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Inflammatory ROS in Fanconi Anemia Hematopoiesis and Leukemogenesis

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1. Introduction

Fanconi anemia (FA) is a genetic disorder characterized by bone marrow failure (BMF), clonal proliferation of hematopoietic stem cells, and transformation to leukemia and other cancers (Ames *et al.,* 1995; Boglilo *et al.,* 2002; Cohen-Haguenauer *et al.,* 2006; Cumming *et al.,* 2001; Fagerlie *et al.,* 2001; Jonkers *et al.,* 2001; Suematsu *et al.,* 2003). Somatic cell fusion studies show FA is genetically heterogeneous. So far mutations in 15 genes have been identified in FA or FA-like patients (Cohen-Haguenauer *et al.,* 2006; Joenje *et al.,* 1987; Jonkers *et al.,* 2001; Lensch *et al.,* 1999; Stoepker *et al.,* 2011; Yamamoto *et al.,* 2011). The genes encoding the groups A (FANCA), B (FANCB), C (FANCC), D1 (FANCD1/BRCA2), D2 (FANCD2), E (FANCE), F (FANCF), G (FANCG), -I (FANCI/KIAA1794), J (FANCJ/ BRIP1), L (FANCL), M (FANCM), N (FANCN/PALB2), O/RAD51C and P/SLX4 proteins have been cloned (de Winter *et al.,* 1998, 2000a, 2000b; Howlett *et al.,* 2002; Joenje *et al.,* 2000; Letitus *et al.,* 2004; Levran *et al.,* 2005; Lo Ten Foe *et al.,* 1996; Meetei *et al.,* 2003, 2004, 2005; Meindl *et al.,* 2010; Reid *et al.,* 2006; Smogorzewska *et al.,* 2007; Somyajit *et al.,* 2010; Strathdee *et al.,* 1992; Timmers *et al.,* 2001; Xia *et al.,* 2006; Yamamoto *et al.,* 2011). The latter two genes are still thought of as tentative as they do not fall within a defined category biologically and the patients carrying these gene mutations are limited. The majority of mutations are found in *FANCA*, *FANCC* and *FANCC* genes in FA patients (Table 1). Recent studies on the biological function of these FA proteins have demonstrated that eight of the FA proteins (namely, FANCA, B, C, E, F, G, L, and M) form a nuclear multiprotein complex (Collins *et al.,* 2005; D'Andrea *et al.,* 2003; de Winter *et al.,* 2000; Meetei *et al.,* 2003; Smogorzewska *et al.,* 2007; Tischkowitz *et al.,* 2003; Walsh *et al.,* 1994), which functions as a nuclear E3 ubiquitin ligase that monoubiquitinates downstream FANCD2/FANCI dimer in response to DNA damage or DNA replication stress. This FANCD2/FANCI heterodimer then recruits other downstream FA proteins including FANCD1 (which is the breast cancer protein BRCA2), and the recently identified FANCJ, FANCN, FANCO and another breast cancer protein, BRCA1 (D'Andrea *et al.,* 2010), to nuclear loci containing damaged DNA and consequently influence important cellular processes such as DNA replication, cell-cycle control, and DNA damage repair. The core complex also interacts with the FAAP100 and FAPP24 proteins, which are also crucial components in the pathway (Ciccia *et al.,* 2007; Horejsi *et al.,* 2009; Collis *et al.,* 2008, Fig 1). FANCM and its interacting proteins, such as FAAP24 and MHF1, MHF2, also play a role in controlling the processing and stabilization of stalled replication forks (Schwab *et al.,* 2010; Luke-Glaser *et al.,* 2010; Singh *et al.,* 2010).

Subtype	FA Patients Estimated %	Chromosome Location	Protein Products (kd)	Function
A	60.9	16q24.3	163	FA core complex
B	2.0	Xp22.31	95 (FAAP95)	FA core complex
C	7.6	9q22.3	63	FA core complex
D1	5.0	13q12-13	380 (BRCA2)	RAD51 recruitment
D2	4.7	3p25.3	155,162	Involved in DNA damage repair
E	3.5	6p21-22	60	FA core complex
F	2.0	11p15	42	FA core complex
G	6.9	9p13	68 (XRCC9)	FA core complex
I	2.8	15q25-16	140 (FANCI/KIAA1794)	Required for maintenance of chromosomal stability
J	1.7	17q22-q24	140 (FANCJ/BACH1/BRIP1)	5'>3' DNA helicase/ATPase
L	0.4	2p16.1	43(FANCL/PHF9/POG)	FA core complex,FAAP43 ubiqutin ligase
M	0.3	14q21.3	250	FA core complex/ATPase/translocase
N	2.1	16p12.1	130 (FANCN/PALB2)	Regulation of BRCA2 location
O	Rare	17q25.1	42 (FANCO/RAD51C)	Involved in HRR of DSB
P	Rare	16p13.3	200 (FANCP/SLX4)	Protect genome stability
BRCA1	-	17q21	208	E3 ubiquitin ligase
				Required for FANCD2 targeting to DNA damage site
FAAP100	-	17q25.1	100	Required for D2 mono-Ub
FAAP24	-	19q13.11	24	Required for D2 mono-Ub
MHF1	-	1p36.22	16 (FAAP16)	Interact with FANCM
MHF2	-	17q25.3	10 (FAAP10)	Interact with FANCM

Table 1. Complementation groups and interaction proteins of Fanconi Anemia.

