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TNF- α signaling in Fanconi anemia

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Abstract

Tumor necrosis factor- α (TNF- α) is a major pro-inflammatory cytokine involved in systemic inflammation and the acute phase reaction. Dysregulation of TNF production has been implicated in a variety of human diseases including Fanconi anemia (FA). FA is a genomic instability syndrome characterized by progressive bone marrow failure and cancer susceptibility. The patients with FA are often found overproducing TNF- α , which may directly affect hematopoietic stem cell (HSC) function by impairing HSC survival, homing and proliferation, or indirectly change the bone marrow microenvironment critical for HSC homeostasis and function, therefore contribute to disease progression in FA. In this brief review, we discuss the link between TNF- α signaling and FA pathway with emphasis on the implication of inflammation in the pathophysiology and abnormal hematopoiesis in FA.

Fanconi anemia (FA) and the FA pathway

Fanconi anemia (FA) is a rare inherited disease associated with bone marrow failure (BMF), variable congenital/developmental abnormalities, and cancer susceptibility (1-3). Approximately 1,000 persons worldwide currently suffer from the disease, 10 to 20 children are born with FA in the United States each year (1). It is genetically heterogeneous, with 16 complementation groups identified thus far (4-22). 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 (FANCI/BRIP1), L (FANCL), M (FANCM), N (FANCN/PALB2), O (FANCO/RAD51C), P (FANCP/SLX4) and Q (FANQ/ERCC4/XPF) proteins have been cloned (4-23, Table 1), of which *FANCA*, *FANCG* and *FANCC* are the most commonly mutated genes in FA populations (2-26, Fig 1). At the cellular level, FA is characterized by chromosomal instability and cross-linker sensitivity, which serves as a clinical diagnostic hallmark of FA (1, 3). Strong evidence indicates that the products of all of the FA genes function together in the FA pathway. In fact, the prominent role of the FA pathway has been implicated in DNA damage response and/or repair (DDR). (27)

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Multifunctionality of FA proteins

Intense studies have been focusing on biological function of FA proteins. Compelling evidence suggested that eight of the FA proteins (namely, FANCA, B, C, E, F, G, L, and M) and 6 associated factors (FAAP100, FAAP24, FAAP20 HES1, MHF1 and MHF2) form a nuclear multiprotein complex, which is required for the efficient mono-ubiquitination of downstream FANCD2/FANCI dimer in response to DNA damage or DNA replication stress (2, 8, 9, 12, 18, 28-39). After ubiquitination, FANCD2/FANCI heterodimer then recruits other downstream FA proteins including FANCD1 (which is the breast cancer protein BRCA2), and the recently identified FANCI (BRIP1), FANCN (PALB2), FANCO (RAD51C) and another breast cancer protein, BRCA1 (40), to nuclear loci containing damaged DNA and consequently influence important cellular processes such as DNA replication, cell-cycle control, and DNA damage repair (Fig 2).

The FA proteins are essential for DNA interstrand cross-linking (ICL) resolution, which is a multistep DNA repair process involving nucleotide excision repair (NER), translesion synthesis (TLS) and homologous recombination (HR). (41) Indeed, cells deficient in the FA pathway exhibit hypersensitivity to DNA damage agents that induce ICL and undergo G2/M arrest as well as profound chromosomal breakage while culturing with mitomycin C (MMC) or diepoxybutane (DEB) (1, 3). Interestingly, 4 of FA genes: FANCD1 (BRCA2), FANCI (BRIP1), FANCN (PALB2), and FANCO (RAD51C) are also breast cancer susceptibility genes, suggesting a crosstalk between the FA pathway and the breast cancer-associated (BRCA) pathway (FA/BRCA pathway, 42). To date, it is believed that the FA pathway plays important role in genome maintenance, while the FA/BRCA pathway is important during S phase of the cell cycle (43).

