



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

Anna Gueiderikh, Frédérique Maczkowiak-Chartois, Filippo Rosselli

► To cite this version:

Anna Gueiderikh, Frédérique Maczkowiak-Chartois, Filippo Rosselli. A new frontier in Fanconi anemia: From DNA repair to ribosome biogenesis. *Blood Reviews*, 2022, 52, pp.100904. 10.1016/j.blre.2021.100904 . hal-03862574

HAL Id: hal-03862574

<https://hal.science/hal-03862574>

Submitted on 17 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Review

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

Anna Gueiderikh^{a,b,c}, Frédérique Maczkowiak-Chartois^{a,b,c}, Filippo Rosselli^{a,b,c,*}^a CNRS - UMR9019, Équipe labellisée "La Ligue contre le Cancer", 94805 Villejuif, France^b Gustave Roussy Cancer Center, 94805 Villejuif, France^c Université Paris-Saclay - Paris Sud, Orsay, France

ARTICLE INFO

Keywords:

Inherited bone marrow failure syndrome
Fanconi anemia
DNA repair
Ribosome biogenesis
Proteostasis

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 (DDR). 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 pathophysiologicals that present diagnostic and therapeutic challenges for clinicians (Tables 1 and 2).

* Corresponding author at: CNRS - UMR9019, CNRS - UMR9019, Équipe labellisée "La Ligue contre le Cancer". Gustave Roussy Institute, 114 Rue Edouard Vaillant, 94805, Villejuif, France.

E-mail addresses: anna.gueiderikh@gustaveroussy.fr (A. Gueiderikh), frederique.maczkowiak@gustaveroussy.fr (F. Maczkowiak-Chartois), filippo.rosselli@gustaveroussy.fr (F. Rosselli).

<https://doi.org/10.1016/j.blre.2021.100904>

Available online 31 October 2021

0268-960X/© 2021 The Authors.

Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

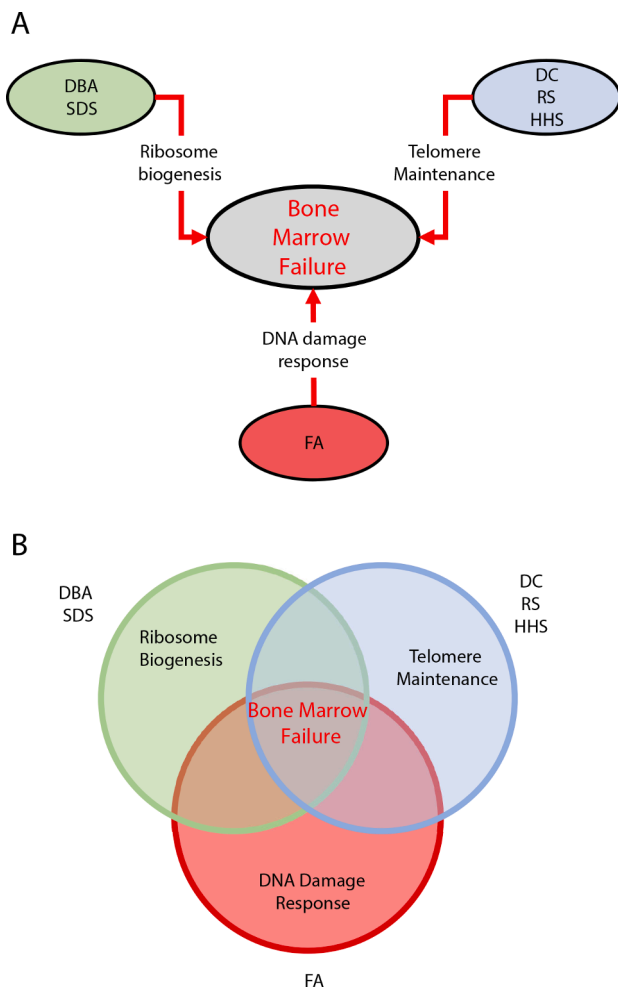


Fig. 1. Models linking genetics and biochemistry to BMF. A) BMF as a consequence of alterations in independent functional pathways. B) BMF as a consequence of the addition and convergence of alternative functions of the proteins encoded by inherited mutated genes.

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					p53-p21 axis constitutive activation	
	Skeletal	Skin/Epithelia	Miscellanea	Cytopenias	Solid cancer	Leukemia	DNA damage Replication stress	Altered Telomeres	Genetic/ Genomic Instability	Intracellular ROS level		Cytokine abnormalities, pro-inflammatory status
Fanconi anemia	Short stature Thumb abnormalities	Café-au-lait spots, Hyperpigmentation Hypopigmentation	Hypogonadism abnormalities Renal and Gastrointestinal anomalies	Pancytopenia Thrombocytopenia Anemia	Head & Neck Cancers Breast, Ovarian & Pancreatic cancers	MDS AML	Present	Present	Present	Increased	Present	Present, at least in some complementation groups
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	MDS AML	Present	Rare patients	Present	Increased	Present	Present
Shwachman-Diamond syndrome		Ichthyosis	Hearing loss Pancreatic insufficiency		Ovary	MDS AML						
Dyskeratosis congenita (Revesz syndrome, Hoyerhaal-Hreidarsson)	Osteopenia Microcephaly Short stature	Hyperpigmentation Nail Dystrophy Oral leukoplakia	Hypogonadism Pulmonary fibrosis	Pancytopenia Thrombocytopenia	Head & Neck cancers, anogenital adenocarcinomas,	MDS AML	Present	Present	Present	Increased	Present	Present, at least in some complementation groups

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 transitorily 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 MutLα [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	RPL18, 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	
Dyskeratosis congenita (DC) Revesz syndrome (RS) Hoyeraal-Hreidarsson (HSS)	Rare <500 families worldwide	<i>WRAP53</i>	AR	Rare	Telomerase Cajal body protein 1	TCAB1	DKCB3	Telomeropathy
		<i>TERC</i>	AD	5%-10%	Telomerase RNA component			
		<i>TERT</i>	AD, AR	1%-7%	Telomerase reverse transcriptase	TERT	DKCA2, DKCB4	
		<i>TINF2</i>	AD	12%-20%	TERF1-interacting nuclear factor 2	TINF2	TIN2, 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.

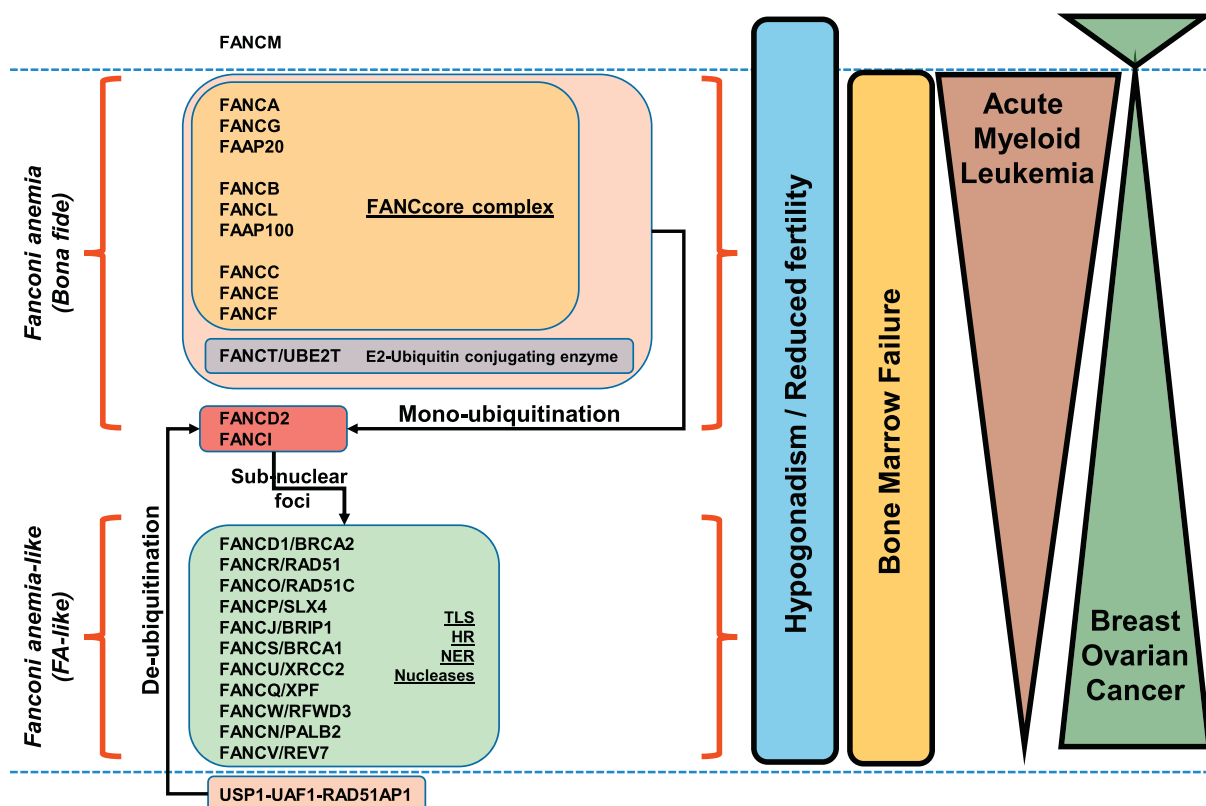


Fig. 2. Fanconi anemia proteins, modules, pathway and key phenotypes.

e., a reduced quiescent cell population) and an increased level of DNA damage. Is DNA damage accumulation the direct link between the FANCM/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 FANCM core complex [67,105–108]. FANCM is at the apex of the FANCM/BRCA pathway, and its loss of function leads to canonical cellular abnormalities associated with FANCM/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 FANCM/BRCA pathway [122].

Thus, although the biochemical and molecular functions of the FANCM/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 TIN2, 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 iBMFSSs, regardless of the “biochemical/molecular” key function(s) of the proteins encoded by the mutated genes. Thus, considering that FANCA/BRCA pathway deficiency is not sufficient *per se* for BMF but that alterations in DDR and/or increased genetic instability are also characteristic of iBMFSSs 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 FANCA/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 FANCA/BRCA pathway [149,150]. Our observations validated and extended previous data generated by Pang’s group demonstrating that FANCA and FANCG interact and stabilize NPM1 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 FANCA core complex interact with both WT and mutated NPM1, participating in NPM1 stability and subcellular localization. FANCA and FANCG loss of function affects rDNA transcription and pre-rRNA processing, and FANCA and FANCG are required, together with FANCG, to maintain the global protein synthesis rate [149,150]. Mass spectrometry analysis revealed that only FANCA, FANCG and FANCD2 were present in the 40S, 60S and 80S ribosome fractions, with FANCD2 and FANCG being the only FANCA/BRCA pathway-associated proteins retrieved in the polysome fraction [149]. FANCD2 and FANCG coimmunoprecipitated with ribosomal protein S27-like (RPS27L), whose downregulation impacts FANCD2 and FANCG 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/FANCG 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 FANCA/BRCA pathway, namely, FANCA, FANCG, FANCG and BRCA1/FANCG.