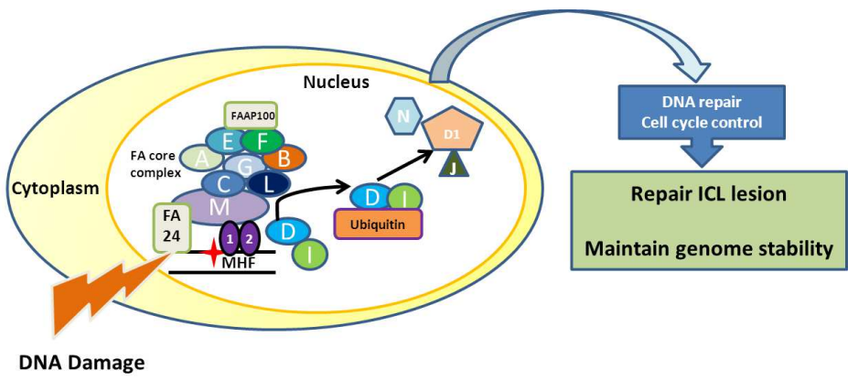

Fig. 1. Function of the FA pathway. Eight FA proteins form a nuclear core complex, which acts as ubiquitin ligase. FANCM interacts with FAAP24, FAAP100 as well as MHF1 and MFH2, resulting in complex chromatin loading and controlling the processing and stabilization of stalled forks, respectively. In response to DNA damage or replication stress, nuclear core complex monoubiquitinates two other FA proteins, FANCD2 and FANCI, which then recruit other downstream FA proteins FANCD1, FANCJ, and FANCN to damaged DNA and involved in DNA repair, cell-cycle control to repair ICL (interstrand crosslink) lesions and to maintain genome stability.

Many studies indicate that FA proteins might play specific roles in hematopoiesis by governing the responses of hematopoietic cells to both genotoxic and cytotoxic stresses. Loss of FA functions causes excessive apoptosis of HSC and progenitor cells (HSC/P) cells leading to BMF in the early stage of FA. As the disease progresses, apoptosis as well as genomic instability impose a selective pressure on FA HSC/P cells and promote the

development of mutant clones, which could be transformed to leukemia (Cumming *et al.,* 1996, 2001; Fagerlie *et al.,* 2001; Haneline *et al.,* 1998, 1999, 2003; Koh *et al.,* 1999; Li X *et al.,* 2004; Li Y *et al.,* 1997; Maciejewski *et al.,* 1995; Nakata *et al.,* 2004; Pang *et al.,* 2001a, 2001b, 2002; Rathbun *et al.,* 1997, 2000; Si *et al.,* 2006; Walsh *et al.,* 1994; Wang *et al.,* 1998; Whitney *et al.,* 1996).

2. FA hematopoiesis

Hematological abnormalities are among the most important clinical features of FA. Children with FA often develop pancytopenia during the first few years of life. Complications of BM failure (BMF) are the major causes of morbidity and mortality of FA, and 80% of FA patients die from BMF (Bagby *et al.,* 2003; Buchwald *et al.,* 1998; Fagerlie *et al.,* 2001; Kutler *et al.,* 2003; Lensch *et al.,* 1999; Liu *et al.,* 2000). In addition, patients with FA have high risk of developing myelodysplasia (MDS) or acute myeloblastic leukemia (AML) (Bagby *et al.,* 2003; Buchwald *et al.,* 1998; D'Andrea *et al.,* 2003; Fagerlie *et al.,* 2001; Kennedy *et al.,* 2005; Tischkowitz *et al.,* 2003). During the BMF-MDS-AML progression, FA patients frequently develop clonal chromosomal abnormalities in the BM HSC/P cells. In fact, secondary occurred clonal cytogenetic abnormalities, such as 3q addition, 5q deletion and monosomy 7, are common in in children with FA who have evolved to MDS and AML and non-FA patients with MDS and AML after alkylating agents treatment (Freie *et al.,* 2004; Fridman *et al.,* 2003; Futaki *et al.,* 2002; Giaccia *et al.,* 1998; Lina-Fineman *et al.,* 1995; Rubin *et al.,* West *et al.,* 2000).

