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Review

A new frontier in Fanconi anemia: From DNA repair to ribosome biogenesis

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ABSTRACT

Described by Guido Fanconi almost 100 years ago, Fanconi anemia (FA) is a rare genetic disease characterized by developmental abnormalities, bone marrow failure (BMF) and cancer predisposition. The proteins encoded by FA-mutated genes (FANC proteins) and assembled in the so-called FANC/BRCA pathway have key functions in DNA repair and replication safeguarding, which loss leads to chromosome structural aberrancies. Therefore, since the 1980s, FA has been considered a genomic instability and chromosome fragility syndrome. However, recent findings have demonstrated new and unexpected roles of FANC proteins in nucleolar homeostasis and ribosome biogenesis, the alteration of which impacts cellular proteostasis. Here, we review the different cellular, biochemical and molecular anomalies associated with the loss of function of FANC proteins and discuss how these anomalies contribute to BMF by comparing FA to other major inherited BMF syndromes. Our aim is to determine the extent to which alterations in the DNA damage response in FA contribute to BMF compared to the consequences of the loss of function of the FANC/BRCA pathway on the other roles of the pathway.

1. Introduction

Fanconi anemia (FA) is a rare genetic disease classified as an inherited bone marrow failure syndrome (iBMFS). Patients with an iBMFS present with quantitative and/or qualitative defects in hematopoietic stem cells (HSCs) and/or their precursor cells (HSPCs), which are associated with pancytopenia or single-lineage cytopenia. These patients are at high risk of their iBMFS progressing toward myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). In addition to BMFs caused by the loss of function of a protein due to the heritage of a mutated allele from each parent or to germline mutations in a single allele, resulting in haploinsufficiency or dominant-negative protein, the diseases are usually associated with a variety of developmental defects, justifying their classification as "syndromes", i.e. diseases with multiple clinical stigmata [1].

iBMFSs were initially described through three main categories of disorders, and each category was associated with mutations in genes defining specific molecular or functional pathways that converge on a common outcome, BMF (Fig. 1A): diseases caused by dysfunction in ribosome biogenesis (RiBi) and called "ribosomopathies", as the

Diamond-Blackfan anemia (DBA) and the Shwachman-Diamond syndrome (SDS); those caused by dysfunctional telomere biology and called "telomeropathies", as the dyskeratosis congenita (DC) and its variants, the Revesz and Hoyeraal-Hreidarsson syndromes (RS and HHS); and FA, associated with alterations in DNA damage responses (DDRs). In addition, the iBMFSs category includes also patients with severe congenital neutropenia of different genetic and molecular origins and individuals with mutations seldom reported in genes associated with BMF; these mutations are generally identified following genome sequencing of patients presenting with an unclassified BMF [1–4]. Each iBMFS affects 1–10 (or considerably fewer) individuals per million live births every year worldwide. However, the incidence of the iBMF and the number of involved genes are probably underestimated because several patients are underdiagnosed, and some of the idiopathic BMFs that develop in adulthood may be caused by previously unrecognized inherited mutations whose effects remain hidden for years [1–4]. Thus, iBMFSs represent a genetically and clinically heterogeneous group of rare pathologies with overlapping phenotypes and pathophysiologies that present diagnostic and therapeutic challenges for clinicians (Tables 1 and 2).

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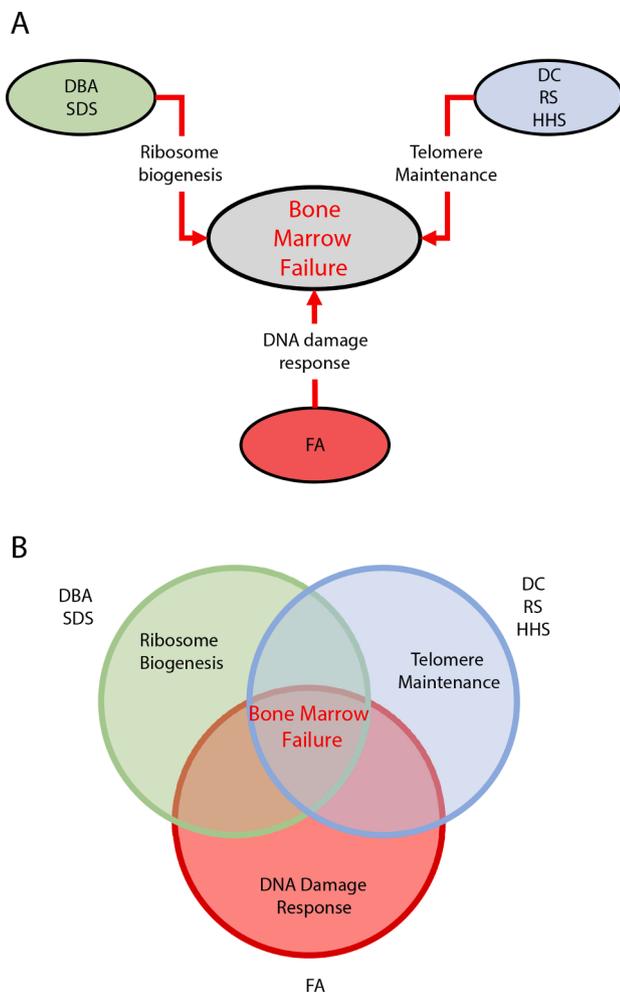


Fig. 1. Models linking genetics and biochemistry to BMF. A) BMF as a consequence of alterations in independent functional pathways. B) BMF as a consequence of the addition and convergence of alternative functions of the proteins encoded by inherited mutated genes.

The ribosomopathies present genetic alterations affecting the RiBi process that requires approximately 80 ribosomal proteins (RPs) and several additional factors encoded by nuclear genes that, following their translation in the cytosol, migrate to the nucleolus where they assemble with four different ribosomal RNAs (rRNAs), three of which had been transcribed inside the nucleolus by RNA-Pol I, to form the 40S and 60S pre-ribosomal subunits. After their return to the cytosol to mature, these two subunits together with several other factors involved in translation initiation, progression and completion, associate with mRNA to polymerize proteins [5,6]. Perturbations in cell homeostasis, induced by DNA damage, replication stress, transcription alterations, nutrient or energy deprivation, generally lead to modifications in the RiBi processes that mediate cellular adaptation to stress through either p53-dependent or p53-independent responses [7–9]. Inversely, mutations/haploinsufficiency in RPs or other RiBi factors, in addition to dysfunction that exerts direct impact on the quantity and/or quality of translated proteins, lead to mitochondrial, nuclear and nucleolar stress impacting the energetic/oxidative status of a cell, as well as its replication, transcription and intra- and extracellular signaling [6,10]. Moreover, beyond of their “indirect” effects on cellular physiology, RPs may affect several pathways and functions *via* their direct interactions with non-ribosomal components of the cell, including the nucleolar protein NPM1 [11,12], the p53 inhibitor MDM2 [13], the oncogene c-Myc [14–16], or the DNA repair protein APE1/OGG1 [17].