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 physiopathology of FA.

3.3. Nucleolar stress and RiBi in other iBMFSSs

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 telomeropathy-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

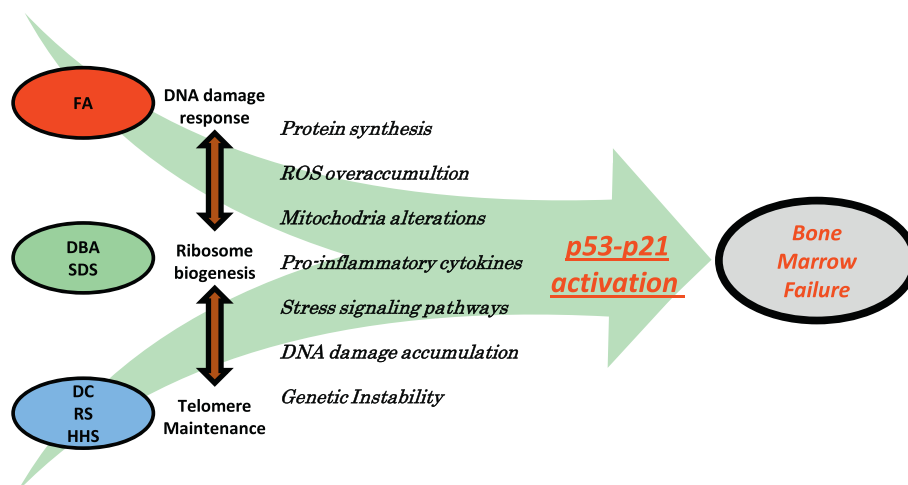


Fig. 3. Convergence of independent genetic defects on BMF via functional aberrancies in several common pathways that lead to p53-p21 axis activation.

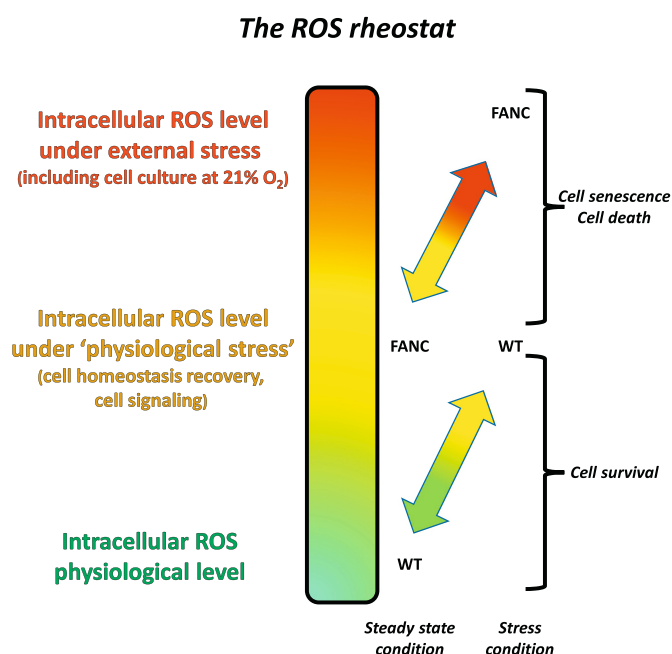


Fig. 4. The ROS rheostat as an example of the proposed dynamic equilibrium that allows survival in a steady state. In a steady state, FA cells can cope with abnormally elevated levels of ROS caused by altered mitochondrial metabolism and with increased DNA damage and/or proinflammatory cytokine production; 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].

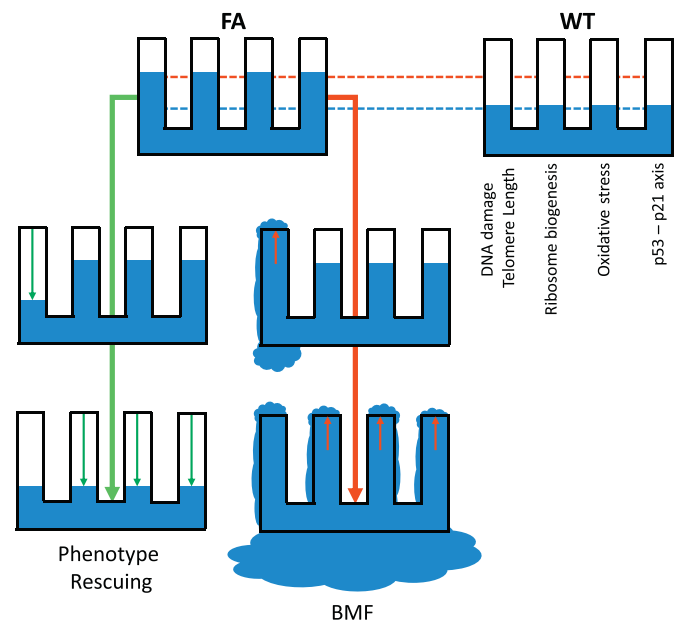


Fig. 5. Cartoon illustrating the dynamic cellular homeostasis that allows FA cell survival and a partial or transient rescue of their phenotypes when one of the altered pathways is normalized.

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 transitorily 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.

Acknowledgments

The authors apologize to colleagues whose work was not mentioned because of space constraints. This work was supported by grants from La Ligue Contre Le Cancer and Electricité de France to FR. AG was a fellow of the INSERM School Liliane Bettencourt.

References

- [1] Kallen ME, Dulau-Florea A, Wang W, Calvo KR. Acquired and germline predisposition to bone marrow failure: diagnostic features and clinical implications. *Semin Hematol* 2019;56:69–82. <https://doi.org/10.1053/j.seminhematol.2018.05.016>.
- [2] Dokal I, Vulliamy T. Inherited bone marrow failure syndromes. *Haematologica* 2010;95:1236–40. <https://doi.org/10.3324/haematol.2010.025619>.
- [3] Savage SA, Dufour C. Classical inherited bone marrow failure syndromes with high risk for myelodysplastic syndrome and acute myelogenous leukemia. *Semin Hematol* 2017;54:105–14. <https://doi.org/10.1053/j.seminhematol.2017.04.004>.
- [4] Bluteau O, Sebert M, Leblanc T, Peffault de Latour R, Quentin S, Lainey E, et al. A landscape of germ line mutations in a cohort of inherited bone marrow failure patients. *Blood* 2018;131:717–32. <https://doi.org/10.1182/blood-2017-09-806489>.
- [5] Frazier MN, Pillon MC, Kocaman S, Gordon J, Stanley RE. Structural overview of macromolecular machines involved in ribosome biogenesis. *Curr Opin Struct Biol* 2021;67:51–60. <https://doi.org/10.1016/j.sbi.2020.09.003>.
- [6] Pecoraro A, Pagano M, Russo G, Russo A. Ribosome biogenesis and cancer: overview on ribosomal proteins. *Int J Mol Sci* 2021;22:5496. <https://doi.org/10.3390/ijms22115496>.
- [7] Houston R, Sekine S, Sekine Y. The coupling of translational control and stress responses. *J Biochem* 2020;168:93–102. <https://doi.org/10.1093/jb/mvaa061>.
- [8] Yang K, Yang J, Yi J. Nucleolar stress: hallmarks, sensing mechanism and diseases. *Cell Stress* 2018;2:125–40. <https://doi.org/10.15698/cst2018.06.139>.
- [9] Russo A, Russo G. Ribosomal proteins control or bypass p53 during nucleolar stress. *Int J Mol Sci* 2017;18:E140. <https://doi.org/10.3390/ijms18010140>.
- [10] Kang J, Brajanovski N, Chan KT, Xuan J, Pearson RB, Sanij E. Ribosomal proteins and human diseases: molecular mechanisms and targeted therapy. *Signal Transduct Target Ther* 2021;6:323. <https://doi.org/10.1038/s41392-021-00728-8>.
- [11] Russo A, Esposito D, Catillo M, Pietropaolo C, Crescenzi E, Russo G. Human rpl3 induces G₀/S arrest or apoptosis by modulating p21 (waf1/cip1) levels in a p53-independent manner. *Cell Cycle* 2013;12:76–87. <https://doi.org/10.4161/cc.22963>.
- [12] Wanzel M, Russ AC, Kleine-Kohlbrecher D, Colombo E, Pelicci P-G, Eilers M. A ribosomal protein L23-nucleophosmin circuit coordinates Miz1 function with cell growth. *Nat Cell Biol* 2008;10:1051–61. <https://doi.org/10.1038/ncb1764>.
- [13] Fähræus R, Olivares-Illana V. MDM2's social network. *Oncogene* 2014;33:4365–76. <https://doi.org/10.1038/onc.2013.410>.
- [14] Dai M-S, Sun X-X, Lu H. Ribosomal protein L11 associates with c-Myc at 5 S rRNA and rRNA genes and regulates their expression. *J Biol Chem* 2010;285:12587–94. <https://doi.org/10.1074/jbc.M109.056259>.
- [15] Dai M-S, Sears R, Lu H. Feedback regulation of c-Myc by ribosomal protein L11. *Cell Cycle* 2007;6:2735–41. <https://doi.org/10.4161/cc.6.22.4895>.
- [16] Dai M-S, Arnold H, Sun X-X, Sears R, Lu H. Inhibition of c-Myc activity by ribosomal protein L11. *EMBO J* 2007;26:3332–45. <https://doi.org/10.1038/sj.emboj.7601776>.
- [17] Hegde V, Wang M, Deutsch WA. Human ribosomal protein S3 interacts with DNA base excision repair proteins hAPE/Ref-1 and hOGG1. *Biochemistry* 2004;43:14211–7. <https://doi.org/10.1021/bi049234b>.
- [18] Lim CJ, Cech TR. Shaping human telomeres: from shelterin and CST complexes to telomeric chromatin organization. *Nat Rev Mol Cell Biol* 2021;22:283–98. <https://doi.org/10.1038/s41580-021-00328-y>.
- [19] Bonnell E, Pasquier E, Wellinger RJ. Telomere replication: solving multiple end replication problems. *Front Cell Dev Biol* 2021;9:668171. <https://doi.org/10.3389/fcell.2021.668171>.
- [20] Liu J, Wang L, Wang Z, Liu J-P. Roles of telomere biology in cell senescence. Replicative and chronological ageing. *Cells* 2019;8:E54. <https://doi.org/10.3390/cells8010054>.
- [21] Chen Y. The structural biology of the shelterin complex. *Biol Chem* 2019;400:457–66. <https://doi.org/10.1515/hsz-2018-0368>.
- [22] Soudet J, Jolivet P, Teixeira MT. Elucidation of the DNA end-replication problem in *Saccharomyces cerevisiae*. *Mol Cell* 2014;53:954–64. <https://doi.org/10.1016/j.molcel.2014.02.030>.
- [23] Fallet E, Jolivet P, Soudet J, Lisby M, Gilson E, Teixeira MT. Length-dependent processing of telomeres in the absence of telomerase. *Nucleic Acids Res* 2014;42:3648–65. <https://doi.org/10.1093/nar/gkt1328>.
- [24] Angrisani A, Vicidomini R, Turano M, Furia M. Human dyskerin: beyond telomeres. *Biol Chem* 2014;395:593–610. <https://doi.org/10.1515/hsz-2013-0287>.
- [25] Benyelles M, O'Donohue M-F, Kermasson L, Lainey E, Borie R, Lagresle-Peyrou C, et al. NHP2 deficiency impairs rRNA biogenesis and causes pulmonary fibrosis and Høyerdaal-Hreidarsson syndrome. *Hum Mol Genet* 2020;29:907–22. <https://doi.org/10.1093/hmg/ddaa011>.
- [26] Yuan F, Xu C, Li G, Tong T. Nucleolar TRF2 attenuated nucleolar stress-induced HCC cell-cycle arrest by altering rRNA synthesis. *Cell Death Dis* 2018;9:518. <https://doi.org/10.1038/s41419-018-0572-3>.
- [27] Berthelot V, Mouta-Cardoso G, Hégaret N, Guillonnet F, François J-C, Giovannangeli C, et al. The human DNA ends proteome uncovers an unexpected entanglement of functional pathways. *Nucleic Acids Res* 2016;44:4721–33. <https://doi.org/10.1093/nar/gkw121>.
- [28] Lyu X, Sang PB, Chai W. CST in maintaining genome stability: beyond telomeres. *DNA Repair (Amst)* 2021;102:103104. <https://doi.org/10.1016/j.dnarep.2021.103104>.

