SnapShot: Fanconi Anemia and Associated Proteins

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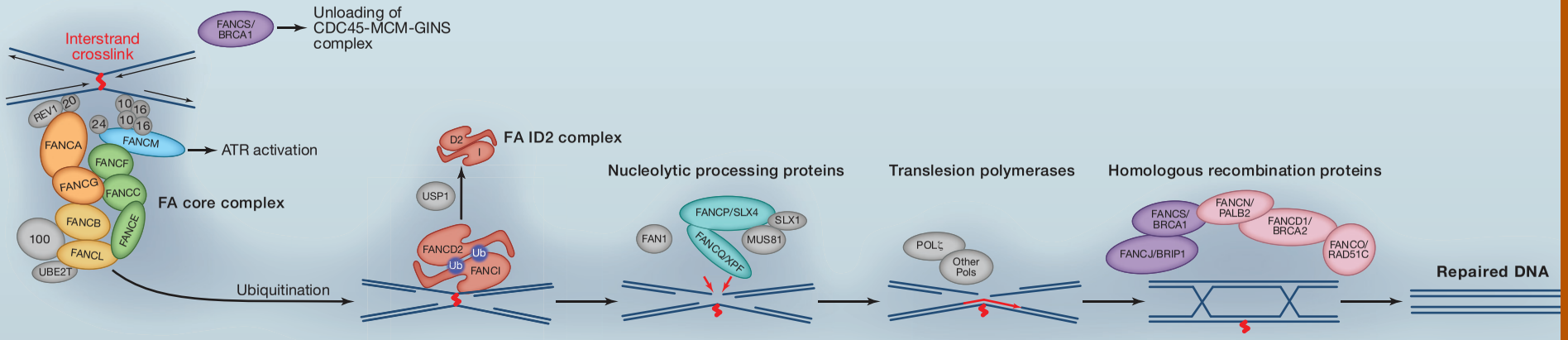

	Gene	Name (alias)	*S. cerevisiae*	*S. pombe*	*D. melanogaster*	*C. elegans*	*D. rerio*	*X. laevis*	Patient frequency	Protein Function
Genes mutated in FA patients	*FANCA*	-	-	-	-	-	*fanca*	*fanca*	64%	FA core complex
	FANCB	-	-	-	-	-	*fancb*	*fancb*	2%	FA core complex
	FANCC	-	-	-	-	-	*fancc*	*fancc*	12%	FA core complex
	FANCD1	*BRCA2*	-	-	*Brca2*	*brc-2*	*brca2*	*brca2*	2%	Homologous recombination
	FANCD2	-	-		*Fancd2*	*fcd-2*	*fancd2*	*fancd2*	4%	FA ID2 complex, gets ubiquitinated by FANCL (in the core complex), directs downstream events
	FANCE	-	-	-	-	-	*fance*	*fance*	1%	FA core complex
	FANCF	-	-	-	-	-	*fancf*	*fancf*	2%	FA core complex
	FANCG	-	-	-	-	-	*fancg*	*fancg*	8%	FA core complex
	FANCI	-	-	-	*Fanci*	*fnci-1*	*fanci*	*fanci*	1%	FA ID2 complex, gets ubiquitinated by FANCL (in the core complex), directs downstream events
	FANCJ	*BRIP1 (BACH1)*	*CHL1*[1]	-	-	*dog-1*	*brip1*	*brip1*	2%	Homologous recombination; 5' - 3' helicase
	FANCL	-	-	-	*Fancl*	*rnf-113?*	*fancl*	*fancl*	0.4%	FA core complex, E3 ubiquitin ligase
	FANCM	-	*MPH1*	*fml1*	*Fancm (CG7922)*	*drh-3*	*fancm*	*fancm*	0.1%	FA core complex; DNA translocase; important for ATR activation during ICL repair; participates in DN repair in other contexts
	FANCN	*PALB2*	-	-	-	-	*palb2*	*palb2*	0.7%	Homologous recombination
	FANCO	*RAD51C*	-	-	*Rad51C*	*rfs-1*[2]	*rad51c*	*rad51c*	0.1%	Homologous recombination
	FANCP	*SLX4 (BTBD12)*	*SLX4*	*slx4*	*mus312*	*him-18*	*slx4*	*slx4*	0.5%	Scaffold/regulator of XPF-ERCC1, MUS81-EME1/2, and SLX1 nucleases
	FANCQ	*ERCC4 (XPF)*	*RAD1*	*rad16*	*mei-9*	*xpf-1*	*ercc4*	*ercc4*	0.1%	Associates with ERCC1 to form a FANCP/SLX4-dependent ICL unhooking nuclease; also participate in nucleotide excision repair independently of FANCP
	FANCS	*BRCA1*	-	-	-	*brc-1*	*brca1*	*brca1*	0.1%	Homologous recombination; inhibition of NHEJ; removal of CMG (CDC45-MCM-GINS) complex during ICL repair
FA-associated genes	*UBE2T*	-	-	*?*	*?*	*ube2t*	*ube2t*	*ube2t*		E2 ubiquitin-conjugating enzyme; works with FANCL
	FAAP100[4]	*C17orf70*	-	-	-	-	*si:dkey-57h18.1*	*MGC83104*		Subunit of FA core complex
	FAAP24[4]	*C19orf40*	-	-	-	-	*zgc:162267*	*C19orf40*		Subunit of FA core complex
	FAAP20[4]	*C1orf86*	-	-	-	-	*si:ch73-70k4.1?*	*LOC101733463*[3]		Subunit of FA core complex
	FAAP16[4]	*APITD1 (MHF1, CENPS)*	*MHF1*	*mhf1*	-	*?*	*apitd1*	*apitd1*		FA core complex; histone-fold containing protein
	FAAP10[4]	*STRA13 (MHF2, CENPX)*	*MHF2*	*mhf2*	-	*F35H10.5*	*stra13*	*stra13*		FA core complex; histone-fold containing protein
	FAN1	*(MTMR15, KIAA1018)*	-	*fan1*	-	*fan-1*	*fan1*	*fan1*		ICL repair nuclease, interacts with monoubiquitinated FANCD2

[1]. *CHL1* has similarity to *FANCJ* and to *DDX11*; [2]. *rfs-1* is the sole RAD51 paralog identified so far in *C. elegans*; [3]. *X.tropicalis* gene; *?* Indicates that the identity of the ortholog is uncertain; [4]. FAAP proteins are indicated as numbers (10, 16, 20, 24, 100).