Telomeropathies harbor defects in the maintenance of the structure

and length of telomeres that depend on several proteins and complexes (see [18] for references). Telomeric complexes play two key roles: they “close” the chromosome extremity, preventing its recognition as a DNA double-strand break, and “limit” the progressive telomere shortening caused by the “end” replication problem [19]. The loss of these preventative processes leads to genetic instability and to a shortened cellular lifespan [20–23]. However, several of the proteins involved in telomere maintenance have “individual”, telomere-independent, biochemical roles in both DNA repair and in the RiBi process [24–30].

Evoked by specific DNA lesions or nuclear stress, several proteins and pathways ensure the maintenance and transmission of the genetic information from mother to daughter cells. In addition to their DNA lesion specificity [31], each pathway is largely interconnected with the others, constituting the DDR network. It emerges that several regulators and effectors are shared between the individual, alternative and parallel DNA repair pathways, as, for instance, the ATM and ATR signaling kinases, the canonical base excision repair (BER) proteins PARP1 or NEIL1–3, or the nucleotide excision repair (NER) XP-F/ERCC1 heterodimer [32–41]. The loss of function of a DDR pathway leads to several inherited human disorders classified as DNA repair and/or chromosome fragility syndromes associated with developmental abnormalities, cancer predisposition, accelerated aging, infertility, immunodeficiency and/or neurodegeneration [42–44]. Recently, however, as for certain proteins associated with FA and discussed below, several key DDR proteins as PARP1, CSA, CSB and DNA-PK have been associated “directly” with the RiBi process and, eventually, telomere maintenance, adding to the complexity of the cellular phenotype associated with their deficiency [45–50].

Even if iBMFSs appear to be specifically related to the loss of a ‘specific’ biochemical activity in RiBi, telomere maintenance or DDR (Fig. 1A), recent findings have revealed that they share several cellular phenotypes, including altered proteostasis, DNA damage accrual and DDR alterations (Fig. 1B). Thus, questions arise regarding the genotype-phenotype relationship that underlies the clinical, cellular, and molecular phenotypes of iBMFSs. These questions are not simply matters of academic curiosity. Establishing biochemical, molecular and functional connections between the proteins encoded by the mutant genes that cause BMF (and similar genetic disorders) is critical to the development of new holistic pharmacological approaches to alleviate/delay symptoms or avoid MDS/AML progression in patients with either inherited or idiopathic BMF. Such new treatments could be used to complement current approaches, which include red blood cell transfusion, transplantation and recently developed strategies based on gene therapy.

Here, we review the different cellular, biochemical and molecular anomalies associated with proteins encoded by mutant FA-associated genes (FANCs) and discuss how they potentially contribute to the phenotype of patients by comparing FA to other major iBMFSs. With the first patients diagnosed with FA approximately 100 years ago by the Swiss pediatrician Guido Fanconi [51], FA is probably the most common iBMFS worldwide and one the most genetically heterogeneous [52]; in fact, FA probably encompasses many slightly different clinical entities (Fig. 2) [53]. The median age at diagnosis is approximately 10 years, with hematological abnormalities present at birth or appearing progressively during infancy and adolescence to adulthood. FA is syndromic, and patients can present with a plethora of extrahematopoietic clinical features, including skeletal, epithelial, endocrine, sensorial, reproductive, immunological and cognitive abnormalities. However, although the majority of patients present with one or more additional physical and/or functional abnormalities, 20–30% of these patients are symptomless before the development of hematopoietic failure, which mainly leads to anemia or thrombocytopenia [54]. The observed clinical heterogeneity of FA patients results from genetic heterogeneity, gene variants differentially affecting encoded protein function(s) and environmental interactions. Compared to individuals of the same age, FA patients have observed/expected risk factor ratios of 6000 and 700 for MDS and AML, respectively [55].

Table 1
Clinical and cellular hallmarks of inherited bone marrow syndromes.

Disease	Major clinic features			Neoplasia risk	Cell Biology							
	Skeletal	Skin/Epithelia	Miscellanea		Cytopenias	Solid cancer	Leukemia	DNA damage Replication stress	Genetic/Genomic Instability	Intracellular ROS level	Cytokine abnormalities, pro-inflammatory status	Nucleolar stress Ribosomal stress
Fanconi anemia	Short stature Thumb abnormalities	Café-au-lait spots, Hyperpigmentation Hypopigmentation	Hypogonadism Eyes & Ears abnormalities Renal and Gastrointestinal anomalies	Pancytopenia Thrombocytopenia Anemia	Head & Neck Cancers Breast, Ovarian & Pancreatic cancers	MDS AML	Present	Present	Increased	Present	Present, at least in some complementation groups	Present
Diamond Blackfan anemia	Short stature Craniofacial defects Thumb abnormalities	Not reported	Visual loss or deafness Genito urinary malformations	Macrocytic anemia Neutropenia Thrombocytopenia	Unfrequent but at multiple sites Ovary	MDS AML	Present	Present	Increased	Present	Present	Present
Shwachman-Diamond syndrome	Thumb defects Ichthyosis	Not reported	Hearing loss Pancreatic insufficiency	Thrombocytopenia	Ovary	MDS AML	Present	Present	Increased	Present	Present	Present
Diskeraetosis congenita (Revesz syndrome, Hoyeraal-Hreidasson)	Osteopenia Microcephaly Short stature	Hyperpigmentation Nail Dystrophy Oral leukoplakia	Hypogonadism Pulmonary fibrosis	Pancytopenia Thrombocytopenia	Head & Neck cancers, anogenital adenocarcinomas,	MDS AML	Present	Present	Increased	Present	Present, at least in some complementation groups	Present

In the remainder of this review, our aim is to highlight the similarities between the major iBMFSs and discuss the extent to which alterations in the DDR contribute to BMF in FA compared to the other defects associated with alternative functions of the mutated proteins. This line of inquiry is of interest since 1) new FANC genes are described on the basis of DDR function maintenance even though more than 30% of the genes critical to iBMFSs remain unrecognized [56]; 2) new findings on the FANC/BRCA pathway have been focused on DDR function and toxic metabolite clearance by FANC proteins; and 3) determining the role of DDR alterations in BMF in FA will help to better define the FA phenotype and its diagnostic criteria [53].

2. BMF in FA: contribution of abnormalities in DNA damage signaling and repair

2.1. Fanconi anemia and the DNA damage response

Considered a “pure” DNA repair and chromosomal fragility syndrome, FA is caused by mutations in more than 20 genes [52] that encode proteins assembled in several biochemical and/or functional modules [57] that act in concert forming the FANC/BRCA-homologous recombination (HR) and the replication rescue DNA repair pathway (FANC/BRCA pathway) [58] (Fig. 2). The first module of the FANC/BRCA pathway consists of FANCM, a large cargo protein with translocase activity that is likely critical for the localization of the second module of the FANC/BRCA pathway acting on the stalled/delayed replication fork. The second module is constituted by the assembly of three subcomplexes into the FANC core complex: FANCA-FANCG-FAAP20 (FA-associated protein 20); FANCB-FANCL-FAAP100; and FANCC-FANCE-FANCF. The FANC core complex acts as a ubiquitin-E3-ligase that transiently interacts with the E2 enzyme UBE2T/FANCT to monoubiquitinate the two proteins of the third module, FANCD2 and FANCI. Monoubiquitinated FANCD2 and FANCI assemble at the chromatin-associated nuclear foci required for the optimal establishment of the downstream steps mediated by the fourth heterogeneous FANC/BRCA pathway module, which includes helicases, translesion DNA polymerases, nucleases and HR-associated proteins, whose action is required for DNA repair and replication restart. Finally, FANCD2- and FANCI-mediated USP1 deubiquitylation is required for their release from chromatin-associated foci, marking the completion of the DNA repair process [52,57,59]. Although no patients with BMF-bearing mutations in USP1 have been described to date, cell and mouse models with USP1 downregulation recapitulate the key FA phenotypes [60,61]. Thus, timely activation and inactivation of the FANC/BRCA pathway is required for cell homeostasis and individual health.

