Review paper

FANCONI ANEMIA GENES AND REACTIVE OXYGEN SPECIES IN CANCER DEVELOPMENT

ABSTRACT

Fanconi Anemia (FA) **is** an autosomal recessive disease of childhood. However, the FA pathway is responsible for the development of leukemia and the other cancers. It has been also demonstrated that FA, an only human genomic instability syndrome is very sensitive to oxidative stress and ROS overproduction. In the present work, we consider major mechanisms of antioxidant protection in FA cells. We showed that there are two types of such mechanisms: the suppression of ROS overproduction by FA genes through the activation of basic FA anemia proteins under the conditions of oxidative stress and the application of free radical scavengers able to react with iron-dependent ROS such as flavonoids rutin and quercetin. The last nontoxic compounds of vitamin P group might be recommended for the treatment of FA anemia patients. Then, we discussed the role of FA anemia proteins in cancer development.

Key words: Fanconi anemia, reactive oxygen species, antioxidants, rutin

Fanconi anemia (FA) is an autosomal recessive disease of childhood characterized by progressive pancytopenia, developmental abnormalities, bone marrow failure, and high disposition to leukemia and other cancers. It has been demonstrated that the FA pathway is an important way in the development of such deadly adult pathologies as breast and cervical cancer [1,2]. These findings sharply increase an interest to studying FA molecular mechanisms. The special interest is attracted to FA because FA is the only human genomic instability syndrome uniquely sensitive to oxidative

stress. Earlier, an importance of reactive oxygen species (ROS) overproduction i.e. oxidative stress has been demonstrated. Joenje *et al*. has shown that erythrocyte superoxide dismutase (SOD) decreased in FA [3]. These authors also proposed that the formation of chromosomal aberrations in FA anemia might be explained by the genetic toxicity of oxygen [4] underlining an important role of oxidative stress in FA development.

EARLIER STUDIES

In 1960, medicine doctors from Russian Institute of Hematology for Children (Moscow) asked us as scientists working in the field of free radical-associated diseases to study the possible application of antioxidants for the treatment of FA patients. We hoped that antioxidants and free radical scavengers could act positively on behalf of FA patients. To study the effects of antioxidants on FA cells, ROS production especially superoxide in these cells was measured. Major results of this *in vitro* study have been summarized as follows [5,6]: ROS formation was measured by lucigenin- and luminol-dependent chemiluminescence (CL) in non-stimulated and stimulated blood and bone marrow leukocytes of FA patients. It was found that the FA blood leukocytes produced the enhanced level of luminol CL in comparison with leukocytes from normal donors. Lucigenin CL was also higher in FA blood leukocytes, although its effect was not very significant. Similar but smaller effects were observed for bone marrow FA leukocytes. Earlier, we have already demonstrated that flavonoids rutin and its aglycone quercetin possess both free radical scavenging and chelating properties. We had shown that both flavonoids were the most effective inhibitors of iron-dependent microsomal lipid peroxidation comparing to lipid peroxidation initiated by carbon tetrachloride [7]. (This work has been cited more than 800 times at present.)

This work had a good response; at present, it has been cited more than 800 times).

We proposed that ROS formation in FA leukocytes was the iron-catalyzed process because it was characterized by the enhanced luminol CL typical for the formation of iron-dependent ROS.

This proposal was supported by studying the effects of various free radical inhibitors on luminol CL of FA leukocytes [5]: SOD inhibited only slightly luminol CL, while mannitol (the typical hydroxyl radical scavenger) and rutin were the strongest inhibitors. Later on, it was also demonstrated that rutin was a strong inhibitor of iron-dependent lipid peroxidation of rat brain homogenates [8] and the free radical formation in iron-overloaded rats [9]. Moreover, it was found that rutin efficiently inhibited free radical formation and oxyhemoglobin oxidation in β-thalassemic red blood cells [10]. These findings reassured us to apply the non-toxic flavonoid rutin for the treatment of FA patients.

The results of rutin therapy for a small group of FA patients were encouraging. Rutin was permitted for application to FA patients under the supervision of our co-authors medical doctors. No toxic side effects were observed." Rutin (vitamin P) was permitted for application to patients (FA patients were under the supervision of medical doctors). No toxic side effects were observed in patients. ROS production by FA leukocytes sharply decreased and patients' health was essentially improved [6]. Unfortunately, there was no possibility to continue our study despite the numerous requests of medical doctors.