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Cell

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Fanconi anemia (FA) is a genetic disorder of chromosomal instability caused by mutations in at least 17 different genes (*FANCA* to *FANCS*). Patients with mutations in one of the FANC genes constitute a complementation group (FA-A to FA-S) (reviewed in Kottemann and Smogorzewska, 2013; Sawyer et al., 2014; LOVD database: http://www.rockefeller.edu/fanconi/mutate/). A minority of patients are not assigned to any complementation group, and their causative mutations still await identification. FA is inherited in an autosomal-recessive fashion with the exception of the FA-B complementation group with mutations in *FANCB*, which is an X-linked gene. Clinically, FA is a heterogeneous disease. Patients may display diverse congenital abnormalities, including growth restriction, skeletal, and other organ malformations (reviewed in Auerbach, 2009). Most FA patients develop bone marrow failure (at a median age of 7 years) that may affect any of the blood lineages. However, patients with mutations in *FANCO/RAD51C* or *FANCS/BRCA1* show no development of bone marrow failure to date and are therefore termed to have FA-like syndrome. FA patients are cancer prone. Patients with biallelic mutations in *FANCD1* (*BRCA2*) and *FANCN* (*PALB2*) develop acute myelogenous leukemia (AML) and embryonal tumors (medulloblastoma, neuroblastoma, and Wilms tumors), usually in the first few years of life. Patients in other complementation groups have a greatly increased risk of AML and squamous cell carcinoma, especially of the head, neck, and genital regions. Cells derived from FA patients show increased genomic instability and cellular hypersensitivity to DNA crosslinking agents, a characteristic that has also been used as a diagnostic marker for FA (reviewed in Auerbach, 2009).

The proteins encoded by the 17 genes identified to be mutated in FA patients (colored in the schematic) are implicated in a common pathway important for the repair of DNA interstrand crosslink (ICL) lesions that covalently link two strands of DNA together (reviewed in Deans and West, 2011; Kim and D'Andrea, 2012; Kottemann and Smogorzewska, 2013). The pathway also involves other associated proteins (gray in the schematic) that have not yet been shown to be mutated in FA patients. ICL lesions may be formed by endogenous metabolites, such as reactive aldehydes (from alcohol detoxification, histone demethylation, or lipid peroxidation) or exogenous chemotherapeutic drugs, including cisplatin (reviewed in Clauson et al., 2013; Garaycoechea and Patel, 2014). This pathway is activated following replication fork stalling at an ICL during S phase, with the FA core complex (FANCA, B, C, E, F, G, L, and M) recruited through multiple mechanisms. Components of the core complex (including FANCM) have additional functions in activating ATR, the DNA damage response kinase, which phosphorylates multiple substrates to facilitate cell-cycle arrest, replication fork stability, and proper repair.

Once the core complex is recruited to the ICL-induced stalled replication fork, FANCL, the catalytic E3 ligase subunit of the core complex, in concert with UBE2T (ubiquitin-conjugating enzyme), ubiquitinates the FANCD2-FANCI (ID2) complex. Patient cell lines with mutations in the genes coding for the core complex components show lack of FANCD2 or FANCI ubiquitination following DNA interstrand crosslink-inducing agents like DEB or mitomycin C (MMC). The ubiquitinated ID2 complex is essential for downstream nucleolytic incisions and translesion synthesis repair events. The deubiquitinating enzyme, USP1, is required to deubiquitinate the ID2 complex, and this event has been shown to be important for ICL repair. Two of the FA proteins, FANCP/SLX4 and FANCQ/XPF, form a complex in which the endonuclease XPF makes incisions to "unhook" the ICL. Other nucleases, including FAN1 (FANCD2/FANCI-associated nuclease), MUS81, and SLX1 might act redundantly to make incisions at the ICL (reviewed in Zhang and Walter, 2014). Unhooking allows for translesion polymerases to repair one duplex, which can then be used for repair of the other strand using homologous recombination. The remaining FA proteins, FANCD1/BRCA2, FANCJ/BRIP1, FANCN/PALB2, FANCO/RAD51C, and FANCS/BRCA1, are all implicated in homologous recombination repair that acts following the unhooking step to resolve resulting double strand breaks. In addition, FANCS/BRCA1 has been most recently implicated in unloading the replicative CMG helicase at stalled replication forks (Long et al., 2014).

All components of the FA pathways are conserved in vertebrates, including frogs and zebrafish. In invertebrates, such as flies and worms, FANCL is the only conserved component of the core complex, whereas the ID2 complex and the rest of the other FA components linked to other repair pathways are present. It remains debatable whether the FA pathway is conserved in lower eukaryotes, including budding yeast and fission yeast as the ID2 complex, the pivotal component of the FA pathway, is not conserved. However, it has been suggested that the orthologs of the most conserved components, FANCM, FAAP10/FAAP16, FANCJ, FANCP, and FANCQ, operate during ICL repair in yeast when the predominant repair pathways are inactivated (McHugh et al., 2012).

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