The FANC/BRCA pathway is embedded in the DDR network and is connected to signaling proteins, including ATM, ATR and CHK1 kinases [62–65]; structural and enzymatic proteins and complexes, such as BLM and the MRE11/RAD50/NBS1 (MRN) and SMC5/SMC6 complexes [66–70]; histone marks [71,72]; chromatin modifiers [73,74]; and key proteins belonging to the BER, NER and mismatch repair (MMR) pathways, including NEIL-1, NEIL-3 MSH2 and MutL α [37,41,75–78]. The DDR network contributes to genome integrity maintenance and optimal DNA replication, allowing cell relief from stress conditions. Accordingly, inactivation of the FANC/BRCA pathway leads to hypersensitivity to replication stress, particularly because of the DNA interstrand crosslinks (ICLs) induced by endogenous or exogenous stress, such as aldehydes, mitomycin C (MMC) and cisplatin. Inhibitors of the replicative machinery, such as aphidicolin or hydroxyurea, also activate the FANC/BRCA pathway and lead to chromosomal instability upon pathway dysfunction [57,79]. Finally, the FANC/BRCA pathway exhibits broadest functions in genome integrity maintenance, including common fragile site protection [80–82], transcription and R-loop homeostasis [83,84], telomere length maintenance [85,86] and mitotic cell division safeguards [87–89].

Table 2
Genetics of inherited bone marrow syndromes.

Syndrome	Estimated prevalence	Gene	Inheritance	Frequency of patients	Protein full name	Usual protein acronym	Protein major aliases	iBMFS subgroup
Fanconi Anemia (FA)	5 x 10 ⁶	<i>FANCA</i>	AR	60%-70%	Fanconi anemia group A protein	FANCA		DNA repair and Chromosome Breakage Syndrome
		<i>FANCB</i>	X-linked	2%	Fanconi anemia group B protein	FANCB	FAAP95	
		<i>FANCC</i>	AR	14%	Fanconi anemia group C protein	FANCC		
		<i>BRCA2</i>	AR	2%	Breast cancer type 2 susceptibility protein	BRCA2	FANCD1	
		<i>FANCD2</i>	AR	3%	Fanconi anemia group D2 protein	FANCD2		
		<i>FANCE</i>	AR	3%	Fanconi anemia group E protein	FANCE		
		<i>FANCF</i>	AR	2%	Fanconi anemia group F protein	FANCF		
		<i>FANCG</i>	AR	10%	Fanconi anemia group G protein	FANCG	XRCC9	
		<i>FANCI</i>	AR	1%	Fanconi anemia group I protein	FANCI		
		<i>BRIP1</i>	AR	1%	Fanconi anemia group J protein	FANCI	BRIP1	
		<i>FANCL</i>	AR	Rare	E3 ubiquitin-protein ligase FANCL	FANCL		
		<i>PALB2</i>	AR	Rare	Partner and localizer of BRCA2	PALB2	FANCN	
		<i>RAD51C</i>	AD	Rare	DNA repair protein RAD51 homolog 3	RAD51	FANCO	
		<i>SLX4</i>	AR	Rare	Structure-specific endonuclease subunit SLX4	SLX4	FANCP	
		<i>ERCC4</i>	AR	Rare	DNA repair endonuclease XPF	XPF	FANCQ	
		<i>RAD51</i>	AD	Rare	DNA repair protein RAD51 homolog 1	RAD51	FANCR	
		<i>BRCA1</i>	AR	Rare	Breast cancer type 1 susceptibility protein	BRCA1	FANCS	
		<i>UBE2T</i>	AR	Rare	Ubiquitin-conjugating enzyme E2 T	UBE2T	FANCT	
		<i>XRCC2</i>	AR	Rare	DNA repair protein XRCC2	XRCC2	FANCU	
		<i>REV7</i>	AR	Rare	Mitotic spindle assembly checkpoint protein MAD2B	REV7	FANCV/ MAD2L2	
		<i>RFWD3</i>	AR	Rare	E3 ubiquitin-protein ligase RFWD3	RFWD3	FANCW	
		<i>RPS7</i>	AD	<5%	40S ribosomal protein S7	eS7	RPS7, DBA8	
		<i>RPS10</i>	AD	Rare	40S ribosomal protein S10	eS10	RPS10, DBA9	
		<i>RPS15A</i>	AD	Rare	40S ribosomal protein S15a	uS8	RPS15A, DBA20	
		<i>RPS17</i>	AD	Rare	40S ribosomal protein S17	eS17	RPS17, DBA4	
		<i>RPS19</i>	AD	Rare	40S ribosomal protein S19	eS19	RPS19, DBA1	
<i>RPS24</i>	AD	Rare	40S ribosomal protein S24	eS24	RPS24, DBA3			
<i>RPS26</i>	AD	Rare	40S ribosomal protein S26	eS26	RPS26, DBA10			
<i>RPS27</i>	AD	<5%	40S ribosomal protein S27	eS27	RPS27, DBA17			
<i>RPS28</i>	AD	<10%	40S ribosomal protein S28	eS28	RPS28, DBA15			
<i>RPS29</i>	AD	<5%	40S ribosomal protein S29	uS14	RPS29, DBA13			
<i>RPL5</i>	AD	Rare	60S ribosomal protein L5	uL18	RPL5, DBA6			
<i>RPL11</i>	AD	<5%	60S ribosomal protein L11	uL5	RPL11, DBA7			
<i>RPL15</i>	AD	25%	60S ribosomal protein L15	eL15	RPL15, DBA12			
Diamond Blackfan Anemia (DBA)	5 -10 x 10 ⁶	<i>RPL18</i>	AD	<5%	60S ribosomal protein L18	eL18	DBA18	Ribosomopathy

(continued on next page)

Table 2 (continued)