THE NATURE OF REACTIVE OXYGEN SPECIES IN FA CELLS

Our findings demonstrated that ROS formation in FA cells was connected with the iron species. In 1992, in accord with the views of that time we proposed that the major damage produced by ROS in cells is the direct interaction of ROS with biomolecules. As the superoxide, a major precursor of ROS in cells is unreactive in free radical processes [11,12], we proposed that the reactive iron-contained species could be responsible for free radical damage in FA cells. It was suggested that the iron-catalyzed superoxide conversion into reactive hydroxyl radicals (the Fenton reaction) was responsible for their formation in FA cells. Indeed, there are some evidences of hypersensitivity of FA cells in the presence of oxygen and iron [13]. Although reactive hydroxyl radicals are probably

unable to achieve the target biomolecules, they can be formed during the contacts of superoxide with DNA “iron fingers” [14].

A major conclusion from our previous work was that FA characterized by the enhanced production of reactive iron-dependent species, which might be the source of fatal disorders in this hereditary disease. At present, many authors agreed that FA cells exist under the conditions of ROS overloading. Thus, Hadjur *et al*. concluded that the abnormality of FA cells depended on ROS overproduction [15]. Du *et al.* pointed out that FA is only human genomic instability syndrome, which was uniquely sensitive to oxidative stress [16]. Therefore, there is no doubt about importance of ROS in Fanconi anemia. However, the damaging mechanisms of ROS activity remain to be investigated.

THE FA GENETIC PATHWAY

The most important discovery in FA molecular mechanisms was the identification of Fanconi anemia genes responsible for synthesis of special FA proteins FANC (among them FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL and FANCM). It was found that eight major FA proteins FANCA, B, C, E, F, G, L, and M) formed a nuclear complex [16]. In response to DNA damage or DNA replication stress FA complex monoubiquitinate into the two FA proteins FANCD2 and FANCI, which then recruite the other downstream FA proteins including FANCD1 (which is also named the breast cancer protein BRCA2), FANCJ, and FANCN to enter nuclear loci containing the damaged DNA.

It has been shown that FA proteins play the critical role in the regulation of oxidative stress. Thus, deficiency in FA genes apparently affects mitochondrial ROS [17]. The redox-sensitive proteins FANCA and FANCF exist as monomers under non-oxidizing conditions but form a new nuclear complex through the intermolecular disulfide bonds in response to oxidative damage [18].

FANCA, FANCC, and FANCG participate in redox processes in mice with combined deficiencies of the genes encoding FANCC and Cu/Zn superoxide dismutase [15].

FA proteins function through the interaction with some enzymes. Saadatzadeh *et al*. showed that *Fancca*-/-cells were highly sensitive to oxidants (hydrogen peroxide) and underwent enhanced apoptosis [19]. Antioxidative compounds enhanced the survival of these cells. Thus, the redox-dependent ASK1 kinase was hyperactive in hydrogen peroxide-treated *Fancca*-/-cells. Another FA protein FANCG interacted with mitochondrial antioxidant enzyme peroxiredoxin-3 and cytochrome P450 2E1 (CYP2E1) [20]. This member of P450 superfamily responsible for ROS production and the activation of carcinogens. These findings suggested that the interaction of FANCG with CYP2E1 might increase DNA oxidation.

It is known that the tumor protein p53 plays an important role in the prevention of cancer. Furthermore, some findings demonstrate that p53 deficiency might enhance cancer development in FA patients and FA mice. Therefore, it was suggested that FA proteins could interact with p53 under the conditions of oxidative stress. Freie *et al*. showed that ionizing radiation (IR) induced p53 elevated levels in cells from *Fancc* mutant mice and that the inactivation of p53 enhanced TNF-induced apoptosis in myeloid cells from *Fancc*-/-mice [21]. Rani *et al*. demonstrated that FA proteins protected cells from the stress-induced proliferative arrest and tumor evolution through the modulation of signaling pathways which connected FA proteins to p53 [22]. Du *et al*. proposed that two major FA proteins FANCA and FANCC might coordinate with p53 in the regulation of oxidative stress response [16].

It has been shown that the *Foxo3a* gene might be involved in ROS formation [23]. For example, Tothova *et al*. showed that ROS levels increased in Foxo-deficient hematopoietic stem cells that correlated with the changes in expression of ROS-regulated genes [24]. Correspondingly, *Foxo3a* plays an important role in ROS regulation in FA cells. Thus, Li *et al*. showed that the

122 treatment of FA cells with hydrogen peroxide stimulated the formation of a complex between
123 FANCD2 and FOXO3a with subsequent monoubiquitination of FANCD2 [25]. It was suggested
124 that the overexpression of *Foxo3a* reduced abnormal accumulation of ROS, enhanced cellular
125 resistance to oxidative stress, and increased antioxidant gene expression only in cells corrected by a
126 FANCD2 protein capable of interacting with FOXO3a.