- [29] Cicconi A, Chang S. Shelterin and the replisome: at the intersection of telomere repair and replication. *Curr Opin Genet Dev* 2020;60:77–84. <https://doi.org/10.1016/j.gde.2020.02.016>.
- [30] Arnault N, Karlseder J. Complex interactions between the DNA-damage response and mammalian telomeres. *Nat Struct Mol Biol* 2015;22:859–66. <https://doi.org/10.1038/nsmb.3092>.
- [31] Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. *Nature* 2001;411:366–74. <https://doi.org/10.1038/35077232>.
- [32] Shiloh Y. ATM and ATR: networking cellular responses to DNA damage. *Curr Opin Genet Dev* 2001;11:71–7. [https://doi.org/10.1016/s0959-437x\(00\)00159-3](https://doi.org/10.1016/s0959-437x(00)00159-3).
- [33] Abraham RT. Cell cycle checkpoint signaling through the ATM and ATR kinases. *Genes Dev* 2001;15:2177–96. <https://doi.org/10.1101/gad.914401>.
- [34] Kirschner K, Melton DW. Multiple roles of the ERCC1-XPF endonuclease in DNA repair and resistance to anticancer drugs. *Anticancer Res* 2010;30:3223–32.
- [35] Manandhar M, Boulware KS, Wood RD. The ERCC1 and ERCC4 (XPF) genes and gene products. *Gene* 2015;569:153–61. <https://doi.org/10.1016/j.gene.2015.06.026>.
- [36] Ray Chaudhuri A, Nussenzweig A. The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. *Nat Rev Mol Cell Biol* 2017;18:610–21. <https://doi.org/10.1038/nrm.2017.53>.
- [37] Li N, Wang J, Wallace SS, Chen J, Zhou J, D'Andrea AD. Cooperation of the NEIL3 and Fanconi anemia/BRCA pathways in interstrand crosslink repair. *Nucleic Acids Res* 2020;48:3014–28. <https://doi.org/10.1093/nar/gkaa038>.
- [38] Liu M, Doublé S, Wallace SS. Neil3, the final frontier for the DNA glycosylases that recognize oxidative damage. *Mutat Res* 2013;743:744–41. <https://doi.org/10.1016/j.mrfmmm.2012.12.003>.
- [39] Martin PR, Couvé S, Zutterling C, Albelazi MS, Groisman R, Matkarimov BT, et al. The Human DNA glycosylases NEIL1 and NEIL3 Excise Psoralen-Induced DNA-DNA Cross-Links in a Four-Stranded DNA Structure. *Sci Rep* 2017;7:17438. <https://doi.org/10.1038/s41598-017-17693-4>.
- [40] Yang Z, Nejad MI, Varela JG, Price NE, Wang Y, Gates KS. A role for the base excision repair enzyme NEIL3 in replication-dependent repair of interstrand DNA cross-links derived from psoralen and abasic sites. *DNA Repair (Amst)* 2017;52:1–11. <https://doi.org/10.1016/j.dnarep.2017.02.011>.
- [41] Semlow DR, Zhang J, Budzowska M, Drohat AC, Walter JC. Replication-dependent unhooking of DNA interstrand cross-links by the NEIL3 glycosylase. *Cell* 2016;167:498–511. e14. <https://doi.org/10.1016/j.cell.2016.09.008>.
- [42] Sharma R, Lewis S, Wlodarski MW. DNA repair syndromes and cancer: insights into genetics and phenotype patterns. *Front Pediatr* 2020;8:570084. <https://doi.org/10.3389/fped.2020.570084>.
- [43] Taylor AMR, Rothblum-Oviatt C, Ellis NA, Hickson ID, Meyer S, Crawford TO, et al. Chromosome instability syndromes. *Nat Rev Dis Primers* 2019;5:64. <https://doi.org/10.1038/s41572-019-0113-0>.
- [44] O'Driscoll M. Diseases associated with defective responses to DNA damage. *Cold Spring Harb Perspect Biol* 2012;4:a012773. <https://doi.org/10.1101/cshperspect.a012773>.
- [45] Okur MN, Lee J-H, Osmani W, Kimura R, Demarest TG, Croteau DL, et al. Cockayne syndrome group A and B proteins function in rRNA transcription through nucleolin regulation. *Nucleic Acids Res* 2020;48:2473–85. <https://doi.org/10.1093/nar/gkz1242>.
- [46] Tiwari V, Baptiste BA, Okur MN, Bohr VA. Current and emerging roles of Cockayne syndrome group B (CSB) protein. *Nucleic Acids Res* 2021;49:2418–34. <https://doi.org/10.1093/nar/gkab085>.
- [47] Qiang M, Khalid F, Phan T, Ludwig C, Scharffetter-Kochanek K, Iben S. Cockayne syndrome-associated CSA and CSB mutations impair ribosome biogenesis, ribosomal protein stability, and global protein folding. *Cells* 2021;10:1616. <https://doi.org/10.3390/cells10071616>.
- [48] Shao Z, Flynn RA, Crowe JL, Zhu Y, Liang J, Jiang W, et al. DNA-PKcs has KU-dependent function in rRNA processing and haematopoiesis. *Nature* 2020;579:291–6. <https://doi.org/10.1038/s41586-020-2041-2>.
- [49] Kim D-S, Challa S, Jones A, Kraus WL. PARPs and ADP-ribosylation in RNA biology: from RNA expression and processing to protein translation and proteostasis. *Genes Dev* 2020;34:302–20. <https://doi.org/10.1101/gad.334433.119>.
- [50] Kim D-S, Camacho CV, Nagari A, Malladi VS, Challa S, Kraus WL. Activation of PARP-1 by snoRNAs controls ribosome biogenesis and cell growth via the RNA Helicase DDX21. *Mol Cell* 2019;75:1270–85. e14. <https://doi.org/10.1016/j.molcel.2019.06.020>.
- [51] Lobitz S, Velleuer E. Guido Fanconi (1892-1979): a jack of all trades. *Nat Rev Cancer* 2006;6:893–8. <https://doi.org/10.1038/nrc2009>.
- [52] Gueiderikh A, Rosselli F, Neto JBC. A never-ending story: the steadily growing family of the FA and FA-like genes. *Genet Mol Biol* 2017;40:398–407. <https://doi.org/10.1590/1678-4685-GMB-2016-0213>.
- [53] Bogliolo M, Surrallés J. Fanconi anemia: a model disease for studies on human genetics and advanced therapeutics. *Curr Opin Genet Dev* 2015;33:32–40. <https://doi.org/10.1016/j.gde.2015.07.002>.
- [54] Fiesco-Roa MO, Giri N, McReynolds LJ, Best AF, Alter BP. Genotype-phenotype associations in Fanconi anemia: a literature review. *Blood Rev* 2019;37:100589. <https://doi.org/10.1016/j.blre.2019.100589>.
- [55] Alter BP. Fanconi anemia and the development of leukemia. *Best Pract Res Clin Haematol* 2014;27:214–21. <https://doi.org/10.1016/j.beha.2014.10.002>.
- [56] Yu Q-H, Wang S-Y, Wu Z. Advances in genetic studies of inherited bone marrow failure syndromes and their associated malignancies. *Transl Pediatr* 2014;3:305–9. <https://doi.org/10.3978/j.issn.2224-4336.2014.07.06>.
- [57] Renaudin X, Rosselli F. The FANCD2/BRCA pathway releases replication blockades by eliminating DNA interstrand cross-links. *Genes (Basel)* 2020;11. <https://doi.org/10.3390/genes11050585>.
- [58] D'Andrea AD, Grompe M. The Fanconi anaemia/BRCA pathway. *Nat Rev Cancer* 2003;3:23–34. <https://doi.org/10.1038/nrc970>.
- [59] Pichierri P, Rosselli F. Fanconi anemia proteins and the S phase checkpoint. *Cell Cycle* 2004;3:698–700.
- [60] Kim JM, Parmar K, Huang M, Weinstock DM, Ruit CA, Kutok JL, et al. Inactivation of murine Usp1 results in genomic instability and a Fanconi anemia phenotype. *Dev Cell* 2009;16:314–20. <https://doi.org/10.1016/j.devcel.2009.01.001>.
- [61] Parmar K, Kim J, Sykes SM, Shimamura A, Stuckert P, Zhu K, et al. Hematopoietic stem cell defects in mice with deficiency of Fancd2 or Usp1. *Stem Cells* 2010;28:1186–95. <https://doi.org/10.1002/stem.437>.
- [62] Andreassen PR, D'Andrea AD, Taniguchi T. ATR couples FANCD2 monoubiquitination to the DNA-damage response. *Genes Dev* 2004;18:1958–63. <https://doi.org/10.1101/gad.1196104>.
- [63] Guervilly J-H, Macé-Aimé G, Rosselli F. Loss of CHK1 function impedes DNA damage-induced FANCD2 monoubiquitination but normalizes the abnormal G2 arrest in Fanconi anemia. *Hum Mol Genet* 2008;17:679–89. <https://doi.org/10.1093/hmg/ddm340>.
- [64] Pichierri P, Rosselli F. The DNA crosslink-induced S-phase checkpoint depends on ATR-CHK1 and ATR-NBS1-FANCD2 pathways. *EMBO J* 2004;23:1178–87. <https://doi.org/10.1038/sj.emboj.7600113>.
- [65] Taniguchi T, Garcia-Higuera I, Xu B, Andreassen PR, Gregory RC, Kim S-T, et al. Convergence of the fanconi anemia and ataxia telangiectasia signaling pathways. *Cell* 2002;109:459–72. [https://doi.org/10.1016/s0092-8674\(02\)00747-x](https://doi.org/10.1016/s0092-8674(02)00747-x).
- [66] Digweed M, Rothe S, Demuth I, Scholz R, Schindler D, Stumm M, et al. Attenuation of the formation of DNA-repair foci containing RAD51 in Fanconi anaemia. *Carcinogenesis* 2002;23:1121–6. <https://doi.org/10.1093/carcin/23.7.1121>.
- [67] Meetei AR, Sechi S, Wallisch M, Yang D, Young MK, Joenje H, et al. A multiprotein nuclear complex connects Fanconi anemia and Bloom syndrome. *Mol Cell Biol* 2003;23:3417–26. <https://doi.org/10.1128/mcb.23.10.3417-3426.2003>.
- [68] Pichierri P, Averbeck D, Rosselli F. DNA cross-link-dependent RAD50/MRE11/NBS1 subnuclear assembly requires the Fanconi anemia C protein. *Hum Mol Genet* 2002;11:2531–46. <https://doi.org/10.1093/hmg/11.21.2531>.
- [69] Pichierri P, Franchitto A, Rosselli F. BLM and the FANCD2 proteins collaborate in a common pathway in response to stalled replication forks. *EMBO J* 2004;23:3154–63. <https://doi.org/10.1038/sj.emboj.7600277>.
- [70] Rossi F, Helbling-Leclerc Anne, Kawasumi R, Jegadesan NK, Xu X, Devulder P, et al. SMCS/6 acts jointly with Fanconi anemia factors to support DNA repair and genome stability. *EMBO Rep* 2020;21:e48222. <https://doi.org/10.15252/embr.201948222>.
- [71] Bogliolo M, Lyakhovich A, Callén E, Castellà M, Cappelli E, Ramírez MJ, et al. Histone H2AX and Fanconi anemia FANCD2 function in the same pathway to maintain chromosome stability. *EMBO J* 2007;26:1340–51. <https://doi.org/10.1038/sj.emboj.7601574>.
- [72] Kim H-M, Beese-Sims SE, Colaiácovo MP. Fanconi Anemia FANCM/FNCL-1 and FANCD2/FCM-2 Are Required for Maintaining Histone Methylation Levels and Interact with the Histone Demethylase LSD1/SPR-5 in *Caenorhabditis elegans*. *Genetics* 2018;209:409–23. <https://doi.org/10.1534/genetics.118.300823>.
- [73] Hejna J, Holtorf M, Hines J, Mathewson L, Hemphill A, Al-Dhalimy M, et al. Tip60 is required for DNA interstrand cross-link repair in the Fanconi anemia pathway. *J Biol Chem* 2008;283:9844–51. <https://doi.org/10.1074/jbc.M709076200>.
- [74] Renaud E, Barascu A, Rosselli F. Impaired TIP60-mediated H4K16 acetylation accounts for the aberrant chromatin accumulation of 53BP1 and RAP80 in Fanconi anemia pathway-deficient cells. *Nucleic Acids Res* 2016;44:648–56. <https://doi.org/10.1093/nar/gkv1019>.
- [75] Couvé S, Macé-Aimé G, Rosselli F, Saparbaev MK. The human oxidative DNA glycosylase NEIL1 excises psoralen-induced interstrand DNA cross-links in a three-stranded DNA structure. *J Biol Chem* 2009;284:11963–70. <https://doi.org/10.1074/jbc.M900746200>.
- [76] Couvé-Privat S, Macé G, Rosselli F, Saparbaev MK. Psoralen-induced DNA adducts are substrates for the base excision repair pathway in human cells. *Nucleic Acids Res* 2007;35:5672–82. <https://doi.org/10.1093/nar/gkm592>.
- [77] Peng M, Litman R, Xie J, Sharma S, Brosh RM, Cantor SB. The FANCD2/MutLalpha interaction is required for correction of the cross-link response in FA-J cells. *EMBO J* 2007;26:3238–49. <https://doi.org/10.1038/sj.emboj.7601754>.
- [78] Peng M, Xie J, Ucher A, Stavnezer J, Cantor SB. Crosstalk between BRCA-Fanconi anemia and mismatch repair pathways prevents MSH2-dependent aberrant DNA damage responses. *EMBO J* 2014;33:1698–712. <https://doi.org/10.15252/emboj.201387530>.
- [79] Moldovan G-L, D'Andrea AD. How the fanconi anemia pathway guards the genome. *Annu Rev Genet* 2009;43:223–49. <https://doi.org/10.1146/annurev-genet-102108-134222>.
- [80] Howlett NG, Taniguchi T, Durkin SG, D'Andrea AD, Glover TW. The Fanconi anemia pathway is required for the DNA replication stress response and for the regulation of common fragile site stability. *Hum Mol Genet* 2005;14:693–701. <https://doi.org/10.1093/hmg/ddi065>.
- [81] Naim V, Rosselli F. The FANCD2 pathway and BLM collaborate during mitosis to prevent micro-nucleation and chromosome abnormalities. *Nat Cell Biol* 2009;11:761–8. <https://doi.org/10.1038/ncb1883>.