Hematopoietic failure and abnormal apoptotic signaling in FA

The most common clinical features of FA are hematological. A majority of children with FA invariably experience pancytopenia during the first few years of life, which is associated with stem cell loss in the hematopoietic compartment. Complications of bone marrow failure (BMF) are the major causes of morbidity and mortality of FA (1, 44-48). In addition, rapid hematopoietic cell loss forces compensatory chronic proliferation, which may lead to leukemogenesis (14, 49-51). In fact, patients with FA have higher risk of developing myelodysplasia (MDS) or acute myeloid leukemia (AML) (1-3, 29, 44, 45). In addition, secondary clonal cytogenetic abnormalities, such as 3q addition, 5q deletion and monosomy 7, are commonly occurred in children with FA who have evolved to MDS and AML after chemotherapies (52-58). It is in the context, a selective pressure of apoptosis as well as genomic instability during the BMF-MDS-AML progression may contribute to FA leukemia transformation (30, 45, 59-76). Therefore, FA has been proposed as an excellent model for studying myeloid leukemia evolution.

Surprisingly, FA murine models (such as *Fanca*, *Fancc*, *Fancd2* or *Fancg* knockout mice) do not recapitulate the major FA clinical manifestations, such as spontaneous hematological defects or leukemia development (76-79). Those null mice only exhibit some compromised defects in response to environmental insults, including ICL and ionizing irradiation (76-80). For instance, *Fanca* and *Fancc* mouse models show normal blood count and comparable number of committed bone marrow (BM) progenitors compared to WT mice in steady state. However, sublethal dose of DNA cross-linking agent MMC, which is well-tolerant in WT mice, induces progressive decrease of all peripheral blood parameters, as well as early and committed progenitors in the mutant mice, and eventually leads to premature death within 8 weeks (76, 77). More interestingly, the phenotype of *Fanca*, *Fancc*, *Fancd2* or *Fancg*- null mice (76, 79, 81-84) and *Fanca/Fancc* double knockout mice is indistinguishable (82),

suggesting that FA proteins function in the same pathway and play an important role in maintaining the bone marrow HSC compartment and disruption of the FA pathway may account for the defects found in both human and mouse.

Although the mechanistic details concerning the roles of FA proteins in promoting hematopoietic stem/progenitor cell (HSPC) survival or proliferation remain to be elucidated, significant evidence supports excessive apoptosis of HSPCs (59, 85), induced by stresses as a critical factor in the pathogenesis of BMF and leukemia progression in FA. Increased apoptosis due to higher level of the death receptor Fas (CD95) in FA was first reported by using CD34⁺ cells from children with FA (85). Conversely, overexpression of the FANCC protein suppresses apoptosis in human hematopoietic factor-dependent progenitor cell lines (61), in CD34⁺ cells from FA-C patients (30, 86), and in hematopoietic progenitor cells from *Fancc* knock-out mice (76). Subsequently, Koh and the coworkers found that FANCC modulates apoptotic responses to tumor necrosis factor- α (TNF- α) and Fas ligand (64). Mechanistically, the enhanced TNF- α -induced apoptosis in FANCC-deficient cells is found dependent on apoptosis signal-regulating kinase 1 (ASK1) (87), which has been considered an important kinase involved in oxidant- and TNF- α -induced apoptosis (88). FANCC also directly suppresses TNF- α production in mononuclear phagocytes by suppressing TLR8 activity, which is a key mediator in pathogen recognition and activation of innate immunity (86). Using *Fancc*^{-/-} mouse model, researchers showed that inactivation of *Fancc* augmented interferon-gamma (IFN- γ)-induced apoptotic responses in hematopoietic cells (72) and resulted in an inability to activate caspase-3 after ionizing radiation (89). A central highly conserved domain of FANCC, which binds to and facilitates the activation of STAT1, an important signal transducer and transcription activator and mediates cellular responses to cytokines and growth factors, has been identified (69). Furthermore, loss of FANCC results in constitutively phosphorylation and increased binding affinity for double-stranded RNA (dsRNA) kinase PKR, a key effector of apoptosis to various extra and intracellular cues (71), suggesting another function of FANCC in suppressing cytokine-induced apoptosis through modulating the activity of a growth inhibitory kinase (80). In addition, elevated expression/release of TNF-related apoptosis-inducing ligand (TRAIL) at the bone marrow level has also been found in FA, which may also implicate in the pathogenesis of FA (90) and MDS.(91) FANCD2 was shown to be a target for apoptosis mediated by caspase(s)- but not proteasome-mediated pathway following DNA damage (92). These data indicate that deregulation of apoptotic responses resulted from loss of FA function in hematopoietic cells, may account at least in part for the nearly universal development of BMF in children with inactivating FA mutations (Fig 3).