Syndrome	Estimated prevalence	Gene	Inheritance	Frequency of patients	Protein full name	Usual protein acronym	Protein major aliases	iBMFS subgroup
Shwachman-Diamond Syndrome (SDS)	1-10x10 ⁶	<i>RPL26</i>	AD	<10%	60S ribosomal protein L26	uL24	RPL26, DBA11	
		<i>RPL27</i>	AD	Rare	60S ribosomal protein L27	eL27	RPL2, DBA16	
		<i>RPL31</i>	AD	Rare	60S ribosomal protein L31	eL31	RPL31	
		<i>RPL35</i>	AD	Rare	60S ribosomal protein L35	uL29	RPL35, DBA19	
		<i>RPL35A</i>	AD	Rare	60S ribosomal protein L35a	eL33	RPL35A, DBA5	
		<i>TSR2</i>	X-linked	Rare	Pre-rRNA-processing protein TSR2 homolog	TSR2	DBA14	
		<i>GATA1</i>	X-linked	Rare	Erythroid transcription factor	GATA1	ERYF1	
		<i>SBDS</i>	AR	>90%	Ribosome maturation protein SBDS	SBDS		
		<i>DNAJC21</i>	AR	Rare	DnaJ homolog subfamily C member 21	DNAJA5	DJC21	
		<i>EFL1</i>	AR	Rare	Elongation factor-like GTPase 1	EFTUD1	EFL1	
		<i>SRP54</i>	AD	Rare	Signal recognition particle 54 kDa protein	SRP54	SCN8	
		<i>ACD</i>	AD, AR	Rare	Adrenocortical dysplasia protein homolog	ACD		
		<i>CTC1</i>	AR	1%-3%	CST complex subunit CTC1	CTC1		
		<i>DKC1</i>	X-linked	20%-25%	H/ACA ribonucleoprotein complex subunit DKC1	Dyskerin	DKC1	
		<i>NHP2</i>	AR	Rare	H/ACA ribonucleoprotein complex subunit 2	DKCB2	NHP2, NOLA2	
<i>NOP10</i>	AR	Rare	H/ACA ribonucleoprotein complex subunit 3	NOP10	DKCB1			
<i>PARN</i>	AR	Rare	Poly(A)-specific ribonuclease PARN	PARN	DKCB6			
<i>RTEL1</i>	AD, AR	2%-8%	Regulator of telomere elongation helicase 1	RTEL1	DKCA4, DKCB5			
<i>WRAP53</i>	AR	Rare	Telomerase Cajal body protein 1	TCAB1	DKCB3			
<i>TERC</i>	AD	5%-10%	Telomerase RNA component					
Dyskeratosis congenita (DC) Revesz syndrome (RS) Hoyeraal-Hreidarsson (HSS)	Rare <500 families worldwide	<i>TERT</i>	AD, AR	1%-7%	Telomerase reverse transcriptase	TERT	DKCA2, DKCB4	Telomeropathy
		<i>TINF2</i>	AD	12%-20%	TERF1-interacting nuclear factor 2	TINF2	DKCA3	

2.2. Evidence showing that the DDR contributes to the BMF in FA and the limitations of the DDR contribution

In the 30 years of elegant cellular, molecular and biochemical studies that followed the cloning of the first FA-associated gene, *FANCC*, [90], the “linear” FANC/BRCA pathway was extensively characterized and its centrality for genetic stability maintenance was thoroughly established [57–59,79,88,91,92]. Thus, it has been proposed that the BMF in FA is caused by intrinsic HSC defects stemming from aberrancies in DNA repair and/or DDR. Indeed, mis- or unrepaired DNA damage in awakened HSCs is thought to trigger signaling that leads to cell death or differentiation, with either outcome affecting the self-renewal capability of HSCs, causing their attrition [93,94]. Accordingly, compared to those in age-matched healthy individuals, HSPCs (CD34+ cells in BM) in FA patient are less numerous and less functional; i.e., they exhibit highly impaired in vitro colony-forming unit (CFU) formation capability [95]. Notably, the percentage of cells in the G0/G1 phase was found to be higher in FA than in control HSPCs. More than 90% of the total BM cells obtained from FA patients were Ki-67 negative (i.e., nonproliferating) compared to 40% of the BM cells isolated from healthy donors, and those

from the FA patients showed a spontaneously increased level of DNA damage (i.e., γ H2AX positive staining) [95]. Recently, it was reported that HSC awakening and proliferation are associated with a “physiological” intracellular burst of aldehydes that generate DNA ICLs that are safely managed in FANC pathway-proficient cells but that cause genetic and chromosomal instability, decreased self-renewal capabilities, an increased cell death rate, telomere shortening and accelerated/increased cellular senescence in FANC/BRCA pathway-deficient cells, globally resulting in HSC attrition and loss of functionality [96–98]. The phenotype of BM cells isolated from *Fanc-KO* mouse models, which poorly recapitulate the canonical clinical phenotype observed in patients, differs from that of BM cells isolated from patients. Similar to HSCs in humans, HSCs released from dormancy in *Fanc-KO* mice induce DNA damage accumulation [99,100] and show decreased repopulating ability [100,101]. However, compared to their WT counterparts, *Fanca*^{-/-}, *Fancc*^{-/-}, *Fancg*^{-/-} and *Fancd2*^{-/-} hematopoietic stem/progenitor cells exhibit increased cycling and diminished quiescence [99,100,102–104]. In conclusion, regardless of their proliferative status or cycling characteristics, BM hematopoietic stem/progenitor cells are associated with decreased repopulating capacity and greater attrition (i.

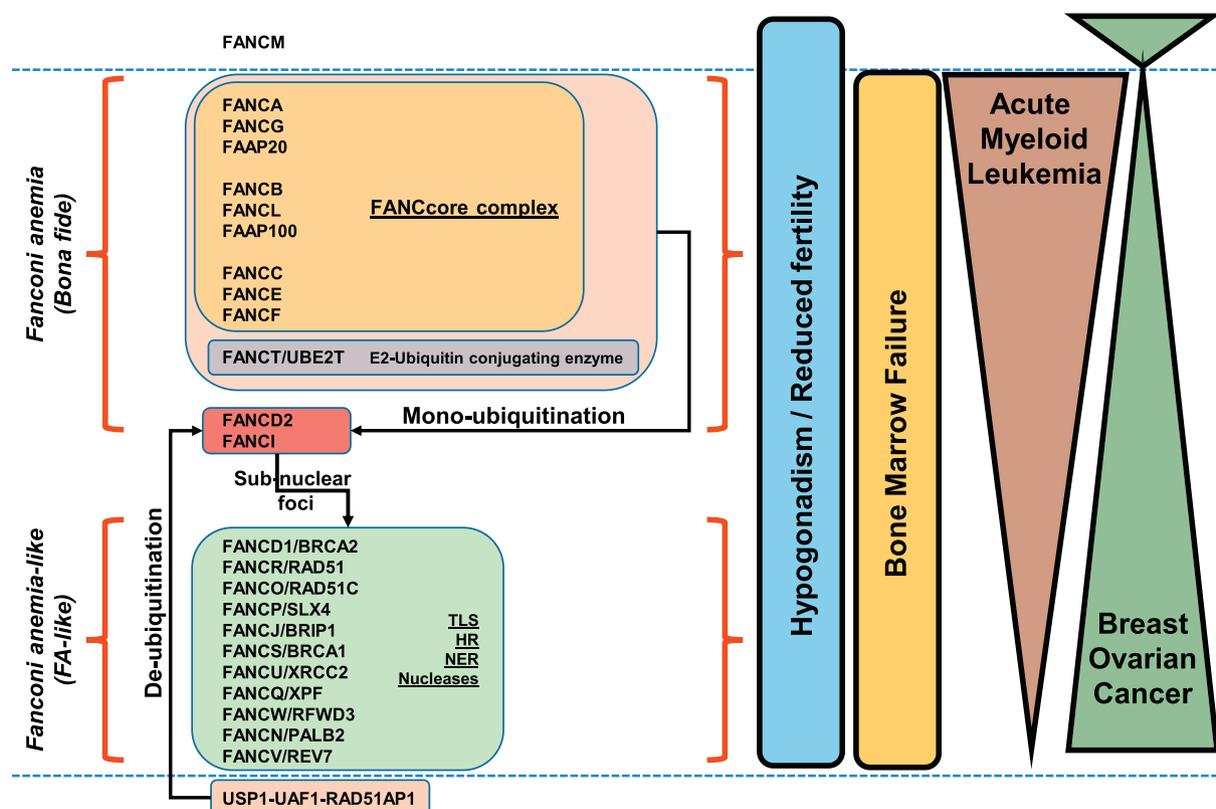


Fig. 2. Fanconi anemia proteins, modules, pathway and key phenotypes.

e., a reduced quiescent cell population) and an increased level of DNA damage. Is DNA damage accumulation the direct link between the FANCD2/BRCA pathway mediated DDR loss of function and BMF in FA?