- [82] Naim V, Wilhelm T, Debatisse M, Rosselli F. ERCC1 and MUS81-EME1 promote sister chromatid separation by processing late replication intermediates at common fragile sites during mitosis. *Nat Cell Biol* 2013;15:1008–15. <https://doi.org/10.1038/ncb2793>.
- [83] García-Rubio ML, Pérez-Calero C, Barroso SI, Tumini E, Herrera-Moyano E, Rosado IV, et al. The Fanconi anemia pathway protects genome integrity from R-loops. *PLoS Genet* 2015;11:e1005674. <https://doi.org/10.1371/journal.pgen.1005674>.
- [84] Schwab RA, Nieminszczy J, Shah F, Langton J, Lopez Martinez D, Liang C-C, et al. The fanconi anemia pathway maintains genome stability by coordinating replication and transcription. *Mol Cell* 2015;60:351–61. <https://doi.org/10.1016/j.molcel.2015.09.012>.
- [85] Hanson H, Mathew CG, Docherty Z, Mackie Ogilvie C. Telomere shortening in Fanconi anaemia demonstrated by a direct FISH approach. *Cytogenet Cell Genet* 2001;93:203–6. <https://doi.org/10.1159/000056985>.
- [86] Leteurtre F, Li X, Guardiola P, Le Roux G, Sergère JC, Richard P, et al. Accelerated telomere shortening and telomerase activation in Fanconi's anaemia. *Br J Haematol* 1999;105:883–93. <https://doi.org/10.1046/j.1365-2141.1999.01445.x>.
- [87] Abdul-Sater Z, Cerabona D, Potchanant ES, Sun Z, Enzor R, He Y, et al. FANCA safeguards interphase and mitosis during hematopoiesis in vivo. *Exp Hematol* 2015;43:1031–46. e12. <https://doi.org/10.1016/j.exphem.2015.08.013>.
- [88] Naim V, Rosselli F. The FANC pathway and mitosis: a replication legacy. *Cell Cycle* 2009;8:2907–11. <https://doi.org/10.4161/cc.8.18.9538>.
- [89] Nalepa G, Enzor R, Sun Z, Marchal C, Park S-J, Yang Y, et al. Fanconi anemia signaling network regulates the spindle assembly checkpoint. *J Clin Invest* 2013;123:3839–47. <https://doi.org/10.1172/JCI67364>.
- [90] Strathdee CA, Gavish H, Shannon WR, Buchwald M. Cloning of cDNAs for Fanconi's anaemia by functional complementation. *Nature* 1992;356:763–7. <https://doi.org/10.1038/356763a0>.
- [91] Ceccaldi R, Sarangi P, D'Andrea AD. The Fanconi anaemia pathway: new players and new functions. *Nat Rev Mol Cell Biol* 2016;17:337–49. <https://doi.org/10.1038/nrm.2016.48>.
- [92] Mirchandani KD, D'Andrea AD. The Fanconi anemia/BRCA pathway: a coordinator of cross-link repair. *Exp Cell Res* 2006;312:2647–53. <https://doi.org/10.1016/j.yexcr.2006.06.014>.
- [93] Flach J, Bakker ST, Mohrin M, Conroy PC, Pietras EM, Reynaud D, et al. Replication stress is a potent driver of functional decline in ageing haematopoietic stem cells. *Nature* 2014;512:198–202. <https://doi.org/10.1038/nature13619>.
- [94] Mohrin M, Bourke E, Alexander D, Warr MR, Barry-Holson K, Le Beau MM, et al. Hematopoietic stem cell quiescence promotes error-prone DNA repair and mutagenesis. *Cell Stem Cell* 2010;7:174–85. <https://doi.org/10.1016/j.stem.2010.06.014>.
- [95] Ceccaldi R, Parmar K, Mouly E, Delord M, Kim JM, Regairaz M, et al. Bone marrow failure in Fanconi anemia is triggered by an exacerbated p53/p21 DNA damage response that impairs hematopoietic stem and progenitor cells. *Cell Stem Cell* 2012;11:36–49. <https://doi.org/10.1016/j.stem.2012.05.013>.
- [96] Hodkinson MR, Bolner A, Sato K, Kamimae-Lanning AN, Rooijers K, Witte M, et al. Alcohol-derived DNA crosslinks are repaired by two distinct mechanisms. *Nature* 2020;579:603–8. <https://doi.org/10.1038/s41586-020-2059-5>.
- [97] Langevin F, Crossan GP, Rosado IV, Arends MJ, Patel KJ. Fancd2 counteracts the toxic effects of naturally produced aldehydes in mice. *Nature* 2011;475:53–8. <https://doi.org/10.1038/nature10192>.
- [98] Shen X, Wang R, Kim MJ, Hu Q, Hsu C-C, Yao J, et al. A surge of DNA damage links transcriptional reprogramming and hematopoietic deficit in fanconi anemia. *Mol Cell* 2020;80:1013–24. e6. <https://doi.org/10.1016/j.molcel.2020.11.040>.
- [99] Walter D, Lier A, Geiselhart A, Thalheimer FB, Huntscha S, Sobotta MC, et al. Exit from dormancy provokes DNA-damage-induced attrition in haematopoietic stem cells. *Nature* 2015;520:549–52. <https://doi.org/10.1038/nature14131>.
- [100] Oppezzo A, Bourseguin J, Renaud E, Pawlikowska P, Rosselli F. Microphthalmia transcription factor expression contributes to bone marrow failure in Fanconi anemia. *J Clin Invest* 2020;130:1377–91. <https://doi.org/10.1172/JCI131540>.
- [101] Haneline LS, Gobbett TA, Ramani R, Carreau M, Buchwald M, Yoder MC, et al. Loss of FancC function results in decreased hematopoietic stem cell repopulating ability. *Blood* 1999;94:1–8.
- [102] Li X, Plett PA, Yang Y, Hong P, Freie B, Srour EF, et al. Fanconi anemia type C-deficient hematopoietic stem/progenitor cells exhibit aberrant cell cycle control. *Blood* 2003;102:2081–4. <https://doi.org/10.1182/blood-2003-02-0536>.
- [103] Barroca V, Mouthon MA, Lewandowski D, Brunet de la Grange P, Gauthier LR, Pflumio F, et al. Impaired functionality and homing of Fancg-deficient hematopoietic stem cells. *Hum Mol Genet* 2012;21:121–35. <https://doi.org/10.1093/hmg/ddr447>.
- [104] Zhang Q-S, Marquez-Loza L, Eaton L, Duncan AW, Goldman DC, Anur P, et al. Fancd2^{-/-} mice have hematopoietic defects that can be partially corrected by resveratrol. *Blood* 2010;116:5140–8. <https://doi.org/10.1182/blood-2010-04-278226>.
- [105] Ciccia A, Ling C, Coulthard R, Yan Z, Xue Y, Meetei AR, et al. Identification of FAAP24, a Fanconi anemia core complex protein that interacts with FANCM. *Mol Cell* 2007;25:331–43. <https://doi.org/10.1016/j.molcel.2007.01.003>.
- [106] Fox D, Yan Z, Ling C, Zhao Y, Lee D-Y, Fukagawa T, et al. The histone-fold complex MHF is remodeled by FANCM to recognize branched DNA and protect genome stability. *Cell Res* 2014;24:560–75. <https://doi.org/10.1038/cr.2014.42>.
- [107] Huang M, Kim JM, Shiotani B, Yang K, Zou L, D'Andrea AD. The FANCM/FAAP24 complex is required for the DNA interstrand crosslink-induced checkpoint response. *Mol Cell* 2010;39:259–68. <https://doi.org/10.1016/j.molcel.2010.07.005>.
- [108] Yan Z, Delannoy M, Ling C, Daee D, Osman F, Muniandy PA, et al. A histone-fold complex and FANCM form a conserved DNA-remodeling complex to maintain genome stability. *Mol Cell* 2010;37:865–78. <https://doi.org/10.1016/j.molcel.2010.01.039>.
- [109] Fouquet B, Pawlikowska P, Caburet S, Guigon C, Mäkinen M, Tanner L, et al. A homozygous FANCM mutation underlies a familial case of non-syndromic primary ovarian insufficiency. *Elife* 2017;6. <https://doi.org/10.7554/eLife.30490>.
- [110] Collis SJ, Ciccia A, Deans AJ, Horejsi Z, Martin JS, Maslen SL, et al. FANCM and FAAP24 function in ATR-mediated checkpoint signaling independently of the Fanconi anemia core complex. *Mol Cell* 2008;32:313–24. <https://doi.org/10.1016/j.molcel.2008.10.014>.
- [111] Schwab RA, Blackford AN, Niedzwiedz W. ATR activation and replication fork restart are defective in FANCM-deficient cells. *EMBO J* 2010;29:806–18. <https://doi.org/10.1038/emboj.2009.385>.
- [112] Singh TR, Ali AM, Paramasivam M, Pradhan A, Wahengbam K, Seidman MM, et al. ATR-dependent phosphorylation of FANCM at serine 1045 is essential for FANCM functions. *Cancer Res* 2013;73:4300–10. <https://doi.org/10.1158/0008-5472.CAN-12-3976>.
- [113] Luo Y, Hartford SA, Zeng R, Southard TL, Shima N, Schimenti JC. Hypersensitivity of primordial germ cells to compromised replication-associated DNA repair involves ATM-p53-p21 signaling. *PLoS Genet* 2014;10:e1004471. <https://doi.org/10.1371/journal.pgen.1004471>.
- [114] Lorenz A, Osman F, Sun W, Nandi S, Steinacher R, Whitby MC. The fission yeast FANCM ortholog directs non-crossover recombination during meiosis. *Science* 2012;336:1585–8. <https://doi.org/10.1126/science.1220111>.
- [115] Crismani W, Girard C, Froger N, Pradillo M, Santos JL, Chelysheva L, et al. FANCM limits meiotic crossovers. *Science* 2012;336:1588–90. <https://doi.org/10.1126/science.1220381>.
- [116] Catucci I, Osorio A, Arver B, Neidhardt G, Bogliolo M, Zanardi F, et al. Individuals with FANCM biallelic mutations do not develop Fanconi anemia, but show risk for breast cancer, chemotherapy toxicity and may display chromosome fragility. *Genet Med* 2018;20:452–7. <https://doi.org/10.1038/gim.2017.123>.
- [117] Bogliolo M, Bluteau D, Lespinasse J, Pujol R, Vasquez N, d'Enghien CD, et al. Biallelic truncating FANCM mutations cause early-onset cancer but not Fanconi anemia. *Genet Med* 2018;20:458–63. <https://doi.org/10.1038/gim.2017.124>.
- [118] Kiiski JI, Fagerholm R, Tervasmäki A, Pelttari LM, Khan S, Jamshidi M, et al. FANCM c.5101C>T mutation associates with breast cancer survival and treatment outcome. *Int J Cancer* 2016;139:2760–70. <https://doi.org/10.1002/ijc.30394>.
- [119] Kiiski JI, Pelttari LM, Khan S, Freysteinsdottir ES, Reynisdottir I, Hart SN, et al. Exome sequencing identifies FANCM as a susceptibility gene for triple-negative breast cancer. *Proc Natl Acad Sci U S A* 2014;111:15172–7. <https://doi.org/10.1073/pnas.1407909111>.
- [120] Neidhardt G, Hauke J, Ramser J, Groß E, Gehrig A, Müller CR, et al. Association between loss-of-function mutations within the FANCM gene and early-onset familial breast cancer. *JAMA Oncol* 2017;3:1245–8. <https://doi.org/10.1001/jamaoncol.2016.5592>.
- [121] Adachi D, Oda T, Yagasaki H, Nakasato K, Taniguchi T, D'Andrea AD, et al. Heterogeneous activation of the Fanconi anemia pathway by patient-derived FANCM mutants. *Hum Mol Genet* 2002;11:3125–34. <https://doi.org/10.1093/hmg/11.25.3125>.
- [122] Karras GI, Yi S, Sahni N, Fischer M, Xie J, Vidal M, et al. HSP90 shapes the consequences of human genetic variation. *Cell* 2017;168:856–66. e12. <https://doi.org/10.1016/j.cell.2017.01.023>.
- [123] Kampen KR, Sulima SO, Verecke S, De Keersmaecker K. Hallmarks of ribosomopathies. *Nucleic Acids Res* 2020;48:1013–28. <https://doi.org/10.1093/nar/gkz637>.
- [124] Da Costa L, Leblanc T, Mohandas N. Diamond-Blackfan anemia. *Blood* 2020;136:1262–73. <https://doi.org/10.1182/blood.2019000947>.
- [125] Doherty L, Sheen MR, Vlachos A, Choesmel V, O'Donohue M-F, Clinton C, et al. Ribosomal protein genes RPS10 and RPS26 are commonly mutated in Diamond-Blackfan anemia. *Am J Hum Genet* 2010;86:222–8. <https://doi.org/10.1016/j.ajhg.2009.12.015>.
- [126] Ling T, Crispino JD. GATA1 mutations in red cell disorders. *IUBMB Life* 2020;72:106–18. <https://doi.org/10.1002/iub.2177>.
- [127] Gripp KW, Curry C, Olney AH, Sandoval C, Fisher J, Chong JX-L, et al. Diamond-Blackfan anemia with mandibulofacial dysostosis is heterogeneous, including the novel DBA genes TSR2 and RPS28. *Am J Med Genet A* 2014;164A:2240–9. <https://doi.org/10.1002/ajmg.a.36633>.
- [128] Cui D, Li L, Lou H, Sun H, Ngai S-M, Shao G, et al. The ribosomal protein S26 regulates p53 activity in response to DNA damage. *Oncogene* 2014;33:2225–35. <https://doi.org/10.1038/ncr.2013.170>.
- [129] Danilova N, Bibikova E, Covey TM, Nathanson D, Dimitrova E, Konto Y, et al. The role of the DNA damage response in zebrafish and cellular models of Diamond Blackfan anemia. *Dis Model Mech* 2014;7:895–905. <https://doi.org/10.1242/dmm.015495>.
- [130] Kapralova K, Jahoda O, Koralkova P, Gursky J, Lanikova L, Pospisilova D, et al. Oxidative DNA damage, inflammatory signature, and altered erythrocyte properties in diamond-blackfan anemia. *Int J Mol Sci* 2020;21. <https://doi.org/10.3390/ijms21249652>.
- [131] D'Allard DL, Liu JM. Toward RNA repair of diamond blackfan anemia hematopoietic stem cells. *Hum Gene Ther* 2016;27:792–801. <https://doi.org/10.1089/hum.2016.081>.