The link between pro-inflammatory cytokine TNF- α , inflammation and diseases

TNF- α is a proinflammatory cytokine produced by multiple immune and non-immune cells, including lymphocytes, mast cells, endothelial cells, fibroblasts and adipocytes. It functions in the regulation of diverse physiological cellular events, including cell proliferation, differentiation and apoptosis as well as various inflammatory processes (93, 94). TNF- α is also involved in pathological actions, such as systematic inflammation, initiation of the acute phase reaction by promoting survival/inflammatory signaling or inducing cell death, especially tumor cell necrosis and apoptosis (95, 96). In fact, dysregulation of TNF- α production has been implicated in the development of diabetes, septic shock, tumorigenesis, cardiovascular diseases, rheumatoid arthritis and inflammatory bowel disease (93). Targeting TNF- α has emerged as an established treatment for these diseases (97). With respect to abnormal hematopoiesis, it is well recognized that TNF- α is involved in many disease situations including anemia, MDS, and leukemia (49-51, 98-101).

Certain chronic inflammatory conditions provoke cell turnover coupled with carcinogen- or phagocyte-induced DNA damage, leading to transformation, therefore have been long linked to cancer. Although the molecular mechanisms by which chronic inflammatory conditions predispose the tumor formation remains unclear, it is believed that cancers are initiated by a combination of oncogenic mutational events and loss of the cellular checkpoints that prevent cell division in the presence of DNA damage. TNF- α is a well-known key mediator of cancer-associated chronic inflammation. Although TNF- α can initiate apoptotic responses (93), these pathways are frequently deactivated within tumor cells. In addition, increasing evidence suggest that in some circumstances, TNF- α can provide a survival signal for the cancer cell and thus act as a direct or indirect tumor promoter by the induction of other proinflammatory cytokines and angiogenic factors involved in cancer development (102, 103). Direct evidence for the involvement of TNF- α in malignancy comes from observations that TNF- α knockout mice are resistant to chemical carcinogenesis of the skin (104). Mechanistically, it has been shown that TNF- α mediates tumor promotion via a PKC α - and AP1- dependent pathway (105). Conversely, neutralization of TNF- α during the early stages of tumor promotion is sufficient to inhibit tumor formation (106). Altogether, as a central mediator of inflammation, TNF- α may serve as a molecular link between chronic inflammation and cancer development (107).

TNF- α signaling in pathophysiology

The molecular mechanisms of TNF- α functions have been intensively investigated. It is believed that the biological activities of TNF- α are mediated by two structurally related but functionally distinct receptors, designated the p55 and p75 TNF- α receptors, TNFR1 and TNFR2, respectively (93). Binding of TNF- α to the receptors initiates a complex array of signaling events in response to TNF- α receptor activation and give rise to the pleiotropic effects of TNF- α on cells (107, 108), mainly through the activation of the MAPK stress signaling cascade including JNK, p38MAPK, and ERK (108, 110, 111), as well as the NF- κ B transcription factor (111-113).

The default pathway TNF- α signaling is the induction of genes involved in inflammation and cell survival. Recent studies have elucidated that the diverse biological responses mediated by TNF- α are achieved, at least in part through TNF- α triggered-activation of the Ikappa B (I κ B) kinase (IKK)/NF- κ B through TRAF2 and RIP1 (114, 115), and mitogen-activated protein kinase (MAPK)/AP-1 pathways through a TRAF2-dependent mechanism (116). These pathways are essential for the expression of pro-inflammatory cytokines. NF- κ B activation also importantly induces negative regulators of apoptosis such as FLIPL (also known as CFLAR), BCL2 and superoxide dismutase (116). If NF- κ B activation is inadequate, apoptosis, a late response to TNF- α can be mediated by the activation of caspase-8 by FADD, and lead to the accumulation of intracellular reactive oxygen (ROS), sustained Jun amino-terminal kinase (JNK) activation and mitochondrial pathways activation (117). Although JNK activation is critical for TNF-stimulated AP-1-dependent gene expression (118), the exact role of JNK in TNF- α -induced apoptosis has been controversial. For instance, some studies indicated that JNK is not essential for TNF-stimulated apoptosis (112, 119-122). In addition, JNK may antagonize TNF-stimulated apoptosis (121, 123-125). On the other hand, other studies suggest JNK activation is required for TNF-induced cell death (113, 126-130). Genetic studies using *Drosophila* demonstrated that JNK may mediate cell death in response to TNF- α (131-133). These studies suggest a complex relationship between JNK and TNF-stimulated cell death (111). TNF- α also induces Fas-mediated apoptosis (134-136) as well as alternative apoptosis pathway involving TNF- α receptor-associated death domain (TRADD), which cascades additional signaling molecules, including FADD, TRAF2 and RIP1 (137, 138). Collectively,

the cellular response to TNF- α , in fact, represents a balance between apoptotic responses and anti-apoptotic responses (111, Fig 4).

