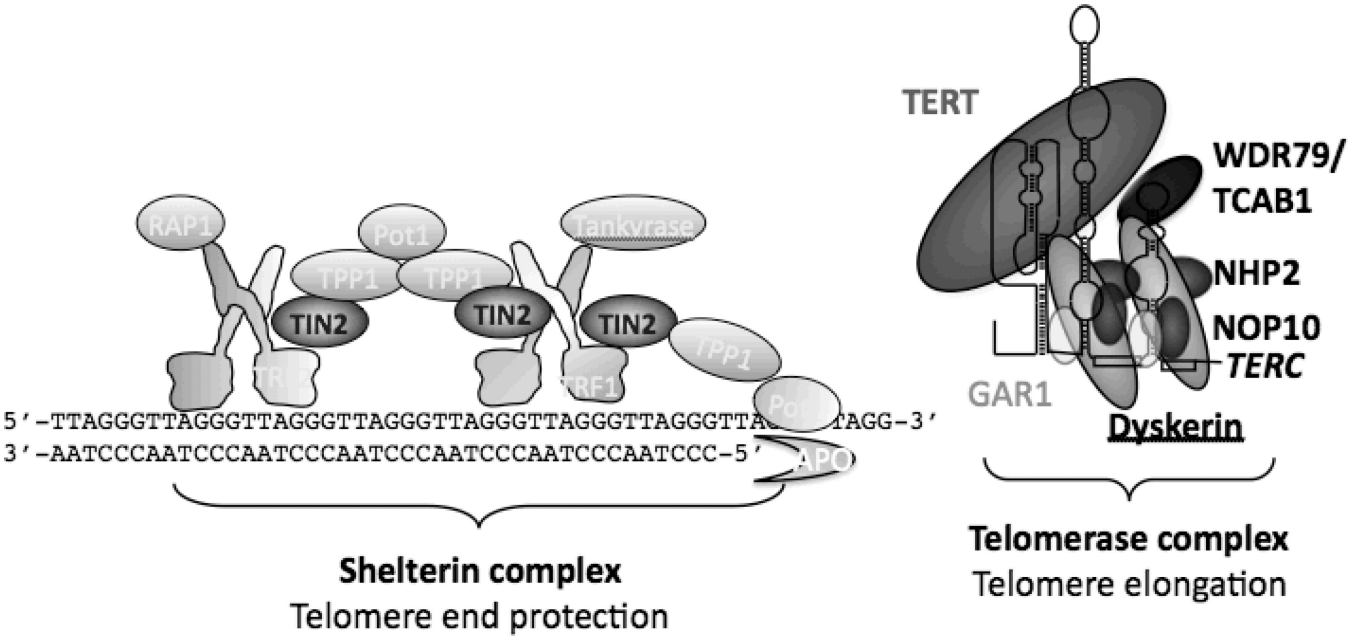

Figure 2. Telomere biology

Telomeres are at the ends of linear chromosomes and are composed of many tandem repeats of a hexanucleotide and associated proteins, called the shelterin complex. As telomeres shorten with cell replication, the telomerase complex is responsible for the elongation of telomeres by adding telomeric repeats to the ends of telomeres. Six of the DC gene products are a part of the telomerase complex (Dyskerin, TERT, TERC, NHP2, NOP10, and WDR79/TCAB1). The seventh (TIN2) is part of the shelterin protein complex.