- [132] Park YJ, Kim SH, Kim TS, Lee SM, Cho BS, Seo CI, et al. Ribosomal protein S3 associates with the TFIIF complex and positively regulates nucleotide excision repair. *Cell Mol Life Sci* 2021;78:3591–606. <https://doi.org/10.1007/s00018-020-03754-x>.
- [133] Sun S, He H, Ma Y, Xu J, Chen G, Sun Y, et al. Inactivation of ribosomal protein S27-like impairs DNA interstrand cross-link repair by destabilization of FANCD2 and FANCI. *Cell Death Dis* 2020;11:852. <https://doi.org/10.1038/s41419-020-03082-9>.
- [134] Park YJ, Kim T-S, Kim E-H, Kim HD, Kim J. Ribosomal protein S3 is a novel negative regulator of non-homologous end joining repair of DNA double-strand breaks. *FASEB J* 2020;34:8102–13. <https://doi.org/10.1096/fj.201903245R>.
- [135] Yang C, Zang W, Ji Y, Li T, Yang Y, Zheng X. Ribosomal protein L6 (RPL6) is recruited to DNA damage sites in a poly(ADP-ribose) polymerase-dependent manner and regulates the DNA damage response. *J Biol Chem* 2019;294:2827–5664. <https://doi.org/10.1074/jbc.RA118.007009>.
- [136] Grosheva AS, Zharkov DO, Stahl J, Gopanenkov AV, Tupin AE, Kabilov MR, et al. Recognition but no repair of abasic site in single-stranded DNA by human ribosomal uS3 protein residing within intact 40S subunit. *Nucleic Acids Res* 2017;45:3833–43. <https://doi.org/10.1093/nar/gkx052>.
- [137] Patil AV, Hsieh T-S. Ribosomal protein S3 negatively regulates unwinding activity of RecQ-like Helicase 4 through their physical interaction*. *J Biol Chem* 2017;292:4313–25. <https://doi.org/10.1074/jbc.M116.764324>.
- [138] Lu H, Zhu Y, Xiong J, Wang R, Jia Z. Potential extra-ribosomal functions of ribosomal proteins in *Saccharomyces cerevisiae*. *Microbiol Res* 2015;177:28–33. <https://doi.org/10.1016/j.micres.2015.05.004>.
- [139] Kim Y, Kim HD, Kim J. Cytoplasmic ribosomal protein S3 (rpS3) plays a pivotal role in mitochondrial DNA damage surveillance. *Biochim Biophys Acta (BBA) – Mol Cell Res* 2013;1833:2943–52. <https://doi.org/10.1016/j.bbamer.2013.07.015>.
- [140] Ko SI, Park J-H, Park MJ, Kim J, Kang L-W, Han YS. Human ribosomal protein S3 (hRPS3) interacts with uracil-DNA glycosylase (hUNG) and stimulates its glycosylase activity. *Mutat Res Fundam Mol Mech Mutagen* 2008;648:54–64. <https://doi.org/10.1016/j.mrfmmm.2008.09.013>.
- [141] Ball HL, Zhang B, Riches JJ, Gandhi R, Li J, Rommens JM, et al. Shwachman-Bodian Diamond syndrome is a multi-functional protein implicated in cellular stress responses. *Hum Mol Genet* 2009;18:3684–95. <https://doi.org/10.1093/hmg/ddp316>.
- [142] Maserati E, Pressato B, Valli R, Minelli A, Sainati L, Patitucci F, et al. The route to development of myelodysplastic syndrome/acute myeloid leukaemia in Shwachman-Diamond syndrome: the role of ageing, karyotype instability, and acquired chromosome anomalies. *Br J Haematol* 2009;145:190–7. <https://doi.org/10.1111/j.1365-2141.2009.07611.x>.
- [143] Morini J, Babini G, Mariotti L, Baiocco G, Nacci L, Maccario C, et al. Radiosensitivity in lymphoblastoid cell lines derived from Shwachman-Diamond syndrome patients. *Radiat Prot Dosimetry* 2015;166:95–100. <https://doi.org/10.1093/rpd/ncv152>.
- [144] Alter BP, Giri N, Savage SA, Rosenberg PS. Telomere length in inherited bone marrow failure syndromes. *Haematologica* 2015;100:49–54. <https://doi.org/10.3324/haematol.2014.114389>.
- [145] Glousker G, Touzot F, Revy P, Tzfati Y, Savage SA. Unraveling the pathogenesis of Hoyerall-Hreidarsson syndrome, a complex telomere biology disorder. *Br J Haematol* 2015;170:457–71. <https://doi.org/10.1111/bjh.13442>.
- [146] Holohan B, Wright WE, Shay JW. Cell biology of disease: telomeropathies: an emerging spectrum disorder. *J Cell Biol* 2014;205:289–99. <https://doi.org/10.1083/jcb.201401012>.
- [147] Savage SA. Human telomeres and telomere biology disorders. *Prog Mol Biol Transl Sci* 2014;125:41–66. <https://doi.org/10.1016/B978-0-12-397898-1.00002-5>.
- [148] Gueiderikh A, Rouvet G, Souquière-Besse S, Apcher S, Diaz J-J, Rosselli F. Fanconi anemia proteins are required to maintain nucleolar homeostasis. *BioRxiv* 2019; 509950. <https://doi.org/10.1101/509950>.
- [149] Gueiderikh A, Maczkowiak-Charotais F, Rouvet G, Souquière-Besse S, Apcher S, Diaz J-J, et al. Fanconi anemia A protein participates in nucleolar homeostasis maintenance and ribosome biogenesis. *Sci Adv* 2021;7. <https://doi.org/10.1126/sciadv.abb5414>.
- [150] Sondalle SB, Longrich S, Ogawa LM, Sung P, Baserga SJ. Fanconi anemia protein FANCI functions in ribosome biogenesis. *Proc Natl Acad Sci U S A* 2019;116:2561–70. <https://doi.org/10.1073/pnas.1811557116>.
- [151] Du W, Li J, Sipple J, Chen J, Pang Q. Cytoplasmic FANCA-FANCC complex interacts and stabilizes the cytoplasm-dislocalized leukemic nucleophosmin protein (NPMc). *J Biol Chem* 2010;285:37436–44. <https://doi.org/10.1074/jbc.M110.113209>.
- [152] Zarka J, Short NJ, Kanagal-Shamanna R, Issa GC. Nucleophosmin 1 mutations in acute myeloid leukemia. *Genes (Basel)* 2020;11:E649. <https://doi.org/10.3390/genes11060649>.
- [153] Falini B, Brunetti L, Sportoletti P, Martelli MP. NPM1-mutated acute myeloid leukemia: from bench to bedside. *Blood* 2020;136:1707–21. <https://doi.org/10.1182/blood.201904226>.
- [154] Renaudin X, Rosselli F. Tipping the scale: MYC gains weight in fanconi anemia bone marrow failure progression. *Cell Stem Cell* 2021;28:8–9. <https://doi.org/10.1016/j.stem.2020.12.013>.
- [155] Rodríguez A, Zhang K, Färkkilä A, Filiatrault J, Yang C, Velázquez M, et al. MYC promotes bone marrow stem cell dysfunction in fanconi anemia. *Cell Stem Cell* 2021;28:33–47. e8, <https://doi.org/10.1016/j.stem.2020.09.004>.
- [156] van Riggelen J, Yetil A, Felsher DW. MYC as a regulator of ribosome biogenesis and protein synthesis. *Nat Rev Cancer* 2010;10:301–9. <https://doi.org/10.1038/nrc2819>.