The phenotypic consequences of the loss of function of FANCM and of certain FANCA mutations epitomize the current difficulty in corroborating a simple and direct link between DNA repair abnormalities and BMF. FANCM is a “cargo” protein, biochemically and/or functionally interacting with several proteins and complexes involved in the DDR, including PCNA, FAAP24, MHF1/2, HCLK2, BLM-associated proteins (BLAP) and the FANCD2 core complex [67,105–108]. FANCM is at the apex of the FANCD2/BRCA pathway, and its loss of function leads to canonical cellular abnormalities associated with FANCD2/BRCA pathway inactivation: cellular and chromosomal hypersensitivity to ICLs and replication stress, severely impaired FANCD2 monoubiquitination, alterations in HR and abnormalities in replication rescue [109]. FANCM is required for optimal DNA damage signaling [109–112] but FANCM mutation-carrying individuals do not present with BMF, MDS, AML or developmental abnormalities [53]. Patients expressing mutated FANCM present with hypogonadism/infertility, which can be logically considered to be related to HR alterations affecting the meiotic process, and a high risk, as validated in heterozygous carriers, of developing breast or ovarian cancer, also likely due to HR deficiency [109,113–120]. The phenotype of FANCM-mutant-expressing individuals suggests that impaired DNA repair and genetic instability are not sufficient *per se* to generate developmental abnormalities, BMF, MDS or AML. Supporting the previous point, it has also been reported that missense mutations in the FANCA-encoding gene (compromised in approximately 2/3 of FA patients worldwide) in patients presenting with BMF can be linked with three phenotypic cellular groups that show high, intermediate and low MMC sensitivity and weak, mild and strong (i.e., normal) FANCD2 monoubiquitination [121]. The observed variability in the severity of the cell phenotypes of the different FANCA mutants has been proposed to be dependent on the interaction of FANCA with chaperones (HSP70 and HSP90), which allows “normal” folding of certain FANCA mutant

proteins, rescuing their DDR functions through the FANCD2/BRCA pathway [122].

Thus, although the biochemical and molecular functions of the FANCD2/BRCA pathway in DNA repair, replication rescue and chromosome integrity maintenance are undoubtedly established, it is becoming increasingly apparent that BMF in FA patients does not rely on DNA damage accumulation or genetic instability *per se* but requires additional events.

2.3. Evidence of the contribution of DNA damage and DDR defects in other iBMFSS

Questioning the role of DNA damage and genetic instability in the BMF of DDR-deficient FA patients raises the question of the role(s), if any, of DDR abnormalities and genetic instability in other iBMFSS. Interestingly, several observations provide evidence of genomic integrity loss, increased DNA damage and/or constitutive overactivation of DNA damage signaling in other major iBMFSS, regardless of the main function(s) associated with the protein encoded by the mutated gene.

Mutations in ribosomal protein-encoding genes (DBAs) or in genes associated with SDS lead to reduced levels of global and/or specific protein synthesis, the major hallmark of ribosomopathy [123]. Similar to FA, DBA is also extremely heterogeneous from a genetic point of view: mutations in at least 21 genes have been identified as the cause of the syndrome [124]. All DBA-associated mutations are in RPs [125], except for mutations in *GATA1* [126] and *TSR2* [127]. However, beyond altered RiBi, several other cellular abnormalities have been described as being associated with DBA gene mutations, including an imbalanced dNTP pool, replication stress, oxidative DNA damage accrual and alterations in DNA damage signaling [128–131]. All reported abnormalities have been considered downstream consequences of qualitative and/or quantitative alterations in protein translation, affecting nuclear and mitochondrial activities. However, recent data indicate that ribosomal proteins or RiBi-associated proteins may directly interact and

affect DDR proteins and pathways [132–140]. This is the case, in SDS: SBDS mutations alter a protein involved in the assembly of mature ribosomes leading to altered RiBi. Nevertheless, SBDS also participates to DNA repair via its interactions with DNA-PK and RPA70, and its loss of function leads to cellular and chromosomal hypersensitivity to DNA damage [141–143]. If mutations in DNAJC21, EFL1, or SRP54, which are rarely identified in SDS patients, participate to altered DDR remains to be determined.

In light of their role in telomere maintenance and in limiting/preventing DNA double-strand break accumulation as a consequence of fusion-breakage cycle caused by downstream telomere fusion events, alterations in the proteins encoded by genes mutated in DCs and their variants, which are components of the telomerase holoenzyme, TERT, TERC, DKC1, NHP2, NOP10, TCAB1, in the shelterin complex TINF2, and RTEL1 and PARN, have direct roles in DNA repair, DDR and genetic stability maintenance. Thus, unsurprisingly, DC, RS and HHS present with higher levels of DNA damage in addition to telomere shortening [144–147].

In conclusion, increased DNA damage and genetic and/or genomic instability are widely associated with different iBMFSS, regardless of the “biochemical/molecular” key function(s) of the proteins encoded by the mutated genes. Thus, considering that FANC/BRCA pathway deficiency is not sufficient *per se* for BMF but that alterations in DDR and/or increased genetic instability are also characteristic of iBMFSS due to defects in telomere maintenance and in RiBi and protein translation, it seems that DDR abnormalities and/or DNA damage accumulation are potentially necessary but not sufficient for BMF.