Signal transduction triggered by TNF- α also induces an increase in intracellular ROS by its direct toxic phenomena and its effects on mitochondrial function (139-142). TNF- α -induced ROS production involves the JNK and NF- κ B pathways (68, 122, 137) and influences a variety of downstream signaling events including activation of redox-sensitive kinases, alteration of intracellular calcium regulation, transcription factor activation and gene expression (143). TNF- α -induced ROS activate JNK, which in turn leads to more ROS production (137). The production of ROS by TNF- α at inflammatory sites causes DNA damage (144-150), which can further lead to TNF- α production either directly (150-153) or through activation of NF- κ B (154, 155). It is believed that TNF- α -induced ROS production plays an important role in the physiopathological cellular processes.

The roles of TNF- α in HSC function and leukemic transformation in general

HSC function is regulated by microenvironment directly through cell-cell interactions or indirectly through production of cytokines (156). Many cytokines and growth factors including TNF- α are known to regulate HSC survival, homing, and proliferation (157). TNF- α plays a pivotal role in directly regulating HSC proliferation or indirectly stimulation of growth factor production and up-regulation of cytokine receptors. While TNF- α induces proliferation of the more primitive subset of progenitors, it simultaneously induces a differentiation block downstream in response to hematopoietic stress and increased demand for mature blood cells (158). Furthermore, TNF- α can elicit either a stimulatory or an inhibitory effect on the *in vitro* growth of hematopoietic progenitors depending on its concentration and on the cytokines microenvironment (51).

TNF- α plays important role in the disease progression of hematopoietic malignancies. The overproduced pro-inflammatory cytokines and subsequent increased oxidative stress may account for profound physiologic changes, including the development of BMF and progression to leukemia (159). For example, diseases characterized by hematopoietic insufficiency, such as aplastic anemia (AA), are often found abnormal expression of pro-inflammatory cytokines (160). In fact, overproduction of TNF- α , known to be the late effector of the damage of the HSC compartment, has been implicated in pathological conditions related to anemia, MDS, and leukemia (2, 3, 51). Autocrine production of TNF- α plays a role in the cytotoxicity of depsiptide against a subset of leukemias (161). In addition, TNF- α induces upregulation of tumor suppressor, PTEN expression through NF- κ B activation in human leukemic cells (162). TNF- α receptor 1 expression on AML blasts predicts differentiation into leukemic dendritic cells (163). Additionally, CD154 (CD40 ligand, CD40L, gp139), a co-stimulatory molecule of the TNF family, is involved in lymphoid malignancies, suggesting some therapeutic implications of CD154 interactions in lymphopoiesis (164). Furthermore, the large majority of primary hematologic tumors are resistant to TRAIL-mediated apoptosis, due to the activation of anti-apoptotic signaling pathway (such as NF- κ B), overexpression of anti-apoptotic proteins (such as FLIP, Bcl-2, XIAP) or expression of TRAIL decoy receptors or reduced TRAIL-R1/-R2 expression (165). In this context, targeting TNF- α signaling pathway in the combination with chemotherapy or radiotherapy, or with proteasome or histone deacetylase or NF- κ B inhibitors, hold promise for future developments in treatment of hematologic malignancies (Fig 5).