- [157] Hou H, Li D, Gao J, Gao L, Lu Q, Hu Y, et al. Proteomic profiling and bioinformatics analysis identify key regulators during the process from fanconi anemia to acute myeloid leukemia. *Am J Transl Res* 2020;12:1415–27.
- [158] Marion W, Boettcher S, Ruiz-Torres S, Lummertz da Rocha E, Lundin V, Morris V, et al. An induced pluripotent stem cell model of Fanconi anemia reveals mechanisms of p53-driven progenitor cell differentiation. *Blood Adv* 2020;4:4679–92. <https://doi.org/10.1182/bloodadvances.2020001593>.
- [159] Johnston R, D'Costa Z, Ray S, Gorski J, Harkin DP, Mullan P, et al. The identification of a novel role for BRCA1 in regulating RNA polymerase I transcription. *Oncotarget* 2016;7:68097–110. <https://doi.org/10.18632/oncotarget.11770>.
- [160] Boussaid I, Le Goff S, Floquet C, Gautier E-F, Raimbault A, Vially P-J, et al. Integrated analyses of transcriptome and proteome identify the roles of translation selectivity in RPS14-deficient cells. *Haematologica* 2021;106:746–58. <https://doi.org/10.3324/haematol.2019.239970>.
- [161] Le Goff S, Boussaid I, Floquet C, Raimbault A, Hatin I, Andrieu-Soler C, et al. p53 activation during ribosome biogenesis regulates normal erythroid differentiation. *Blood* 2021;137:89–102. <https://doi.org/10.1182/blood.2019003439>.
- [162] Lefevre C, Bondu S, Le Goff S, Kosmider O, Fontenay M. Dyserythropoiesis of myelodysplastic syndromes. *Curr Opin Hematol* 2017;24:191–7. <https://doi.org/10.1097/MOH.0000000000000325>.
- [163] Schütz S, Michel E, Damberger FF, Oplová M, Peña C, Leitner A, et al. Molecular basis for disassembly of an importin:ribosomal protein complex by the escortin Tsr2. *Nat Commun* 2018;9:3669. <https://doi.org/10.1038/s41467-018-06160-x>.
- [164] He H, Zhu D, Sun J, Pei R, Jia S. The novel protein TSR2 inhibits the transcriptional activity of nuclear factor-kappaB and induces apoptosis. *Mol Biol (Mosk)* 2011;45:496–502.
- [165] Gutiérrez L, Caballero N, Fernández-Calleja L, Karkoulia E, Strouboulis J. Regulation of GATA1 levels in erythropoiesis. *IUBMB Life* 2020;72:89–105. <https://doi.org/10.1002/iub.2192>.
- [166] Khajuria RK, Munschauer M, Ullrich JC, Fiorini C, Ludwig LS, McFarland SK, et al. Ribosome levels selectively regulate translation and lineage commitment in human hematopoiesis. *Cell* 2018;173:90–103. e19, <https://doi.org/10.1016/j.cell.2018.02.036>.
- [167] Ludwig LS, Gazda HT, Eng JC, Eichhorn SW, Thiru P, Ghazvinian R, et al. Altered translation of GATA1 in Diamond-Blackfan anemia. *Nat Med* 2014;20:748–53. <https://doi.org/10.1038/nm.3557>.
- [168] Sankaran VG, Ghazvinian R, Do R, Thiru P, Vergilio J-A, Beggs AH, et al. Exome sequencing identifies GATA1 mutations resulting in Diamond-Blackfan anemia. *J Clin Invest* 2012;122:2439–43. <https://doi.org/10.1172/JCI63597>.
- [169] Tummala H, Walne AJ, Williams M, Bockett N, Collopy L, Cardoso S, et al. DNAJC21 mutations link a cancer-prone bone marrow failure syndrome to corruption in 60S ribosome subunit maturation. *Am J Hum Genet* 2016;99:115–24. <https://doi.org/10.1016/j.ajhg.2016.05.002>.
- [170] Weis F, Giudice E, Churcher M, Jin L, Hilcenko C, Wong CC, et al. Mechanism of eIF6 release from the nascent 60S ribosomal subunit. *Nat Struct Mol Biol* 2015;22:914–9. <https://doi.org/10.1038/nsmb.3112>.
- [171] Wild K, Halic M, Sinning I, Beckmann R. SRP meets the ribosome. *Nat Struct Mol Biol* 2004;11:1049–53. <https://doi.org/10.1038/nsmb853>.
- [172] Halic M, Blau M, Becker T, Mielke T, Pool MR, Wild K, et al. Following the signal sequence from ribosomal tunnel exit to signal recognition particle. *Nature* 2006;444:507–11. <https://doi.org/10.1038/nature05326>.
- [173] Benyelles M, Episkopou H, O'Donohue M-F, Kermasson L, Frange P, Poulain F, et al. Impaired telomere integrity and rRNA biogenesis in PARN-deficient patients and knock-out models. *EMBO Mol Med* 2019;11:e10201. <https://doi.org/10.15252/emmm.201810201>.
- [174] Ibáñez-Cabellós JS, Seco-Cervera M, Picher-Latorre C, Pérez-Machado G, García-Giménez JL, Pallardó FV. Acute depletion of telomerase components DKC1 and NOP10 induces oxidative stress and disrupts ribosomal biogenesis via NPM1 and activation of the P53 pathway. *Biochim Biophys Acta Mol Cell Res* 1867;2020:118845. <https://doi.org/10.1016/j.bbamer.2020.118845>.
- [175] Penzo M, Rocchi L, Brugiere S, Carnicelli D, Onofrillo C, Couté Y, et al. Human ribosomes from cells with reduced dyskerin levels are intrinsically altered in translation. *FASEB J* 2015;29:3472–82. <https://doi.org/10.1096/fj.15-270991>.
- [176] Rinker EB, Dueber JC, Qualtieri J, Tedesco J, Erdogan B, Bosompem A, et al. Differential expression of ribosomal proteins in myelodysplastic syndromes. *J Clin Pathol* 2016;69:176–80. <https://doi.org/10.1136/jclinpath-2015-203093>.
- [177] Nguyen THD, Tam J, Wu RA, Greber BJ, Toso D, Nogales E, et al. Cryo-EM structure of substrate-bound human telomerase holoenzyme. *Nature* 2018;557:190–5. <https://doi.org/10.1038/s41586-018-0062-x>.
- [178] Essers MAG, Offner S, Blanco-Bose WE, Waibler Z, Kalinke U, Duchosal MA, et al. IFN α activates dormant haematopoietic stem cells in vivo. *Nature* 2009;458:904–8. <https://doi.org/10.1038/nature07815>.
- [179] Pietras EM. Inflammation: a key regulator of hematopoietic stem cell fate in health and disease. *Blood* 2017;130:1693–8. <https://doi.org/10.1182/blood-2017-06-780882>.
- [180] Joenje H, Arwert F, Eriksson AW, de Koning H, Oostra AB. Oxygen-dependence of chromosomal aberrations in Fanconi's anaemia. *Nature* 1981;290:142–3. <https://doi.org/10.1038/290142a0>.
- [181] Joenje H, Oostra AB. Effect of oxygen tension on chromosomal aberrations in Fanconi anaemia. *Hum Genet* 1983;65:99–101. <https://doi.org/10.1007/BF00286642>.