3. BMF in FA: contributions of nucleolar stress and altered RiBi

3.1. Fanconi anemia: nucleolar stress and RiBi

To better understand the biochemical and molecular basis of the origin of BMF in FA, several recently published manuscripts revealing previously unsuspected links between the FANC/BRCA pathway and nucleolar and RiBi homeostasis are worth highlighting. The loss of function of FANCA and, to a lesser extent, that of its partner FANCG, observed in more than 75% of FA patients worldwide (60–70% of patients lose FANCA plus 10–15% for FANCG), induce nucleolar stress and nucleolar protein mislocalization [148,149]. FANCA coimmunoprecipitated with Nucleolin and Nucleophosmin 1 (NPM1), two of the major nucleolar proteins, suggesting its participation in the process of protein aggregation inside the nucleolus, the membrane-less condensate assembled around ribosomal DNA (rDNA) repeats, whose structural and genetic integrity requires the FANC/BRCA pathway [149,150]. Our observations validated and extended previous data generated by Pang’s group demonstrating that FANCC and FANCA interact and stabilize NMP1 proteins confined in the cytoplasm because their NLS is mutated [151]. These mutations have been observed in approximately 30% of sporadic AML [152,153]. Thus, members of the FANC core complex interact with both WT and mutated NPM1, participating in NPM1 stability and subcellular localization. FANCA and FANCI loss of function affects rDNA transcription and pre-rRNA processing, and FANCA and FANCI are required, together with FANCG, to maintain the global protein synthesis rate [149,150]. Mass spectrometry analysis revealed that only FANCA, FANCI and FANCD2 were present in the 40S, 60S and 80S ribosome fractions, with FANCD2 and FANCI being the only FANC/BRCA pathway-associated proteins retrieved in the polysome fraction [149]. FANCD2 and FANCI coimmunoprecipitated with ribosomal protein S27-like (RPS27L), whose downregulation impacts FANCD2 and FANCI stability, leading to impairment in DNA ICLs repair [133]. The first single-cell transcriptome profile of primary HSPCs from healthy donors and FA patients showed higher expression levels of MYC and its targets in an important fraction of BM-derived FA cells, which was counterbalanced by elevated induction of p53- and TGF β -associated intracellular signaling pathways in the remaining minority of the cells

[154,155]. MYC is a recognized master regulator of RiBi and protein synthesis [156]. Accordingly, the expression of several mRNAs encoding ribosomal proteins and translation factors, including RPL19, RPL13, eIF4A1, eIF4E, eIF4B, RPL5, and RPL27A, is deregulated in HSPCs of FA patients [155]. Hence, the analysis of the transcriptional profile in patient-derived models of hematopoietic differentiation as well as the proteomic profile of BM samples obtained from FA patients revealed enriched signatures consistent with alterations in RiBi and translation in FANCA-deficient cells [157,158]. Accordingly, we reported that FANCA deficiency led to imbalances in the stoichiometry of ribosomal proteins and translation factors associated with ribosome subunits, monosomes and polysomes, including eIF4G1, eIF4E, eIF5A and RPL22A [149]. Moreover, BRCA1/FANCS colocalized with RNA Pol I at the rDNA repeat and coimmunoprecipitated with the RNA Pol I holoenzyme, which is critical for rDNA transcription, which is reduced in the absence of BRCA1 [159]. Thus, alterations in RiBi may be associated and directly linked to at least 4 proteins encoded by genes defining three different modules of the FANC/BRCA pathway, namely, FANCA, FANCG, FANCI and BRCA1/FANCS.

3.2. Evidence showing that nucleolar stress and altered RiBi contribute to BMF in FA and the limits of their contributions

The discovery of proteostasis alterations in FA is very recent, and no study has yet focused on the direct involvement of these alterations in BMF. However, in an induced pluripotent stem cell (iPS) model, Marion and collaborators demonstrated that alterations in terminal erythropoiesis in FA are associated with altered expression of RiBi-encoding genes, supporting the idea that these alterations are involved in red cell aplasia in FA [158]. Therefore, the evidence of nucleolar stress and altered RiBi in FA cell lines and hematopoietic cell models implies that they contribute to the phenotype of both FA cells and patients. This conclusion is important to a better understanding of the pathophysiology of FA.

3.3. Nucleolar stress and RiBi in other iBMFSS

Indeed, it has been clearly demonstrated that altered proteostasis impacts erythropoiesis, mainly through studies of human patients, mouse models or cells haploinsufficient for DBA- or SDS-associated genes [160–162].

DBA is associated with heterozygous inactivating mutations in genes encoding ribosomal proteins or regulators of the ribosomal machinery devoted to mRNA translation [123]. DBA mutations were identified in genes encoding: a) the small ribosome subunit (40S) components RPS7, RPS10, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28 and RPS29; b) the large ribosome subunit (60S) components RPL5, RPL11, RPL15, RPL18, RPL26, RPL27, RPL31, RPL35, RPL35A; and, c) TSR2, a pre-rRNA processing protein (TSR2) that appears to repress the transcription of NF- κ B and plays an essential role in the formation of a mature ribosome, potentially *via* its interaction with the ribosomal protein RPS26 [163,164], encoded by a known DBA-causing gene [125]. Finally, DBA has been also associated to mutations of the key lineage-determining erythropoietic transcription factor GATA1 [165]. Notably, the expression of GATA1 is generally downregulated in all DBA cases [166–168]. Thus, diminished GATA1 expression appears to be the key trigger for altered erythropoiesis in DBA patients. Similar to DBA, SDS is associated with alterations in RiBi owing to mutations in the genes encoding SBDS, DNAJC21, EFL1, or SRP54. SBDS, DNAJC21 and EFL1 promote the assembly and stabilization of monosome 80S, and SRP54 facilitates protein trafficking from the ribosome to the membrane [169–172].

Several, but not all, of the telomereopathy-related proteins, namely, Dyskerin, NHP2, PARN, NOP10 and TCAB1, in addition to their roles in telomere maintenance, have clearly established direct roles in RiBi and nucleolar homeostasis, affecting proteostasis [24,25,173–177]. Whether

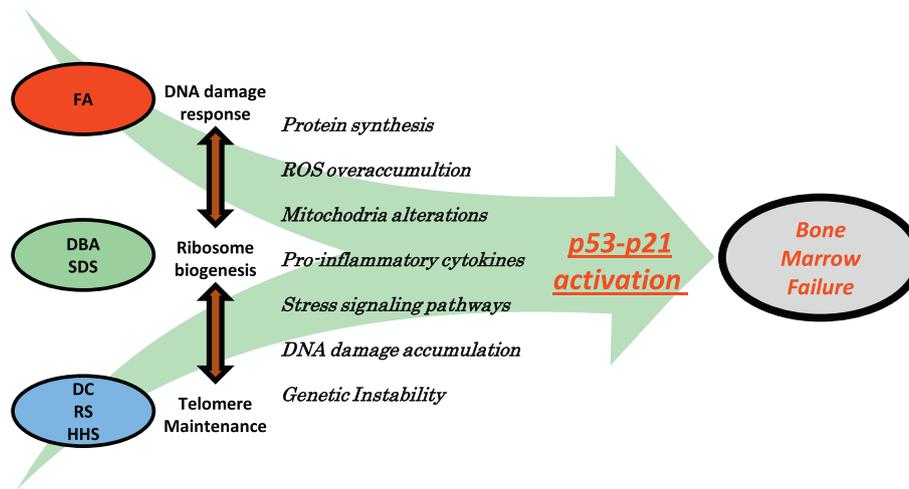


Fig. 3. Convergence of independent genetic defects on BMF via functional aberrancies in several common pathways that lead to p53-p21 axis activation.