Excessive apoptosis and subsequent failure of the HSC compartment led to progressive BMF in FA patients have been documented from *in vitro* and *in vivo* studies. However, the molecular etiology of BMF and leukemia in FA remains to be elucidated. Compelling evidence suggest that altered expression of certain growth factors and cytokines, such as reduced expression of interleukin-6 (IL-6) and granulocyte-macrophage colony stimulating factor (GM-CSF) but increased secretion of mitotic inhibitor TNF-α in patient BM cells, may in part be responsible for hematopoietic disease progression in FA (de Cremoux *et al.,* 1996; Dufour *et al.,* 2003; Rosselli *et al.,* 1992; 1994; Schultz *et al.,* 1993; Stark *et al.,* 1993). It is conceivable that these alterations may change the BM microenvironment (for instance, leading to factor deprivation or constant exposure to mitogenic inhibitors) and cause deregulation of cellular homeostasis. It has also been shown that FA BM cells are hypersensitive to a variety of extracellular cytokines, including interferon-γ (IFN-γ) and tumor necrosis factor α (TNF-α) (Dufour *et al.,* 2003; Fagerlie *et al.,* 2001; Haneline *et al.,* 1998; Koh *et al.,* 1999; Li X *et al.,* 2004; Li Y *et al.,* 2004; Nakata *et al.,* 2004; Pang *et al.,* 2001a, 2001b, 2002; Rathbun *et al.,* 1997, 2000; Reid *et al.,* 2006; Rosselli *et al.,* 1992; Schultz *et al.,* 1993; Si *et al.,* 2006; Wang *et al.,* 1998; Whitney *et al.,* 1996), which may subsequently lead to cell apoptosis. Indeed, studies of FA patients have demonstrated that BM from FA patients has decreased number of colony-forming progenitors, as well as a reduction in colony size (Doneshbod–Skibba *et al.,* 1980; Gluckman *et al.,* 1989). These data demonstrate defective hematopoiesis in FA (Bagby *et al.,* 2003; Fagerlie *et al.,* 2001; Tischkowitz *et al.,* 2003).

In contrast to FA patients, mouse models deficient for several FA genes, including *Fanca*, *Fancc*, *Fancd2* and *Fancg*, do not show no spontaneous hematological defects or leukemia development (Cheng *et al.,* 2000; Whitney *et al.,* 1996; Wong & Buchwald, 2002; Yang *et al.,* 2001). Studies in the Fanca and Fancc mouse models show that while blood count and the

number of committed BM progenitors are normal in FA mice as compared to WT mice; however, when subjected to sublethal dose of DNA cross-linking agent mitomycin C (MMC), which does not affect WT mouse cells, to the mutant mice experienced progressive decrease of all peripheral blood parameters, as well as early and committed progenitors, and eventually died within 8 weeks (Chen *et al.,* 1996; Whitney *et al.,* 1996). These results suggest that loss of FA genes in mouse models results in compromised defects in response to environmental insults (Chen *et al.,* 1996; Whitney *et al.,* 1996; Pang *et al.,* 2000; Rathbun *et al.,* 1997; Haneline *et al.,* 1998; Wong & Buchwald, 2002).

Similar to FA-C patients, BM cells from *Fancc-/-* mice show compromised colony growth capacity following IFN-γ, TNF-α and MIP-1α treatment (Haneline *et al.,* 1998). Literatures suggest that IFN-γ and TNF-α suppress colony growth forming ability of FA mouse BM cells by upregulating other cellular receptors, such as the fas receptor (CD95) (Young *et al.,* 1997). Increase in CD95 expression has been found in CD34+ cells from children with FA as well as the CD34+ fraction of hematopoietic progenitors in *Fancc-/-* mice, which is associated with increased apoptosis (Cumming *et al.,* 1996; Otsuki *et al.,* 1999). The hypersensitivity of *Fancc-/-* hematopoietic cells to IFN-γ and TNF-α is also mediated through activation of the RNA-dependent protein kinase (PKR) pathway, which is reported to initiate apoptosis in some instances, as an elevated level of activated PKR was found in *Fancc-/-* mouse embryonic fibroblasts (Pang *et al.,* 2001, 2002; Zhang *et al.,* 2004). Several groups independently showed compromised hematopoietic engraftment and reconstitution after BM transplantation of FA HSCs (Haneline *et al.,* 2003; Zhang *et al.,* 2007). Deregulation of apoptotic responses in hematopoietic cells may account at least in part for the nearly universal development of BM failure in children with inactivating FA mutations.

3. Inflammation and FA

Inflammation is a biological process orchestrated mainly by myeloid cells and accompanied by infection or phagocytosis (Balwill *et al.,* 2001). Increased oxidative stress in FA patients may be the result of an increased burden of endogenously produced oxidants as well as increased amounts of ROS generated by various inflammatory cytokines. Many studies indicate a correlation between elevated circulating pro-inflammatory cytokines and anemia in patients with leukemia-related BM diseases (Hakim *et al.,* 1993), but direct evidence for the mechanistic link between inflammation and BMF or leukemia is lacking.

There is evidence showing that patients with FA have abnormally high levels of TNF-α (Fagerlie *et al.,* 2001; Fiers *et al.,* 1999; Freie *et al.,* 2003), which is a major mediator of inflammation and ROS production (Liu *et al.,* 2003; Lohrum *et al.,* 1999). Inappropriate induction or activation of TNF-α signaling has been implicated in the pathogenesis of numerous common diseases such as arthritis, heart attacks, and cancer (Ekbom *et al.,* 1990; Jonsson *et al.,* 2005; Mantovani *et al.,* 2002; Marx *et al.,* 2004). It is conceivable that the presence of TNF-α and increased oxidative stress in FA BM may account for profound physiologic changes, including the development of BMF and progression to leukemia.