- [182] Schindler D, Hoehn H. Fanconi anemia mutation causes cellular susceptibility to ambient oxygen. *Am J Hum Genet* 1988;43:429–35.
- [183] Joenje H, Youssoufian H, Kruyt FA, dos Santos CC, Wevrick R, Buchwald M. Expression of the Fanconi anemia gene FAC in human cell lines: lack of effect of oxygen tension. *Blood Cells Mol Dis* 1995;21:182–91. <https://doi.org/10.1006/bcmd.1995.0021>.
- [184] Saito H, Hammond AT, Moses RE. Hypersensitivity to oxygen is a uniform and secondary defect in Fanconi anemia cells. *Mutat Res* 1993;294:255–62. [https://doi.org/10.1016/0921-8777\(93\)90008-5](https://doi.org/10.1016/0921-8777(93)90008-5).
- [185] Pagano G, Youssoufian H. Fanconi anaemia proteins: major roles in cell protection against oxidative damage. *Bioessays* 2003;25:589–95. <https://doi.org/10.1002/bies.10283>.
- [186] Pagano G, Tiano L, Pallardó FV, Lyakhovich A, Mukhopadhyay SS, Di Bartolomeo P, et al. Re-definition and supporting evidence toward Fanconi Anemia as a mitochondrial disease: Prospects for new design in clinical management. *Redox Biol* 2021;40:101860. <https://doi.org/10.1016/j.redox.2021.101860>.
- [187] Ruppitsch W, Meisslitz C, Weirich-Schwaiger H, Klocker H, Scheidereit C, Schweiger M, et al. The role of oxygen metabolism for the pathological phenotype of Fanconi anemia. *Hum Genet* 1997;99:710–9. <https://doi.org/10.1007/s004390050437>.
- [188] Kumari U, Ya Jun W, Huat Bay B, Lyakhovich A. Evidence of mitochondrial dysfunction and impaired ROS detoxifying machinery in Fanconi anemia cells. *Oncogene* 2014;33:165–72. <https://doi.org/10.1038/ncr.2012.583>.
- [189] Kruiy FA, Hoshino T, Liu JM, Joseph P, Jaiswal AK, Youssoufian H. Abnormal microsomal detoxification implicated in Fanconi anemia group C by interaction of the FAC protein with NADPH cytochrome P450 reductase. *Blood* 1998;92:3050–6.
- [190] Putaki M, Igarashi T, Watanabe S, Kajigaya S, Tatsuguchi A, Wang J, et al. The FANCG Fanconi anemia protein interacts with CYP2E1: possible role in protection against oxidative DNA damage. *Carcinogenesis* 2002;23:67–72. <https://doi.org/10.1093/carcin/23.1.67>.
- [191] Cumming RC, Lightfoot J, Beard K, Youssoufian H, O'Brien PJ, Buchwald M. Fanconi anemia group C protein prevents apoptosis in hematopoietic cells through redox regulation of GSTP1. *Nat Med* 2001;7:814–20. <https://doi.org/10.1038/89937>.
- [192] Mukhopadhyay SS, Leung KS, Hicks MJ, Hastings PJ, Youssoufian H, Plon SE. Defective mitochondrial peroxiredoxin-3 results in sensitivity to oxidative stress in Fanconi anemia. *J Cell Biol* 2006;175:225–35. <https://doi.org/10.1083/jcb.200607061>.
- [193] Sumpter R, Sirasanagandla S, Fernández ÁF, Wei Y, Dong X, Franco L, et al. Fanconi anemia proteins function in mitophagy and immunity. *Cell* 2016;165:867–81. <https://doi.org/10.1016/j.cell.2016.04.006>.
- [194] Briot D, Macé-Aimé G, Subra F, Rosselli F. Aberrant activation of stress-response pathways leads to TNF-alpha oversecretion in Fanconi anemia. *Blood* 2008;111:1913–23. <https://doi.org/10.1182/blood-2007-07-099218>.
- [195] Dufour C, Corcione A, Svahn J, Haupt R, Poggi V, Béka'ssy AN, et al. TNF-alpha and IFN-gamma are overexpressed in the bone marrow of Fanconi anemia patients and TNF-alpha suppresses erythropoiesis in vitro. *Blood* 2003;102:2053–9. <https://doi.org/10.1182/blood-2003-01-0114>.
- [196] Ibáñez A, Río P, Casado JA, Bueren JA, Fernández-Luna JL, Pipaón C. Elevated levels of IL-1beta in Fanconi anemia group A patients due to a constitutively active phosphoinositide 3-kinase-Akt pathway are capable of promoting tumour cell proliferation. *Biochem J* 2009;422:161–70. <https://doi.org/10.1042/BJ20082118>.
- [197] Rosselli F, Sanceau J, Gluckman E, Wietzerbin J, Moustacchi E. Abnormal lymphokine production: a novel feature of the genetic disease Fanconi anemia. II. In vitro and in vivo spontaneous overproduction of tumor necrosis factor alpha. *Blood* 1994;83:1216–25.
- [198] Zanier R, Briot D, Dugas du Villard J-A, Sarasin A, Rosselli F. Fanconi anemia C gene product regulates expression of genes involved in differentiation and inflammation. *Oncogene* 2004;23:5004–13. <https://doi.org/10.1038/sj.onc.1207677>.
- [199] Liebetrau W, Rünger TM, Mehling BE, Poot M, Hoehn H. Mutagenic activity of ambient oxygen and mitomycin C in Fanconi's anaemia cells. *Mutagenesis* 1997;12:69–77. <https://doi.org/10.1093/mutage/12.2.69>.
- [200] Heinrich MC, Hoatlin ME, Zigler AJ, Silvey KV, Bakke AC, Keeble WW, et al. DNA cross-linker-induced G2/M arrest in group C Fanconi anemia lymphoblasts reflects normal checkpoint function. *Blood* 1998;91:275–87.
- [201] Pagano G, Talamanca AA, Castello G, Pallardó FV, Zatterale A, Degan P. Oxidative stress in Fanconi anaemia: from cells and molecules towards prospects in clinical management. *Biol Chem* 2012;393:11–21. <https://doi.org/10.1515/BC-2011-227>.
- [202] Zhang Q-S, Eaton L, Snyder ER, Houghtaling S, Mitchell JB, Finegold M, et al. Tempol protects against oxidative damage and delays epithelial tumor onset in Fanconi anemia mice. *Cancer Res* 2008;68:1601–8. <https://doi.org/10.1158/0008-5472.CAN-07-5186>.
- [203] Columbaro M, Ravera S, Capanni C, Panfoli I, Cuccarolo P, Stroppiana G, et al. Treatment of FANCA cells with resveratrol and N-acetylcysteine: a comparative study. *PLoS One* 2014;9:e104857. <https://doi.org/10.1371/journal.pone.0104857>.
- [204] Zhang Q-S, Marquez-Loza L, Sheehan AM, Watanabe-Smith K, Eaton L, Benedetti E, et al. Evaluation of resveratrol and N-acetylcysteine for cancer chemoprevention in a Fanconi anemia murine model. *Pediatr Blood Cancer* 2014;61:740–2. <https://doi.org/10.1002/pbc.24780>.
- [205] Ponte F, Sousa R, Fernandes AP, Gonçalves C, Barbot J, Carvalho F, et al. Improvement of genetic stability in lymphocytes from Fanconi anemia patients through the combined effect of α -lipoic acid and N-acetylcysteine. *Orphanet J Rare Dis* 2012;7:28. <https://doi.org/10.1186/1750-1172-7-28>.
- [206] Calado RT, Clé DV. Treatment of inherited bone marrow failure syndromes beyond transplantation. *Hematology* 2017;2017:96–101. <https://doi.org/10.1182/asheducation-2017.1.96>.
- [207] Garbati MR, Hays LE, Keeble W, Yates JE, Rathbun RK, Bagby GC. FANCA and FANCC modulate TLR and p38 MAPK-dependent expression of IL-1 β in macrophages. *Blood* 2013;122:3197–205. <https://doi.org/10.1182/blood-2013-02-484816>.
- [208] Anur P, Yates J, Garbati MR, Vanderwerf S, Keeble W, Rathbun K, et al. p38 MAPK inhibition suppresses the TLR-hypersensitive phenotype in FANCC- and FANCA-deficient mononuclear phagocytes. *Blood* 2012;119:1992–2002. <https://doi.org/10.1182/blood-2011-06-354647>.
- [209] Li Y, Zhao L, Sun H, Yu J, Li N, Liang J, et al. Gene silencing of FANCF potentiates the sensitivity to mitoxantrone through activation of JNK and p38 signal pathways in breast cancer cells. *PLoS One* 2012;7:e44254. <https://doi.org/10.1371/journal.pone.0044254>.
- [210] Pearl-Yafe M, Halperin D, Scheuerman O, Fabian I. The p38 pathway partially mediates caspase-3 activation induced by reactive oxygen species in Fanconi anemia C cells. *Biochem Pharmacol* 2004;67:539–46. <https://doi.org/10.1016/j.bcp.2003.09.024>.
- [211] Sejas DP, Rani R, Qiu Y, Zhang X, Fagerlie SR, Nakano H, et al. Inflammatory reactive oxygen species-mediated hematopoietic suppression in FANCC-deficient mice. *J Immunol* 2007;178:5277–87. <https://doi.org/10.4049/jimmunol.178.8.5277>.
- [212] Svahn J, Lanza T, Rathbun K, Bagby G, Ravera S, Corsolini F, et al. p38 Mitogen-activated protein kinase inhibition enhances in vitro erythropoiesis of Fanconi anemia, complementation group A-deficient bone marrow cells. *Exp Hematol* 2015;43:295–9. <https://doi.org/10.1016/j.exphem.2014.11.010>.
- [213] Danilova N, Wilkes M, Bibikova E, Youn M-Y, Sakamoto KM, Lin S. Innate immune system activation in zebrafish and cellular models of Diamond Blackfan Anemia. *Sci Rep* 2018;8:5165. <https://doi.org/10.1038/s41598-018-23561-6>.
- [214] Ambekar C, Das B, Yeger H, Dror Y. SBDs-deficiency results in deregulation of reactive oxygen species leading to increased cell death and decreased cell growth. *Pediatr Blood Cancer* 2010;55:1138–44. <https://doi.org/10.1002/pbc.22700>.
- [215] Henson AL, Moore JB, Alard P, Wattenberg MM, Liu JM, Ellis SR. Mitochondrial function is impaired in yeast and human cellular models of Shwachman Diamond syndrome. *Biochem Biophys Res Commun* 2013;437:29–34. <https://doi.org/10.1016/j.bbrc.2013.06.028>.
- [216] Sen S, Wang H, Nghiem CL, Zhou K, Yau J, Taylor CS, et al. The ribosome-related protein, SBDs, is critical for normal erythropoiesis. *Blood* 2011;118:6407–17. <https://doi.org/10.1182/blood-2011-02-335190>.
- [217] Zambetti NA, Ping Z, Chen S, Kensiw KJ, Mylona MA, Sanders MA, et al. Mesenchymal inflammation drives genotoxic stress in hematopoietic stem cells and predicts disease evolution in human pre-leukemia. *Cell Stem Cell* 2016;19:613–27. <https://doi.org/10.1016/j.stem.2016.08.021>.
- [218] Pereboeva L, Hubbard M, Goldman P, Westin ER. Robust DNA damage response and elevated reactive oxygen species in TINF2-mutated dyskeratosis congenita cells. *PLoS One* 2016;11:e0148793. <https://doi.org/10.1371/journal.pone.0148793>.
- [219] Westin ER, Aykin-Burns N, Buckingham EM, Spitz DR, Goldman FD, Klingelutz AJ. The p53/p21(WAF/CIP) pathway mediates oxidative stress and senescence in dyskeratosis congenita cells with telomerase insufficiency. *Antioxid Redox Signal* 2011;14:985–97. <https://doi.org/10.1089/ars.2010.3444>.
- [220] Pereboeva L, Westin E, Patel T, Flaniken I, Lamb L, Klingelutz AJ, et al. DNA damage responses and oxidative stress in dyskeratosis congenita. *PLoS One* 2013;8:e76473. <https://doi.org/10.1371/journal.pone.0076473>.
- [221] Ibáñez-Caballeros JS, Seco-Cervera M, Perez-Machado G, Garcia-Gimenez JL, Pallardó FV. Characterization of the antioxidant systems in different complementation groups of Dyskeratosis Congenita. *Free Radic Biol Med* 2014;75(Suppl. 1):S34. <https://doi.org/10.1016/j.freeradbiomed.2014.10.771>.
- [222] Gu B-W, Fan J-M, Bessler M, Mason PJ. Accelerated hematopoietic stem cell aging in a mouse model of dyskeratosis congenita responds to antioxidant treatment. *Aging Cell* 2011;10:338–48. <https://doi.org/10.1111/j.1474-9726.2011.00674.x>.
- [223] Fischer M. Census and evaluation of p53 target genes. *Oncogene* 2017;36:3943–56. <https://doi.org/10.1038/ncr.2016.502>.
- [224] El-Deiry WS. p21(WAF1) mediates cell-cycle inhibition, relevant to cancer suppression and therapy. *Cancer Res* 2016;76:5189–91. <https://doi.org/10.1158/0008-5472.CAN-16-2055>.
- [225] Lessard F, Brakier-Gingras L, Ferbeyre G. Ribosomal proteins control tumor suppressor pathways in response to nucleolar stress. *Bioessays* 2019;41:e1800183. <https://doi.org/10.1002/bies.201800183>.
- [226] Xiao J, Zhang Z, Chen GG, Zhang M, Ding Y, Fu J, et al. Nucleophosmin/B23 interacts with p21WAF1/CIP1 and contributes to its stability. *Cell Cycle* 2009;8:889–95. <https://doi.org/10.4161/cc.8.6.7898>.
- [227] Rosselli F, Ridet A, Soussi T, Duchaud E, Alapetite C, Moustacchi E. p53-dependent pathway of radio-induced apoptosis is altered in fanconi anemia. *Oncogene* 1995;10:9–17.
- [228] Yamamoto K, Nihirane A, Aglipay J, Sironi J, Arkin S, Lipton JM, et al. Upregulated ATM gene expression and activated DNA crosslink-induced damage response checkpoint in fanconi anemia: implications for carcinogenesis. *Mol Med* 2008;14:167–74. <https://doi.org/10.2119/2007-00122.Yamamoto>.