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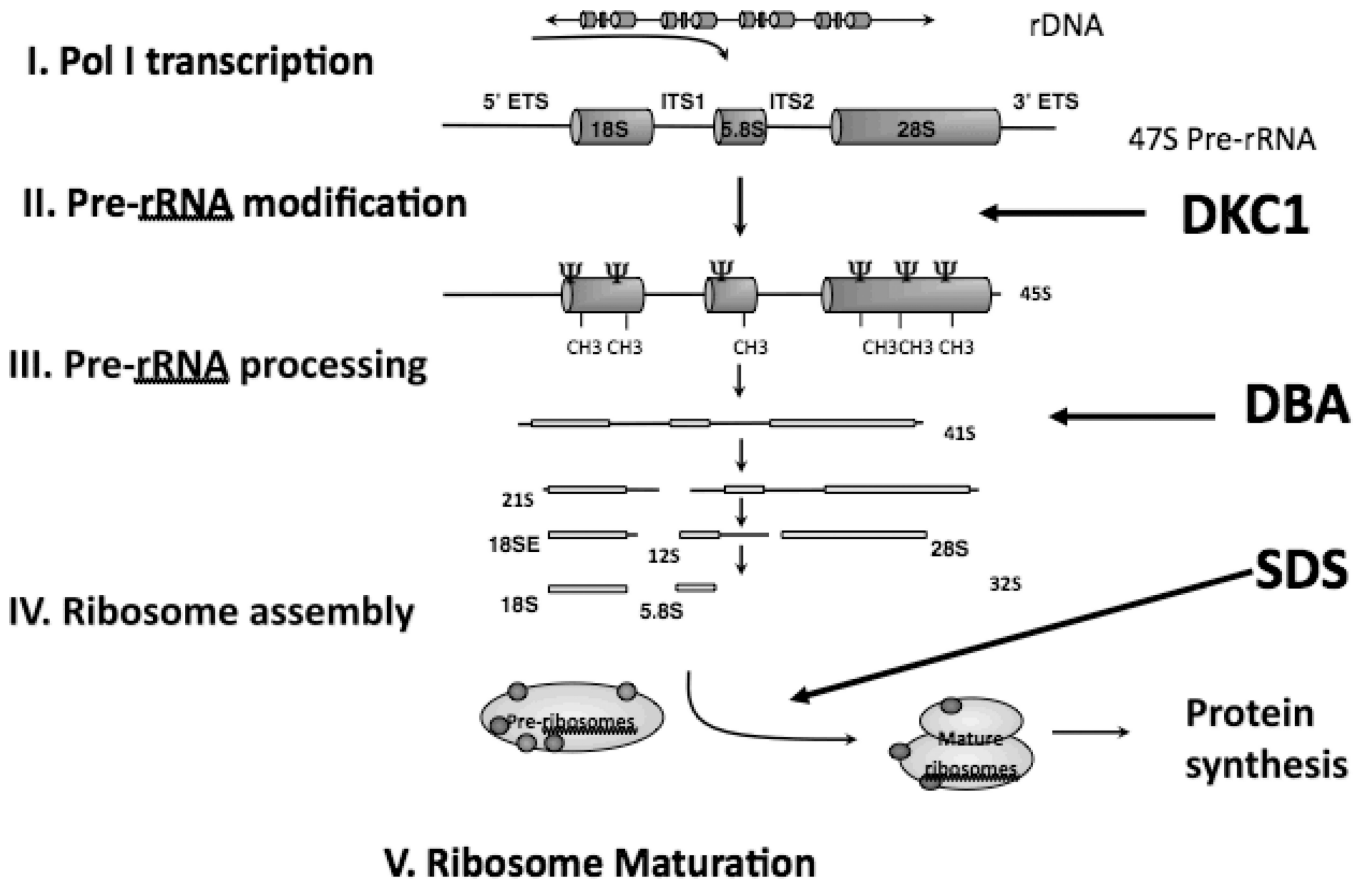

Figure 3. Eukaryotic ribosome biogenesis

This process requires the coordinated synthesis of 4 ribosomal rRNAs (*18S, 28S, 5.8S, 5S*), several additional core ribosomal proteins and other associated proteins. Several diseases are implicated along the process of ribosome biogenesis, including Diamond-Blackfan Anemia (DBA), Shwachman Diamond Syndrome SDS), and Dyskeratosis Congenita (DC) secondary to *DKC1* mutations.