Similar to TNF-α, IL-1β and IL-6 are also well-known pro-inflammatory cytokines with a wide range of biological activities in immune regulation, hematopoiesis, inflammation and oncogenesis (Ibanez *et al.,* 2009). It has been demonstrated that IL-1β is overexpressed in FA-A patients (de Cremoux *et al.,* 1996). The elevated levels of IL-1*β* were completely reverted

by complementation of functional FANCA into FA-A lymphocytes. In addition, the constitutive activation of the PI3K-Akt pathway in FA cells upregulates the expression of IL-1β through an NF-κB independent mechanism and this overproduction activates the proliferation of tumour cells (Ibanez *et al.,* 2009). IL-6 is the chief stimulator of the production of most acute phase proteins (Scheller *et al.,* 2011), whereas the other implicated cytokines influence subgroups of acute phase proteins. Recent studies demonstratethe presence of a defect in IL-6 production in FA patients (Coussens *et al.,* 2002; Cumming *et al.,* 1996), suggesting that this cytokine may partly be responsible for pancytopenia associated with BMF, the major clinical feature of FA, in FA patients. In addition, it has been reported that *Fancc-/-* HSC/P cells had altered growth and apoptosis responses to combinations of stimulatory cytokines, most dramatically in response to a combination of factors that included interleukin-3 (IL-3) and IL-6 (Aubé *et al.,* 2002).

4. FA oxidant hypersensitivity

Even in steady state, hematopoietic cells are exposed to various ROS, which are routinely generated during metabolic or inflammatory process. ROS induce a variety of responses in hematopoietic cells, including cellular proliferation and growth inhibition (Howlett *et al.,* 2002; Ichijo *et al.,* 1997). Like cells from other tissues, hematopoietic cells have developed several mechanisms to prevent the damage induced by oxidative stress. First, antioxidant enzymes, including superoxide dismutases (SODs), catalase, glutathione peroxidases and peroxiredoxins, can directly eliminate ROS. Secondly, other cellular enzymes can function to repair DNA damage induced by ROS in hematopoietic tissues. While FA murine models do not recapitulate some of the major FA clinical manifestations such as BM failure and leukemia, hematopoietic cells from FA knockout mice exhibit extreme oxidant sensitivity. Extensive studies have demonstrated FA oxidant hypersensitivity by using primary and immortalized cell cultures as well as *ex vivo* materials from patients (Bogliolo *et al.,* 2002; Cohen–Haguenauer *et al.,* 2006; Cumming *et al.,* 1996; Futaki *et al.,* 2002; Hadjur *et al.,* 2001; Kruyt *et al.,* 1998; Pagano *et al.,* 2005; Park *et al.,* 2004; Saadatzadeh *et al.,* 2004). It has also been shown that reoxygenation-generated oxidative stress, which is associated with significant DNA damage and inhibition of colony formation capacity (Ames *et al.,* 1993; Hammond *et al.,* 2003; Chen *et al.,* 2000), induced senescence of bone marrow progenitor cells from *Fancc-/-* mice compared to their counterparts. While these studies suggest a correlation between oxidative stress and FA disease progression, the mechanism by which oxidative stress influences the function of FA HSC/P cells has not been systematically studied. A number of hypotheses regarding the effect of oxidative stress in FA have been suggested, including the proposal that ROS could damage DNA and inability of FA HSC/P cells to repair such damage would result in exacerbated genomic instability leading to apoptosis and malignant transformation.

Three major FA core complex components, FANCA, FANCC, and FANCG (Bagby *et al.,* 2003; Kennedy *et al.,* 2000; Green *et al.,* 2009), were found to interact with a variety of cellular factors that primarily function in redox-related processes (Table 2), such as FANCC protein interacts with NADPH cytochrome P450 reductase and glutathione S-transferase P1-1 (Cumming *et al.,* 1996; Kruyt *et al.,* 1998), which are involved in either triggering or detoxifying reactive intermediates including ROS. It has also been demonstrated that *Fancc-/-* mice with deficiency in the anti-oxidative enzyme Cu/Zn superoxide dismutase

demonstrated a defective hematopoiesis (Hadjur *et al.,* 2001). *Fancc-/-* cells exhibit hyperactivation of ASK1, a serine-threonine kinase that plays an important role in redox apoptotic signaling (Saadatzadeh *et al.,* 2004). Another FA protein, FANCG, interacts with cytochrome P450 2E1, which is associated with the production of reactive oxygen intermediates, and mitochondrial anti-oxidant enzyme peroxiredoxin-3 (Futaki *et al.,* 2002, Mukhopadhyay *et al.,* 2006), which suggested a possible role of FANCG in protection against oxidative DNA damage. Furthermore, FANCA and FANCG interact upon oxidative stress (Park *et al.,* 2004). These findings indicate a crucial role of FA proteins in oxidative stress signaling. We recently found that FANCD2 associated with FOXO3a, a master regulator in response to oxidative stress (Huang *et al.,* 2007; Li *et al.,* 2010; Tsai *et al.,* 2008). While these observations point to the involvement of FA proteins in oxidative stress response, the molecular pathways in which FA proteins function to modulate physiologic oxidative stress have not been defined.