The roles of TNF- α in HSC function and leukemic transformation in FA

Elevated levels of serum, plasma or intracellular TNF- α are often found in patients with FA. The increased secretion of TNF- α along with altered production of other growth factors and cytokines, including reduced expression of interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor, may change the BM microenvironment by leading to factor deprivation or constant exposure to mitogenic inhibitors (159). These expression alterations may cause deregulation of cellular homeostasis and have been considered as an important pathological factor involved in the abnormal hematopoiesis in FA (49-51, 98, 166, 167). Increasing evidence indicates that progressive BMF in children with FA is resulted from excessive apoptosis in the HSC compartment (1, 3). Indeed, studies using (*Fanca*^{-/-}, *Fancc*^{-/-}, and *Fancg*^{-/-} mouse models suggested that FA cells exhibit cytokine hypersensitivity apoptotic cues, including TNF- α (3, 47, 168) and contribute to pathogenesis of BMF in FA (169). Indeed, our previous study using *Fancc*^{-/-} murine hematopoietic stem and progenitor cells showed that TNF- α overproduction results in bone marrow hypoplasia, and long-term exposure of these cells to TNF- α induces clonal evolution that leads to myelogenous leukemia (170). Consistently, *ex vivo* culture of *Fancc*^{-/-} BM cells leads to an increase in cytogenetic abnormalities and myeloid malignancies that are associated with an acquired resistance to TNF- α , suggesting FA hematopoietic cells are prone to clonal hematopoiesis and malignancy (169, 170). A direct association of FANCD2 and NF- κ B consensus sequence (κ B1 site) in TNF- α promoter, which leads to the repression of its transcriptional activation, has been reported (171). This may explain, at least in part, a transcriptional mechanism for the elevated TNF- α level in FA patients and suggest that artificial modulation of TNF- α production could be a promising therapeutic approach to FA.

TNF- α -induced ROS is another pathological factor playing important roles in the disease progression of FA. Various *in vitro* studies and clinical observations suggest that FA patients are deficient in detoxifying superoxide anions (O₂⁻) released by TNF- α or IFN- γ -activated phagocytes (172). Although further studies on the role of FA proteins in the regulation of TNF- α -induced ROS production remains to be elucidated, it is likely FA proteins can disrupt downstream ROS signaling by protecting chromosomal DNA from ROS attack or facilitating the repair of oxidative DNA damage. Indeed, the persistent high levels of oxidative DNA damage was observed in HSC/progenitor cells from TNF- α -injected *Fancc*^{-/-} mice (172, 173), suggesting that loss of FA protein renders chromosomal DNA susceptible to ROS attack, thereby increasing oxidative DNA damage. Our previous study also suggested that major antioxidant defense genes are down-regulated in the BM cells of FA patients and that the down-regulation is selectively associated with increased oxidative DNA damage in the promoters of these antioxidant defense genes (174). In this context, FA proteins play critical role in protecting these major antioxidant defense genes from oxidative damage. 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 evidenced by long-term exposure of *Fancc*^{-/-} BM cells to TNF- α *in vitro* provoking the outgrowth of TNF- α -resistant cytogenetically abnormal clones which leads to acute myelogenous leukemia (AML) upon transplantation into congenic wild-type mice (170). More strikingly, the leukemic clones were TNF- α -resistant but retained their characteristic hypersensitivity to mitomycin C (MMC), and exhibited high levels of chromosomal instability. 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 (Fig 6).

Therapies targeting inflammatory cytokines in treatment of human diseases including hematologic diseases

Cytokines are a large family of small proteins that function in essentially all biological processes. Abnormalities in cytokines expression, their receptors, and the signaling pathways are involved in variety of diseases, such as immune and inflammatory disorders, and cancers (93). As cytokines are potent rate-limiting extracellular molecules, therapies targeting cytokines by greater surface of interaction of receptors and antibodies with their targets have gained variable successes. For example, IL-1 blockade in the form of IL-1 receptor antagonist (IL-1Ra) is effective and approved in Rheumatoid Arthritis (RA, 175); targeting CD30/CD30L have been applied in oncology and autoimmune and inflammatory diseases (176); three interferon β preparations (Betaseron, Avonex, and Rebif) have shown efficacy in the treatment of relapsing-remitting multiple sclerosis (177).