127 It has been shown that ROS accelerated the development of hydrocephalus (abnormal
128 accumulation of cerebrospinal fluid in the brain) in mouse model of FA [26]. The deletion of
129 *Foxo3a* in FA mice increased the ROS accumulation and subsequently deregulated mitosis and
130 ultimately apoptosis in the neural stem and progenitor cells NSPCs, leading to hydrocephalus
131 development. N-acetylcysteine (NAC) and quercetin reduced ROS formation in both neural stem
132 cell NSCs and in the brain of double knockout (DKO) offspring mice. Importantly, quercetin
133 greatly diminished the synthetic lethality imposed by DKO and completely eliminated
134 hydrocephalus in DKO mice.

135

136 **MECHANISMS OF ANTIOXIDANT PROTECTION IN FANCONI ANEMIA**

137 **ANTIOXIDANTS AND FREE RADICAL SCAVENGERS**

138 As it was aforementioned, it has been previously shown that oxidative stress (ROS overproduction)
139 in FA cells might be diminished by the application of flavonoid rutin, an antioxidant and free radical
140 scavenger [5,6]. It was suggested that rutin might be able to scavenge reactive iron-depend ROS.
141 Rutin is a nontoxic compound permitted for the treatment of patients. Therefore, medical doctors
142 were allowed to use rutin for the treatment of FA patients. They observed certain positive effects in
143 patients. (It should be mentioned that several FA families asked us to prolong the treatment of FA
144 children but we were unable to continue our work).

Now we were encouraged to find out that in subsequent studies flavonoids were used for the suppression of oxidative stress in FA. It has been shown that quercetin (the aglycone of rutin) turned out to be an effective antioxidant in FA cells. Antioxidant effect of quercetin was also shown in FA animals. Li *et al.* found that mice deficient for the *Fanca* or *Fancc* genes were diabetes-prone when fed with a high-fat diet [27]. Treatment of FA mice with quercetin diminished diabetes and obesity. It was already demonstrated that quercetin reduced ROS formation and eliminated hydrocephalus in double knockout mice [26]. Ponte *et al.* proposed that the cocktail of antioxidants lipoic acid and NAC might be applied as a prophylactic approach to delay progressive clinical symptoms in FA patients [28].

ANTIOXIDANT EFFECTS OF FA GENES

In 2001, Hadjur *et al.* showed that encoding *Fancc* and Cu/Zn superoxide dismutase genes might be useful for the treatment of defective hematopoiesis and hepatic steatosis in mice [13]. These findings suggested an important role of FA genes in protection of FA cells from oxidative stress. In subsequent work, it was confirmed that FA genes were able to suppress ROS overproduction. Du *et al.* showed that major antioxidant defense genes were downregulated in FA patients due to the increased oxidative DNA damage in the promoters of antioxidant genes [29]. They showed that FA proteins together with the chromatin-remodeling factor BRG1 protected the promoters of antioxidant defense genes. Oxidative stress activated FA pathway through monoubiquitination of FANCD2. After this, FANCA or FANCD2 proteins formed the ternary complex with BRG1 at the promoters of antioxidant genes. It has been suggested that this complex played essential role in the protection of promoters from ROS damage. As it has been mentioned, ROS influenced the

development of hydrocephalus in mouse model of FA [26]. Combined deficiency of two FA genes *Fancc* and *Fancd2* led to the inactivation of *Foxo3a* gene, the enhancement of ROS level, and apoptosis of neural stem and progenitor cells. Antioxidants quercetin and NAC reduced ROS formation in the brain of mice, while quercetin completely suppressed hydrocephalus. Mukhopadhyay *et al.* identified the FA group G (FANCG) protein in mitochondria, which interacted with the mitochondrial peroxidase peroxiredoxin-3 (PRDX3) [30]. The formation of this complex prevented the destruction of PRDX3 peroxidase and diminished ROS formation.