FA proteins	*Redox-related factors*	*References*
FANCA	FANCG	Park *et al*., 2004
FANCC	NADPH cytochrome P450 (RED)	Kruyt *et al*., 1998
	Glutathine S-transferase P1-1 (GSTP1)	Cumming *et al*., 2001
	Cu/Zn superoxide dismutase (SOD)	Hadjur *et al*., 2001
	Apoptosis signal-regulating kinase 1 (ASK1)	Saadatzadeh *et al*., 2004
FANCG	Cytochrome P450 2E1 (CYP2E1)	Futaki *et al*., 2002
	Mitochondrail anti-oxidant enzyme peroxiredoxin-3	Mukhopadhyay *et al*., 2006
FANCD2	Forkhead transcription factor FOXO3a	Li *et al*., 2010

Table 2. Fanconi anemia proteins in redox signaling.

5. Oxidative stress response in FA hematopoietic cells: a FOXO3a connection

Forkhead transcription factors of the FOXO class O including FOXO1, FOXO3a, FOXO4 and FOXO6, are implicated in the regulation of diverse physiologic processes, including cell cycle arrest, apoptosis, DNA repair, stress resistance, and metabolism (Brunet *et al.,* 2004; Huang *et al.,* 2007). It has been established previously that members of the FOXO family are negatively regulated by PKB/c-Akt in response to insulin/IGF signaling, and are involved in regulating cell cycle progression and cell death (Geert *et al.,* 2002; Essers *et al.,* 2004). Among these FOXO proteins, FOXO3a functions as a master regulator of oxidative stress (Huang *et al.,* 2007; Tsai *et al.,* 2008). Several recent studies demonstrate that FOXO3a protects quiescent HSCs from oxidative stress (Tothova *et al.,* 2002, 2007; Miyamoto *et al.,* 2005). Some other studies also indicatethat Foxo3a is involved in inflammatory responses, such as inflammatory arthritis, intestinal inflammation, rheumatoid blood and synovial tissue, angiogenesis and postnatal neovascularization etc. (Turrel-Davin *et al.,* 2009; Potente *et al.,* 2005; Jonsson *et al.,* 2005; Walbert *et al.,* 2004).

While strong evidence indicates that FA cells, including hematopoietic cells from FA patients, are intolerant to oxidative stress (Cohen-Haguenauer *et al.,* 2006; Cumming *et al.,* 2001; Du *et al.,* 2008; Futaki *et al.,* 2002; Hadjur *et al.,* 2001; Kruyt *et al.,* 1998; Paganno *et al.,*

2005; Park *et al.,* 2004; Saadatzadeh *et al.,* 2004; Schindler *et al.,* 1988; Zhang *et al.,* 2005) and certain FA proteins interact with cellular factors involved in redox metabolism (Aggarwal *et al.,* 2003; Ames *et al.,* 1995; Bagby *et al.,* 2003), the molecular pathways in which FA proteins function to modulate physiologic oxidative stress have not been defined. Our recent identification of the FANCD2-FOXO3a complex (Li *et al.,* 2010) and preliminary characterization of impaired anti-oxidant defense in primary BM cells from FA patients opened new research opportunities to extend the functional study on the roles of FA proteins in the context of oxidative stress. We envision a model (Fig 2) in which the FA proteins regulate oxidative stress response through mechanisms involving functional interplay with the major oxidative stress-responsive transcription factor FOXO3a and protection of anti-oxidant genes from oxidative damage. Loss of these FA protein functions leads to elevated levels of ROS. As a consequence, FA HSC/P cells accumulate excessive DNA damage and increased genomic instability. However, further studies remains to be done in this context.

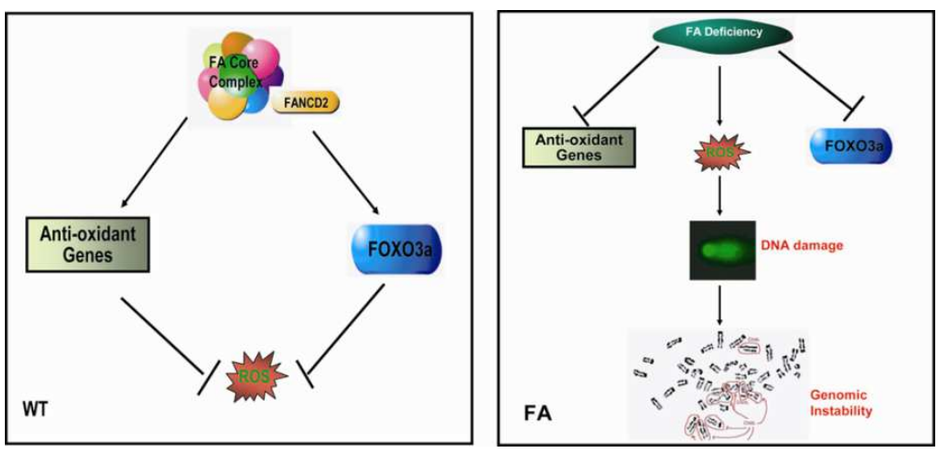

Fig. 2. A model for the role of FA proteins in oxidative stress signaling. In WT cells, the FA pathway helps keep cellular levels of ROS in check through functional interaction with the FOXO3a oxidative stress responsive pathway and safeguarding cellular anti-oxidant genes. In FA cells, both the FOXO3a pathway and the anti-oxidant defense are impaired due to loss of the FA protein functions. As a result, FA cells accumulate high levels of ROS, which damages DNA leading to genomic instability.