As a major mediator of molecular cascade leading to inflammation, TNF- α plays an important role in driving the pathological process. To date, the TNF signaling pathway appears to be a valuable target in the therapy of inflammation-associated diseases. Indeed, five TNF- α -blocking biologicals, including infliximab (also known as Remicade; Centocor ortho Biotech), etanercept (enbrel; Amgen/Pfizer), adalimumab (Humira; Abbott), golimumab (Simponi; Centocor ortho Biotech), Certolizumab pegol (Cimzia; uCB Celltech) have emerged as important agents in the treatment of many chronic inflammatory diseases, especially in cases refractory to conventional treatment modalities (95, 103, 178). TNF- α or the effects of TNF- α are also inhibited by a number of natural compounds, including curcumin (a compound present in turmeric), and catechins (in green tea). In addition, activation of cannabinoid CB1 or CB2 receptors by cannabis or *Echinacea purpurea*, which can be isolated from flowering plants, seems to have anti-inflammatory properties through TNF- α inhibition (179). By their ability to interfere with inflammatory processes at multiple levels, these TNF- α blockers have become invaluable tools to inhibit the inflammation-induced damage and allow recovery of the affected tissues. So far, the safety and tolerance of anti-TNF- α therapy is well established (180). Specifically, the first TNF- α blocker used in inflammatory bowel disease has been infliximab, a monoclonal chimeric IgG1 anti-TNF neutralizing antibody that is effective in adult and pediatric patients with active, luminal and perianal Crohn Disease (181, 182), and adult patients with active ulcerative colitis (183). In the context of FA, the safety and efficacy of anti-TNF- α therapy using etanercept, a recombinant protein that fuses the soluble TNF receptor 2 (TNFR2, the receptor that binds to TNF- α) to the constant end of human IgG1 antibody, has been tested (184). Although further studies to improve the clinical outcome are required, etanercept shows effect in BMF treatment in children with FA through neutralizing TNF- α (185).

However, anti-TNF- α therapy also has some drawbacks, including increased risk of infection and malignancy, and other reactions (185). Moreover, significant hematological disorders with serious complications, and in particular, profound neutropenia have been reported in patients receiving anti-TNF- α therapy (186, 187). Some of these effects are caused by the undesirable abrogation of beneficial TNF- α signaling. It is also striking that many of the mechanisms by which TNF- α enhances cancer development, including promotion of angiogenesis, leukocyte infiltration, and stimulation of other cytokines and chemokines (188). In patients with advanced cancer, TNF- α antagonists are more likely to be active in combination with other treatments (189).

To take these cytokine-targeting therapies forward, more specific targeting of the pathological TNF-induced signaling without producing serious complications or even promoting cancer is urgently needed for broader applicability and improved safety. Specificity might be increased by inhibiting the soluble TNF/TNFR1 axis without affecting

the often beneficial transmembrane TNF/TNFR2 signaling. These may inhibit the pathological effects of TNF and reduces the side effects thereby providing new opportunities for the treatment of those diseases in which TNFR2 inhibition is detrimental (179). In addition, targeting tumor necrosis factor apoptosis ligand (TRAIL), a type II membrane-bound ligand expressed in a broad range of tissues and exhibited a high grade of homology with the cytotoxic Fas ligand, have shown some potential therapeutic potentials with the induction of TRAIL-mediated signaling destroyed malignant cells while sparing normal cells (190). Furthermore, combinatorial therapies using TRAIL with chemotherapy or radiotherapy, or with proteasome or histone deacetylase or NF- κ B inhibitors, hold promise for future developments in treatment of hematologic malignancies (163).

Summary

The pro-inflammatory cytokine, TNF- α has been considered as one important pathological factor involved in the abnormal hematopoiesis most commonly found in BMF diseases including FA, an excellent disease model for studying BMF and leukemogenesis. Although the molecular pathogenesis of FA remains to be elucidated, overproduction of TNF- α in FA most likely plays dual roles. It may act as both a death mediator and a leukemic promoter. Understanding the relationship between inflammation and FA disease progression provides a unique opportunity to mechanistically comprehend and potentially intervene in these physiologically important processes, and therefore, will yield valuable information on whether targeting the multi-step pathogenesis of TNF- α may be therapeutically useful in the treatment of BMF and the prevention of leukemia and other malignancies.

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FIG. 1. Estimated percentage of FA patients in FA complementation groups
Based on the data from references 24, 26,191,192.

FIG. 2. Multifunctionality of FA proteins

Eight FA proteins (FANCA, B, C, E, F, G, L and M) and 6 associated factors (FAAP20, FAAP24, FAAP100, HES1, MHF1 and MHF2) form a nuclear core complex, which acts as ubiquitin ligase. 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, FANCI, FANCN, FANCO and FANQ to damaged DNA and involved in DNA repair, cell-cycle control to repair ICL lesions and to maintain genome stability.