- [229] Rani R, Li J, Pang Q. Differential p53 engagement in response to oxidative and oncogenic stresses in fanconi anemia mice. *Cancer Res* 2008;68:9693–702. <https://doi.org/10.1158/0008-5472.CAN-08-1790>.
- [230] Li X, Wilson AF, Du W, Pang Q. Cell-cycle-specific function of p53 in fanconi anemia hematopoietic stem and progenitor cell proliferation. *Stem Cell Rep* 2018;10:339–46. <https://doi.org/10.1016/j.stemcr.2017.12.006>.
- [231] Dokal I. Heightened DNA damage response impairs hematopoiesis in Fanconi anemia. *Haematologica* 2012;97:1117. <https://doi.org/10.3324/haematol.2012.073643>.
- [232] Kupfer GM, D'Andrea AD. The effect of the fanconi anemia polypeptide, FAC, upon p53 induction and G2 checkpoint regulation. *Blood* 1996;88:1019–25. <https://doi.org/10.1182/blood.V88.3.1019.1019>.
- [233] Zhang X, Li J, Sejas DP, Pang Q. The ATM/p53/p21 pathway influences cell fate decision between apoptosis and senescence in reoxygenated hematopoietic progenitor cells. *J Biol Chem* 2005;280:19635–40. <https://doi.org/10.1074/jbc.M502262200>.
- [234] Martinez A, Hinz JM, Gómez L, Molina B, Acuña H, Jones IM, et al. Differential expression of TP53 associated genes in Fanconi anemia cells after mitomycin C and hydroxyurea treatment. *Mutat Res Genet Toxicol Environm Mutagen* 2008;656:1–7. <https://doi.org/10.1016/j.mrgentox.2008.06.012>.
- [235] Mansilla SF, de la Vega MB, Calzetta NL, Siri SO, Gottifredi V. CDK-independent and PCNA-dependent functions of p21 in DNA replication. *Genes (Basel)* 2020;11. <https://doi.org/10.3390/genes11060593>.
- [236] Rodríguez A, Yang C, Furutani E, García de Teresa B, Velázquez M, Filiatrault J, et al. Inhibition of TGFβ1 and TGFβ3 promotes hematopoiesis in Fanconi anemia. *Exp Hematol* 2021;93:70–84. e4, <https://doi.org/10.1016/j.exphem.2020.11.002>.
- [237] Zhang H, Kozono DE, O'Connor KW, Vidal-Cardenas S, Rousseau A, Hamilton A, et al. TGF-β inhibition rescues hematopoietic stem cell defects and bone marrow failure in fanconi anemia. *Cell Stem Cell* 2016;18:668–81. <https://doi.org/10.1016/j.stem.2016.03.002>.
- [238] Bagby GC, Alter BP. Fanconi anemia. *Semin Hematol* 2006;43:147–56. <https://doi.org/10.1053/j.seminhematol.2006.04.005>.