6. The FA syndrome links inflammatory ROS to leukemogenesis

Certain chronic inflammatory conditions have long been known to link to cancer. There is compelling evidence that chronic inflammation increases the risk of human cancers such as hepatocellular carcinoma, colon and bladder cancers, B cell lymphomas, and visceral malignancies (Kuper *et al.,* 2000; Mackay *et al.,* 2001; Martin *et al.,* 2011; Suematsu *et al.,* 2003; Umeda *et al.,* 2002; Ziech *et al.,* 2010), probably through the unbalanced machinery between DNA damage and repair (Fig. 3.).

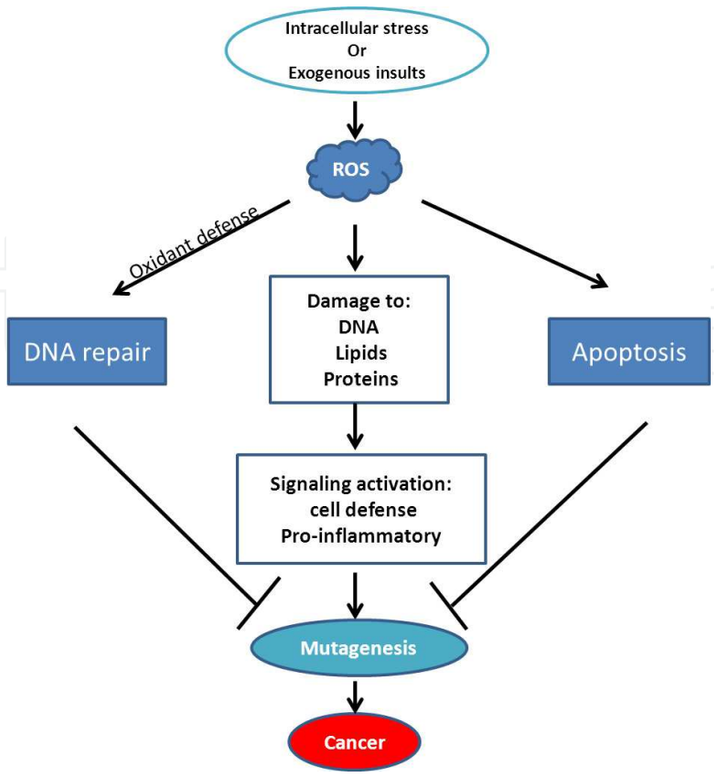

Fig. 3. Possible mechanisms for induction of oxidative stress and DNA damage and the roles in carcinogenesis. Intracellular stress or exogenous insults induces ROS production, which damages DNA, lipids and proteins. Over-produced ROS leads to cell death and activates cell defense machinery, including DNA repair and other cellular signaling pathways to maintain genome stability. Insufficient DNA repair or apoptosis causes mutagenesis, which results in cancer development.

Oxidative stress is considered as an important pathogenic factor in leukemia-prone bone marrow diseases like FA (Bogliolo *et al.,* 2002; Cohen–Haguenauer *et al.,* 2006; Cumming *et al.,* 1996; Futaki *et al.,* 2002; Hadjur *et al.,* 2001; Joenje *et al.,* 1987; Kruyt *et al.,* 1998; Mukhopadhyay *et al.,* 2006; Pagano *et al.,* 2005; Park *et al.,* 2004; Saadatzadeh *et al.,* 2004; Schindler *et al.,* 1988; Zhang *et al.,* 2005a, 2005b). The expression of inflammatory mediators, particularly the pro-inflammatory cytokines TNF-α, interleukin-1beta (IL-1β), and IL-6 in these patients is often associated with increased production of ROS either as a component of their immune response or as a consequence of increased metabolism (Macciò *et al.,* 1998; Mantovani *et al.,* 1997; Mantovani *et al.,* 2002; Tischkowitz *et al.,* 2004). Many studies have shown a correlation between elevated circulating pro-inflammatory cytokines and anemia in patients with leukemia-related BM diseases but direct evidence for the mechanistic link between inflammation and leukemia is lacking.

Normal hematopoiesis is maintained by dynamic interactions between HSCs and the bone marrow microenvironment, which is a complex system consisting of a variety of cell types, including stromal cells of nonhematopoietic, mesenchymal origin as well as hematopoietically derived stromal macrophages producing extracellular matrix components and hematopoietic growth factors (Bhatia *et al.,* 1995; Konopleva & Michael, 2007; Marina *et*

al., 2007). Alterations of pro-inflammatory cytokine expression such as reduced IL-6 and increased TNF-α, which are often found in FA patient cells, may account for BM microenvironment changes such as growth factor deprivation or constant exposure to mitogenic inhibitors. These alterations may subsequently cause deregulation of cellular homeostasis in FA (de Cremoux *et al.,* 1996; Dufour *et al.,* 2003; Rosselli *et al.,* 1992, 1994; Schultz *et al.,* 1993; Stark *et al.,* 1993) at least partially through upregulation of ROS production.