FIG. 3. Hematopoietic failure and abnormal apoptotic signaling in FA

Mutations in any of FA genes lead to enhanced apoptotic signaling therefore cause excessive HSPC apoptosis. Compensatory chronic proliferation along with the FA genomic instability provoke leukemogenesis and results in typical phenotype such as developmental abnormalities, bone marrow failure, and cancer in FA patients. BMF = bone marrow failure

FIG. 4. TNF- α signaling in inflammation and apoptosis

Binding of TNF- α to TNF receptor (TNFR) results in the recruitment of intracellular adapter proteins, such as TRADD (TNFR-associated death domain) and FADD (Fas-associated death domain). TRADD complex then recruits the adapter protein TRAF2 (TNFR-associated factor 2), whereas FADD stimulates the caspase cascade. NIK (NF- κ B-inducing kinase), RIP (receptor-interacting protein) and ASK1 (apoptosis signal-regulating kinase 1) are known downstream signaling molecules that interact with TRAF2, therefore leads to activate multiple signal transduction pathways, including the induction of cell cycle proteins, anti-apoptotic proteins, inflammatory cytokines and chemokines; and the induction of apoptosis through activation of caspases. Binding of FasL to FAS or TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) to TRAIL-R also result in cell death through FADD.

FIG. 5. Role of TNF- α in hematopoietic diseases

Under physiological condition, TNF- α regulates hematopoietic stem cell (HSCs) function by directly promoting HSC proliferation or indirectly stimulating growth factor secretion/upregulating cytokine receptor expression. However, in the pathological circumstance, overproduced TNF- α results in oxidative stress, overactivated NF- κ B and expression changes in other tumor suppressor protein/anti-apoptotic molecules, therefore leads to either cell death or leukemia evolution.

FIG. 6. The pro-inflammatory cytokine TNF- α and its potential role in FA pathophysiology
 FA deficiency results in overproduction of TNF- α . Elevated level of TNF- α leads to accumulation of inflammatory ROS and deregulated stress kinases (p38 and JNK) activation in FA marrow cells, therefore provoke premature apoptosis of marrow cells as well as clonal proliferation, eventually which lead to BMF, MDS or AML in FA patients. BMF=bone marrow failure

Table 1
COMPLEMENTATION GROUPS AND INTERACTION PROTEINS OF FANCONI ANEMIA

Subtype	Chromosome Location	Protein Products (kd)	Functions	Ref
A	16q24.3	163 (FANCA)	FA core complex	6
B	Xp22.31	95 (FAAP95)	FA core complex	13
C	9q22.3	63 (FANCC)	FA core complex	5
D1	13q12-13	380 (BRCA2)	RAD51 recruitment	11
D2	3p25.3	155,162 (FANCD2)	Involved in DNA damage repair	4
E	6p21-22	60 (FANCE)	FA core complex	9
F	11p15	42 (FANCF)	FA core complex	8
G	9p13	68 (FANCG/XRCC9)	FA core complex	7
I	15q25-16	140 (FANCI/KIAA1794)	Required for maintenance of chromosomal stability	10, 18
J	17q22-q24	140 (FANCI/BACH1/BRIP1)	5'→3' DNA helicase/ATPase	15
L	2p16.1	43(FANCL/PHF9/POG)	FA core complex, FAAP43 ubiquitin ligase	12
M	14q21.3	250 (FANCM)	FA core complex/ATPase/translocase	14
N	16p12.1	130 (FANCN/PALB2)	Regulation of BRCA2 location	16; 17
O	17q25.1	42 (FANCO/RAD51C)	Involved in HRR of DSB	19; 20; 21
P	16p13.3	200 (FANCP/SLX4)	Protect genome stability	22
Q	16p13.12	101 (FANCO/ERCC4/XPF)	Required for ICL repair	23
FAAP100	17q25.1	100	Required for D2 mono-Ub	36
FAAP24	19q13.11	24	Required for D2 mono-Ub	28
FAAP20	22q12	20	Required for D2 mono-Ub	34
HES1	3q28-q29	30	FA-associated factor	35
MHF1	1p26.22	16	FANCM-associated protein	33
MHF2	17q25.3	10	FANCM-associated protein	33