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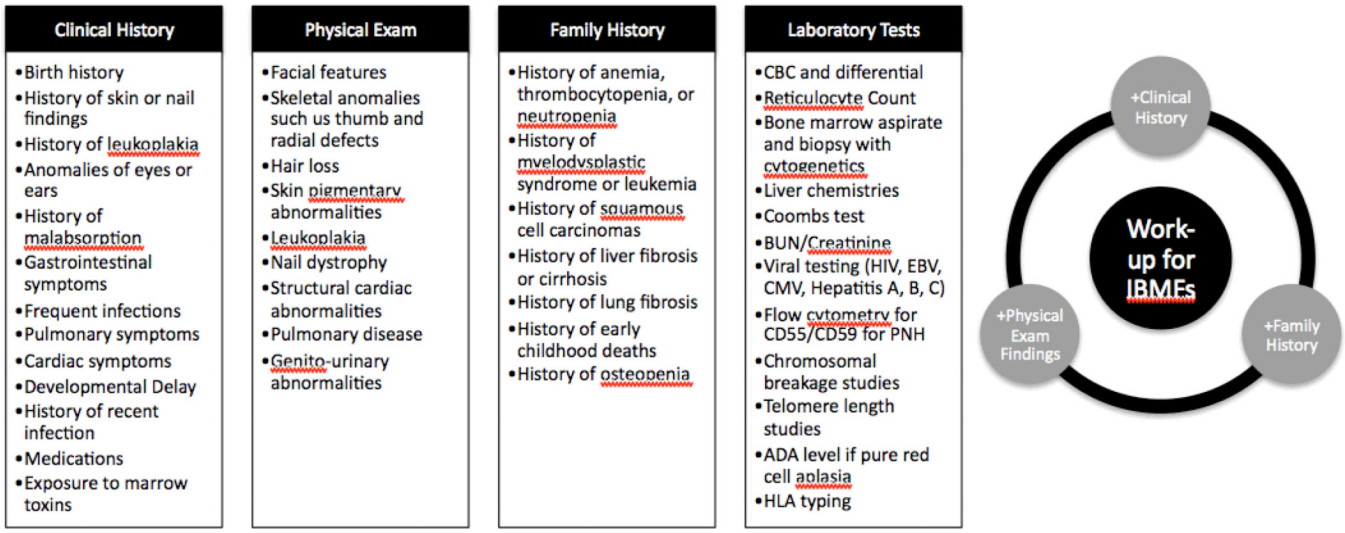

Figure 4.

Findings in the clinical history, physical exam, and family history that can provide clues to IBMFs. Suggested laboratory testing is also listed.

Key: CBC=complete blood count, BUN=blood urea nitrogen, HIV=human immunodeficiency virus, EBV=Epstein Barr virus, CMV=cytomegalovirus, PNH=paroxysmal nocturnal hemoglobinuria, ADA= red cell adenosine deaminase activity, HLA=human leukocyte antigen

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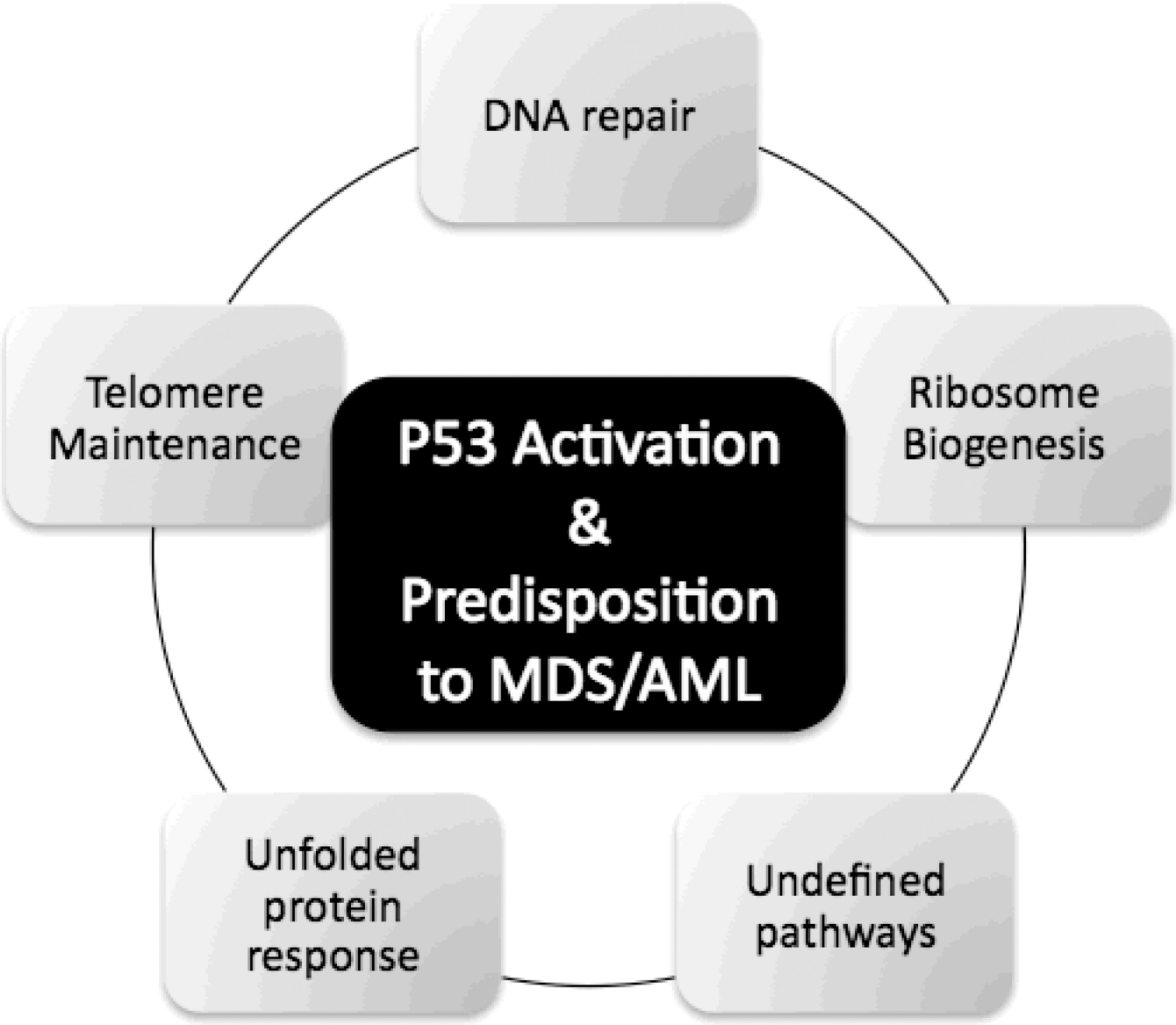