ROS induce a variety of responses in HSCs, including cellular proliferation and apoptosis (Nakamura *et al.,* 1997; Nakata *et al.,* 2004). ROS can also cause DNA damage and drive HSCs into cell division, which is essential for DNA repair processes (Wilson A *et al.,* 2008). There is strong evidence that HSCs are activated and thus functionally exhausted by oxidative stress. Mice with mutations in the ATM or FOXO genes, as well as various DNA repair genes exhibit premature exhaustion of HSCs due to accumulation of ROS or DNA damage, indicating that cellular balance between ROS and antioxidant defense as well as DNA repair is crucial for the maintenance of HSC self-renewal and hematopoietic function (Rossi *et al.,* 2007; Nijnik *et al.,* 2007).

The inflammatory cytokine TNF-α, which is overproduced in FA patients, has been considered as one important pathological factor involved in the abnormal hematopoiesis in FA. Extensive evidence demonstrated that excessive apoptosis of FA hematopoietic cells induced by TNF-α, may contribute to at least partially the pathophysiology of BM failure in FA. The c-JUN NH2-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB) pathways are two well-established pathway involved in TNF-α-induced ROS production (Nakata *et al.,* 2004; Ma *et al.,* 2009; Ventura *et al.,* 2004). The JNK kinase can be activated by TNF-α-induced ROS. This activation then in turn leads to more ROS production, and sustained JNK activation in NF-κB-deficient cells was suggested to depend on ROS. It has been shown that TNF-α–induced ROS production at inflammatory sites causes DNA damage and therefore cause mutation and cancer (Aggarwal *et al.,* 2003; Kryston *et al.,* 2011; Martin *et al.,* 2011 Sedelnikova *et al.,* 2010; Suematsu *et al.,* 2003; Wajant *et al.,* 2003; Ziech *et al.,* 2010). One possible mechanism is through Oxidation of bases and generation of DNA strand interruptions. However, the accurate measurement of oxidative stress is a hallmark of disease diagnosis as well as treatment. Recently, HPLC associated with tandem mass spectrometry (MS/MS) or electrochemical detector (ECD) together with optimized DNA extraction conditions has been developed as a relevant analytical approach for measuring oxidatively base damage in cellular DNA (Cadet *et al.,* 2006, 2010). Our recent studies demonstrated the inflammatory ROS-mediated hematopoietic suppression and increased chromosomal aberrations in *Fancc-/-* mice, which is associated with impaired oxidative DNA-damage repair, implicating a role of FA pathway in maintaining genomic stability (Sejas *et al.,* 2007; Zhang *et al.,* 2007). Further studies indicated that TNF-α not only is a pro-apoptotic signal suppressing FA hematopoietic progenitor activity, but also promotes leukemic transformation of FA hematopoietic stem/progenitor cells (Li *et al.,* 2007). Therefore, FA disease progression to leukemia is governed not only by genetic changes intrinsic to the FA cells, but also by epigenetic and environmental factors and that TNF-α-mediated inflammation is one of the most important epigenetic and environmental factors contributing to FA leukemogenesis. Recent study indicate that FA hematopoietic cells are prone to clonal hematopoiesis and malignancy, which is associated with increased

cytogenetic abnormalities and myeloid malignancies in *Fancc-/-* BM cells (Haneline *et al.*, 1998, 1999, 2003; Li X *et al.*, 2004; Si *et al.*, 2006). While the role of FA proteins in the regulation of TNF-α-induced ROS production remains to be elucidated, several hypotheses have been proposed, including that FA proteins protect chromosomal DNA from ROS attack or facilitate the repair of oxidative DNA damage, which in turn downstream ROS signaling. It is also possible that FA proteins can regulate the biosynthesis of ROS metabolic molecules, such as glutathione and the expression of antioxidant enzymes (such as glutathione Stransferases and catalase). However, there is no direct evidence for any of these assumptions so far. Another potential target is the redox-sensitive transcription factor NF-κB, a major player involved in transcription regulating during differentiation and inflammation (Dhar *et al.*, 2006). The activation of NF-κB is known to enhance inflammation and promote cancer (Coussens *et al.*, 2002; Fiers *et al.*, 1999; Macdougal *et al.*, 2002). In addition, chronic exposure of FA BM cells to proinflammatory cytokine TNF- α creates an environment selects for somatically mutated preleukemic stem cell clones which are apoptosis-resistant and acquire proliferative advantage (Li *et al.*, 2007). Patients with these TNF-α-resistant BM cells may advance to MDS and AML via a mechanism involving genomic instability, coupled with inflammation driven by high NF-κB transcriptional activity (Fig. 4).