The ROS rheostat

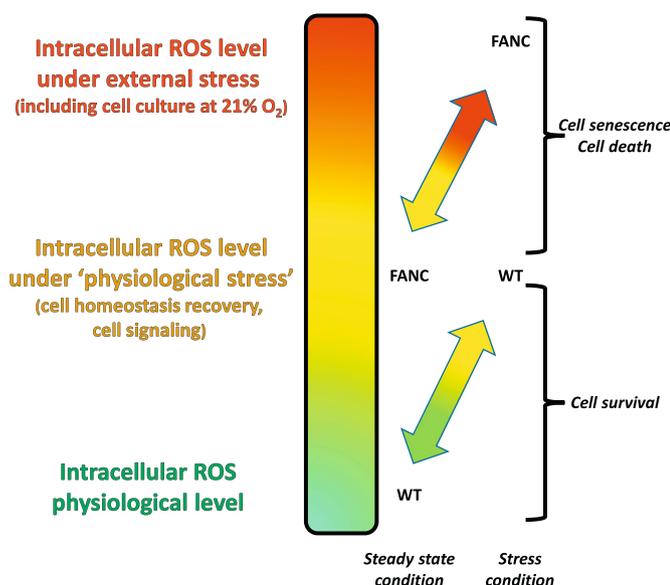


Fig. 4. The ROS rheostat as an example of the proposed dynamic equilibrium that allows survival in a steady state. In a steady state, FA cells can cope with abnormally elevated levels of ROS caused by altered mitochondrial metabolism and with increased DNA damage and/or proinflammatory cytokine production; this situation is equivalent to that reached in WT cells under mild “physiological” stress, for example, in response to unavoidable DNA damage due to individual lifestyle or life events, including sun exposure, smoking and drinking alcohol, therapeutic or accidental exposure to chemicals and radiation, infections and bleeding. When FA cells experience similar additive stress, however, ROS levels overcome the already overloaded antioxidant defenses of these cells, seriously damaging or killing them.

defects in telomeric protein that are not directly involved (either biochemically or molecularly) in RiBi or nucleolar homeostasis affect proteostasis, by disturbing the physiology of their partners, remains to be determined.

Consequently, in addition to DNA damage accumulation and DDR abnormalities, all major iBMFSs share defective RiBi, even if not all the proteins encoded by the mutated genes have direct consequences on proteostasis. Notably and more importantly, altered proteostasis is not a simple perturbation of cellular homeostasis due to mutations in DNA repair or telomere maintenance proteins but is a direct consequence of

the loss of additive functions performed by the same proteins whose inherited mutation leads to the disorder.

4. BMF in FA: downstream DNA repair, DNA damage responses and ribosome biogenesis involving redox homeostasis and the p53-p21 axis

Independent of the key functions attributed to each individual protein encoded by their mutated genes, iBMFSs share DNA repair deficiency, DNA damage accumulation, genetic instability, telomere shortening, nucleolar stress, and ribosomal and translational abnormalities. All previous alterations converge on two usual suspects: the control of redox homeostasis and the overactivation of the p53-p21 axis (Fig. 3).

Increased ROS levels and/or inflammation *per se* are known to influence HSC exit from dormancy or to bias differentiation toward specific lineages [178,179]. In FA, altered redox homeostasis has been considered a major physiological abnormality for 40 years [180–182], although its origins and consequences for in terms of clinical and cellular phenotype acquisition are still debated [183,184]. The reduced ability to cope with intracellular free radical oxygen species (ROS) has been proposed as a major determinant of FA clinical and cellular phenotypes, suggesting that altered redox metabolism likely plays a greater role and is not a mere hallmark of the syndrome [185–188]. However, although certain FANC core complex proteins, e.g., FANCC and FANCG, have been identified in immunocomplexes in conjunction with proteins involved in mitochondrial activities [189–192], how the FANC/BRCA pathway, as a whole, associates with oxidative metabolism is still poorly understood. Indeed, the ROS increases in FA cells are probably results of accumulated old/damaged misfunctioning mitochondria, a consequence of altered mitophagy [193], with widely observed abnormalities in the secretion of proinflammatory factors, including cytokines (TNF α), lymphokine (IL1 β), growth factor (TGF β) and/or interferons (IFNs), and/or in the activation of their signaling pathways (the p38, SMAD, and NF- κ B pathways, respectively) [155,194–198]. Moreover, the majority of the data attesting to ROS overaccumulation or hypersensitivity in FA stems from *in vitro* or *ex vivo* studies, which are potentially corrupted by O₂ tension caused by exposure to atmospheric air, which contains 21% oxygen. Data generated under condition of 3%-5% of O₂, i. e. a level of O₂ close to the physiological level similar to that inside tissues demonstrated reduced, if any, sensitivity to oxygen than at 21% O₂ [180–184,187,199]. Therefore, the data seem to support a pathological problem in ROS accumulation/detoxication under stress that is minimal present under basal physiological conditions. In other words, we speculate that FA cells “*in vivo*” can survive with a basal level of ROS

that is probably higher than in WT cells but not pathological *per se* until additive stresses overload saturated cell defenses (Fig. 4). Heinrich and collaborator proposed a similar explanation for the prolonged G2/M arrest, a key FA hallmark, of FA cells treated with low doses of DNA cross-linking agents [200]. On the basis of their experimental approach, they suggested that aberrant G2/M arrest does not reflect an abnormal cell cycle response but represents a normal cellular response to “excessive” genotoxic stress induced in FA cells as a consequence of the additive DNA lesions caused by exposure to DNA-damaging agents [200]. Regardless of the cause(s), increased ROS levels in FA appear to be a potential and promising therapeutic targets [201]. Based on the rescue effect of antioxidant treatment *in vitro* and in animal models [202–205], a clinical trial of quercetin, a flavonoid polyphenol with antioxidant properties, is ongoing (clinicaltrials.gov NCT01720147) to address its effects on hematopoiesis [206].

Contributing to the argument that accumulating ROS and/or a proinflammatory status can be a key contributor to BMF, these hallmarks characterize other major iBMFSs. In DBA, an FA-like inflammatory signature indicated by TNF α , IL6 and IL1 β overexpression was observed in patients and in a zebrafish model, and it was associated, similar to FA [100,194,207–212], with p38 activation [130,213]. Importantly, in DBA, proinflammatory cytokine inhibition partially attenuates oxidative DNA damage levels and restores hematopoiesis [130,213]. SDS is also characterized with impaired energetic metabolism (i.e., altered mitochondrial homeostasis) and increased intracellular ROS levels [214–217]. Oxidative stress is an established hallmark of DC, and it is involved in the prosenescent DC phenotype [218–221]. In a *Dkc1* mouse model of DC, treatment with the antioxidant N-acetyl cysteine partially reversed the growth disadvantage conferred by mutant cells *in vitro* and in competitive BM repopulation experiments *in vivo*, suggesting that increased oxidative stress might play a role in the pathogenesis of DC and that some manifestations of DC may be prevented or delayed by antioxidant treatment [222]. Thus, ROS accumulation and the inflammatory phenotype appear to be potential mediators of the BMF observed in FA, DBA, DC and associated syndromes.

Increased intracellular ROS levels, which lead to an increase in oxidative DNA lesions and alters enzymatic activities through protein oxidation, together with alterations in DNA repair, telomere metabolism, nucleolar homeostasis and RiBi contribute to the activation of p53 and its major target p21 [223], which are constitutively turned on in FA, DBA, DC and associated disorders. Indeed, p53 is activated as a consequence of replication stress, DNA damage and telomere attrition that leads to ATM/ATR-mediated p53 phosphorylation [224] but also downstream the ‘inhibition’ of its inhibitor, MDM2, which is sequestered *via* its interaction with nucleolar or ribosomal proteins [8,225]. Moreover, p21 expression, at both the transcriptional and post-transcriptional levels, can be induced in a p53-independent manner, notably by NPM1 when the protein is displaced outside the nucleolus under nucleolar stress conditions [148,226].