Figure 5. Biologic Pathways Involved in IBMFs

The pathways affected in the major forms of IBMFS are house-keeping pathways important for the growth and cell division of all cells: Defective DNA repair pathways is responsible for Fanconi Anemia, defective telomere maintenance causes Dyskeratosis Congenita, defective ribosomal processing is seen in Diamond-Blackfan Anemia, and is also thought to have implications in Shwachmann Diamond Syndrome and Dyskeratosis Congenita. Unfolded protein response is involved in some forms of Severe Congenital Neutropenia and is thought to play a role in apoptosis of granulocytic precursors. Additional pathways remain to be determined. The pathways involved in the IBMFs all lead to the activation of p53 causing cell cycle arrest, cell senescence or cell death, which are all features of bone marrow failure. Interestingly what these pathways also share is a predisposition to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), but the pathways(s) of leukemic transformations remain to be determined.

Key: MDS=myelodysplastic syndrome, AML=Acute myeloid leukemia

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Table 1

Genes associated with inherited bone marrow failure syndromes.

Disease / Genes	Chromosome Locus	Mode of Inheritance	Frequency (% of pts)
Fanconi Anemia			
FANCA	16q24.3	AR	60
FANCB	Xp22.31	XLR	2
FANCC	9q22.3	AR	14
FANCD1/BRCA2	13q12.3	AR	3
FANCD2	3p25.3	AR	3
FANCE	6p21.3	AR	3
FANCF	11p15	AR	2
FANCG/XRCC9	9p13	AR	10
FANCI	15q25-26	AR	1
FANCJ/BACH1/BRIP1	17q22.3	AR	2
FANCL	2p16.1	AR	0.2
FANCM	14q21.3	AR	0.2
FANCN/PALB2	16p12.1	AR	0.7
FANCO	17q22	AR	I case
FANCP	16p13.3	AR	I case
Dyskeratosis Congenita			
DKC1	Xq28	XLR,DN	30
TINF2	14q11.2	AD,DN	15
TERC	3q26.3	AD	10
TERT	5p15.53	AD, AR,DN	5-10
NOP10/NOLA3	15q14-q15	AR	<1
NHP2/NOLA2	5q35.5	AR	<1
TCAB1/WDR79/WRP53	17p13.1	AR	2 cases
Diamond-Blackfan Anemia			
RPS19	19q13.2	AD,DN	25
RPL5	1p22.1	AD,DN	7
RPL11	1p36.1-p35	AD,DN	5
RPL35a	3q29-qter	AD,DN	3
RPS26	12q13.2	AD,DN	6
RPS24	10q22-q23	AD,DN	2
RPS17	15q25.2	AD,DN	1
RPS7	2p25.3	AD,DN	1
RPS10	6p21.31	AD,DN	3
Shwachman-Diamond Syndrome			
SBDS	7q11	AR	>90

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Disease / Genes	Chromosome Locus	Mode of Inheritance	Frequency (% of pts)
Severe Congenital Neutropenia			
ELA-2/ELANE	19p13.3	AD,DN	75
GFI1	1p22	AD	<1
HAX1	1q21.3	AR	1
WAS	Xp11.33-11.22	XLR	<1
G6PC3	17q21.31	AR	<1
CSF3R	1p35-34.3	AD,DN	<1

AR=autosomal recessive, XLR=X-linked recessive, DN=de novo, AD=autosomal dominant.