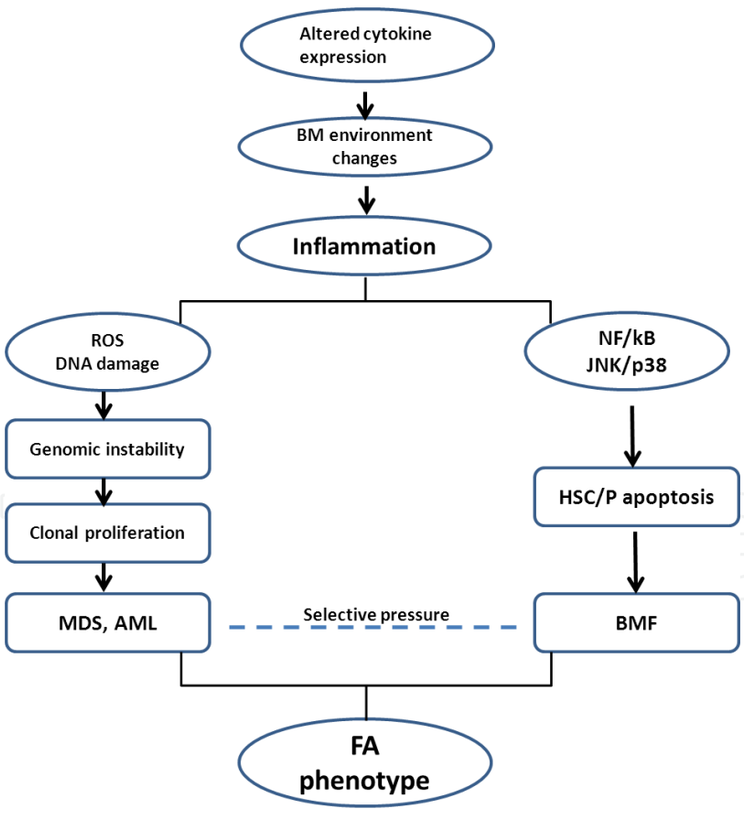

Fig. 4. The pro-inflammatory cytokines and their potential role in FA pathophysiology. Overproduced pro-inflammatory cytokines (TNF-α, IL-6, IL-1β etc.) plays roles in not only pro-apoptotic signal suppressing FA hematopoietic progenitor activity, but also promoting leukemic transformation of FA HSC/P cells, which lead to typical phenotype of FA patients.

7. Functional interaction between the FA proteins and other oxidative stress response pathways

Recent findings of a reduction of the HSC pool and a deficient repopulating capacity in Foxo3a knockout animals (Miyamoto *et al.,* 2007) indicate that FOXO3a plays essential regulatory roles in HSC maintenance through a mechanism of regulating ROS. This is consistent with our recent finding that FANCD2 forms complex with FOXO3a in response to oxidative stress (Li *et al.,* 2010). In addition, we observed several hematopoietic defects in FA mice deficient for Foxo3a (unpublished data). These results suggest that the FA proteins functionally interplay with other oxidative stress response pathways. Indeed, our preliminary results with primary BM cells from FA-A patients show that certain genes functioning in anti-oxidant defense and ROS metabolism fail to respond to oxidative stress (unpublished data). This suggests that one critical function of FA proteins under oxidative stress is to safeguard the expression of these anti-oxidant defense genes through DNA damage repair or gene promoter protection. While these observations indicate that the FA pathway functionally interacts with other cellular oxidative stress response pathways, the molecular mechanisms by which FA proteins function to modulate physiologic oxidative stress remain to be elucidated. Further investigation into the roles of FA proteins in oxidative DNA-damage response and repair, and the functional relationship between inflammatory ROS and genomic instability during FA leukemogenesis not only will advance our understanding of the function of FA proteins in hematopoiesis but also may suggest new targets for therapeutic prevention and treatment of BM failure and cancer progression of the disease.

8. Conclusion

Given other known genomic instability syndromes such as ataxia telangiectasia, Nijmegen breakage syndrome, xeroderma pigmentosum, and Werner syndrome rarely develop BM failure and leukemia, FA has been considered an excellent disease model for studying oxidative stress response in cancer development. Further investigation into the function of FA proteins in oxidative damage response and repair will help shed new light on the role of FA proteins in the maintenance of normal hematopoiesis under conditions of oxidative stress, and yield valuable information on whether targeting components of FA-related oxidative stress signaling pathways may be therapeutically useful in the prevention and treatment of FA BMF and leukemia. In addition, while FA is a rare disease, understanding functional interaction between FA proteins and other critical oxidative stress signaling pathways provides a unique opportunity to mechanistically comprehend and potentially intervene in these physiologically important processes.

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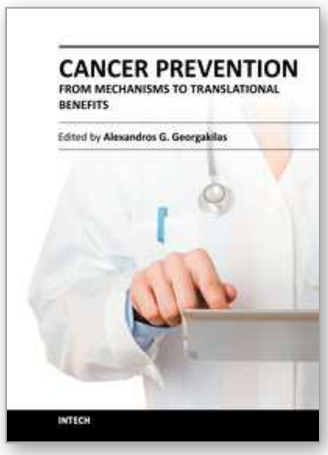

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