In FA, p53 overexpression in the absence of exogenous stress was described 30 years ago, extensively validated, considered a consequence of increased DNA damage and obviously associated with increased apoptosis and senescence, which are potentially major causes of HSC attrition and BMF [95,155,227–234]. It has been recently shown with patient samples that depletion of p53 or p21 restores the clonogenicity of CD34⁺ cells isolated from FA patients [95]. This observation is intriguing because it suggests that is the overexpression of p21, and not that of p53, that affects BM homeostasis in FA. Thus, it is tempting to hypothesize that BMF emerges, at least in FA and possibly in the other iBMFSs, as a result of crosstalk among components of several functional abnormalities that result in constitutive p21 expression due to its increased transcription and stabilization, which are known to be pernicious to cell physiology [235].

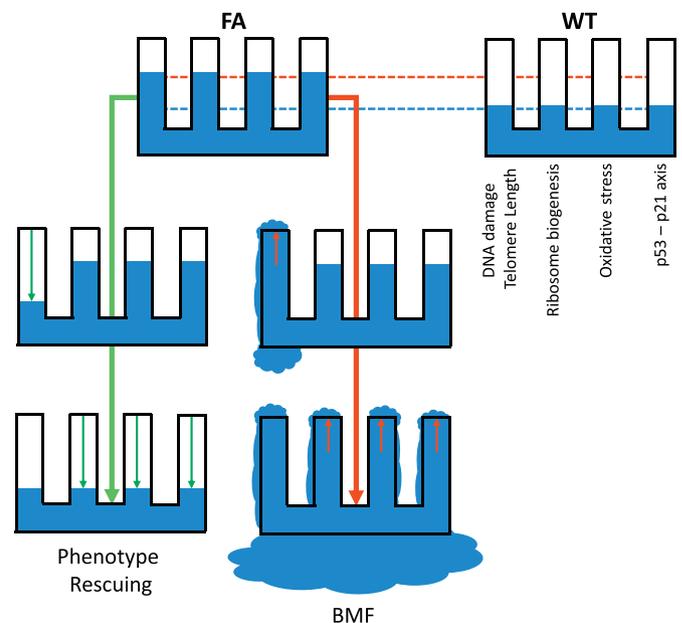


Fig. 5. Cartoon illustrating the dynamic cellular homeostasis that allows FA cell survival and a partial or transient rescue of their phenotypes when one of the altered pathways is normalized.

5. Conclusions and future considerations

In conclusion, we propose that BMF in FA is a sum of events (and not necessarily the same events in each complementation group and/or in each kind of primary cell in organisms and *in vitro* and animal models) leading to alterations in both genetic and protein homeostasis, ultimately impacting redox (inflammatory) metabolism and (p53)-p21 axis expression, which probably represents the central hub in the pathological traits of the syndrome.

Nevertheless, two paradoxes remain unresolved: i) How does FA progress from BMF to MDS or AML? and ii) Despite the unscheduled and potential toxicity of the improper activation of several cellular and molecular pathways in FA cells, why is the normalization of just one end point, as in the case of p53 or p21 [95], TGF β [236,237] or TNF α [197], sufficient for rescuing, at least transiently, several cellular and tissue phenotypes?

FA and the other iBMFSs globally present a growth inhibitory phenotype with p53-p21 axis overactivation, compromised mitochondrial metabolism, altered levels and quality of proteins and accelerated cellular senescence. How does these phenotypes progress toward hyperproliferative MDS and/or AML? All previous outcomes of BMF may represent the “Darwinian pressure” required to enable selected cells to overcome their initial inhibitory/hypoproliferative growth phenotype leading to MDS and leukemia. The recent observation that the BM of FA patients shows a higher frequency of cells with overexpression of MYC and MYC-dependent pathways cohabitating with p53-overexpressing cells supports the previous posit [155].

How do FANC cells survive against the “Darwinian pressure” generated by the addition of the described abnormalities in nuclear, nucleolar, mitochondrial and ribosomal (i.e., cytoplasmic) homeostasis? We assume that an FA cell “survives” despite a situation in which several physiological parameters are “individually” deregulated and potentially toxic because, ultimately, this cell has found an alternative “homeostatic” point, in which the relative balance between the different parameters is maintained as it is in normal cells. Such “higher” homeostasis enables cell and individual survival at the expense of tissue health in the long term (BMF develops progressively and is often absent at birth). According to the principle of communicating vessels, modifying the level of liquid in one vessel (one of the parameters) re-equilibrates the

level in the others. Thus, “normalizing” one of the pathways is enough to rescue at least transiently some FA phenotypes, whereas increasing the level of one “vessel” is sufficient to collapse the system (Fig. 5).

In conclusion, although the idea that one of the proteins associated with the FANC/BRCA pathway has novel functions in addition to functions in DNA repair has long been considered unsubstantiated, it is time to reconsider this possibility. A better understanding of the cellular and clinical phenotypes of FA, as well as a better management of patients with FA, requires “a shared axiom” [186], in which several alternative functions of FA proteins, spanning from DNA repair to ribosome biogenesis, are included. FA depends on the association of several abnormalities in cellular, biochemical and molecular pathways outside DNA repair [238]. Obviously, the loss of DNA repair functions clearly remains central to the FA phenotype and they are, probably, key for the BMF-to-MDS/AML transition. However, in addition to their DNA repair functions, at least FANCA, FANCG, FANCI and BRCA1 clearly have biochemical/functional activities and are involved in RNA and/or protein metabolism, the loss of which impact BM functionality. and providing further support for the importance of nucleolar activity and RiBi involved in BM physiology with the dependence on a virtuous cycle linking gene maintenance and protein expression. Thus, to the question posed at the end of a manuscript authored by Sondalle and collaborators, who asked whether FA must also be considered a ribosomopathy [150], our answer is yes: FA is also a ribosomopathy.

Practice points

- A future goal is to determine how impairment of ribosome biogenesis in FA impacts the bone marrow microenvironment and contributes to bone marrow failure (BMF) and myelodysplastic syndrome/acute myeloid leukemia (AML) initiation/progression.
- Describing differences in cell physiology, in addition to those associated with DNA damage responses, and the biology of hematopoietic stem cells may lead to new therapeutic opportunities that merit further exploration with patients and in vivo models.
- Therapeutic approaches targeting recombinant DNA transcription, ribosome biogenesis and/or translation may attenuate BMF and/or delay AML initiation or progression.

Research agenda

- Collaborative studies involving experts from different disciplines are needed to better understand the pathophysiology of FA and IBMFS and their cell biology.
- How do FANC proteins ensure erythropoietic and megakaryocytic differentiation? Is it through their contribution to DNA repair and genetic stability or through their involvement in ribosome biogenesis and proteostasis? Or is it a result of FANC protein involvement in processes other than those of ribosome biogenesis and proteostasis?
- How does altered proteostasis associated with the loss of function of the FANC/BRCA pathway contribute to the progression of MDS and AML in FA?
- Is rDNA transcription in MDS and AML of FA patients a novel therapeutic target?

Declaration of Competing Interest

Nothing to declare.

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