DISCUSSION

Fanconi anemia is a rare chromosome instability syndrome, which is characterized by aplastic anemia in childhood. It is known that FA possesses high disposition to leukemia and other cancers. Now, there are new findings, which make us reconsider more carefully the connection between FA and cancer. Some new contemporary data demonstrate that the FA pathway is an important route for the development of such deadly adult pathologies as breast and cervical cancer. Thus, D'Andrea pointed out that abnormalities in the FA pathway are found not only in childhood Fanconi anemia but also in sporadic cancers in adults [1]. Narayan *et al.* investigated the molecular genetic basis and the role of (FA)-BRCA pathway in cervical cancer (CC) [2]. These authors showed that the *fancf* gene was disrupted by either the promoter hypermethylation or the deregulated gene expression in cervical cancer. It was also found that gene inactivation in the FA-BRCA pathway by epigenetic alterations showed its major role in the development of cervical cancer. Chen *et al.* demonstrated that the regulation of FANCD2 by m-TOR pathway led to the resistance of cancer cells to DNA double-strand breaks [31]. It is not surprising that among thirteen FA genes one gene is the well-known breast cancer susceptibility gene *brca2*.

In normal cells, the FA pathway is not constitutively active but it activates by DNA damage. As

DNA damage depends on oxidative stress, ROS overproduction should be an important factor of FA pathway activation. Mechanism of response of FA genes to DNA damage is not fully established, but it has been shown that FA genes exist as nuclear complex before activation. In response to the DNA damage or DNA replication stress FA complex monoubiquitinate into two FA proteins FANCD2 and FANCI, which then recruite the other downstream FA proteins including the breast cancer protein BRCA2, FANCJ, and FANCN to enter nuclear loci containing the damaged DNA. Then FANCA and FANCF form a new complex through the intermolecular disulfide bonds after exposure to oxidative stress [16]. Thus, FA genes accomplish important defense function, which is confirmed by high sensitivity of *Fanc*-/- cells to ROS.

We now can visualize the complete defense scheme of ROS inhibition in FA cells. It has been shown that the oxidative stress (ROS overproduction) initiates the activation of FA genes, which remain inactive under unstressed conditions. After activation, FANCA and FANCF proteins form a complex through the intermolecular disulfide bonds, and we might propose that the disulfide complex formed by the reaction of superoxide with these proteins:

$$\text{FANCA-SH} + \text{FANCF-SH} + O_2^{-\cdot} \rightarrow \text{FANCA-SS-FANCF} + H_2O_2$$

This proposal supported by the effect of SOD on the redox processes of FANCA, FANCC, and FANCG in mice [13].

Another mode of antioxidant activity of FA proteins is the protection of antioxidant gene promoters from ROS overproduction. Du *et al.* pointed out that oxidative stress is an important pathogenic factor in leukemia-prone marrow diseases such as Fanconi anemia [29]. It has been proposed that the FA pathway plays a crucial role in protecting major antioxidant defense genes from oxidative damage. This protection probably accomplished in response to oxidative stress by the interaction with the chromatin-remodeling machinery. Indeed, it has been shown that the oxidative stress-induced activation of FA pathway (FANCD2 ubiquitination) required for the

formation of the FA-BRG1-promoter complex. This complex is essential for the protection of the antioxidant gene promoters from oxidative damage.

Thus, the activation of FA pathway under the conditions of oxidative stress led to cellular protection through various ways. Taking into account the above-mentioned consideration, these ways have been presented in Table 1.

Table 1

FA PATHWAYS OF CELLULAR PROTECTION

1. **Protection of antioxidant gene promoters**

FANCD2 ubiquitination
↓
FA-BRG1-promoter complex
↓
Protection of antioxidant gene promoters

2. Formation of the disulfide complex

FANCA + FANCF + $O_2^{\cdot-}$ → FANCA-SS-FANCF

3. Suppression of DNA double-strand breaks

FANCD2 → m-TOR pathway → DNA double-strand breaks

4. Suppression of ROS overproduction

Antioxidants (quercetin and NAC) → ROS↓ (diabetes and hydrocephalus in FA patients)

5. Enhancement of gene antioxidant activity

The interaction of genes with enzymes (Foxo3a, p50, p450)

CONCLUSIONS

(1) Direct interaction of FANCA and FANCF with ROS (superoxide) forms a complex through the intermolecular disulfide bonds.

(2) The regulation of FANCD2 by the m-TOR pathway might lead to the resistance of cells to DNA double-strand breaks as in cervical cancer.

(3) FANCD2 ubiquitination follows the formation of FA-BRG1-promoter complex capable of protection of antioxidant gene promoters.

(4) Antioxidant activity of FA genes has been enhanced by the interaction with various enzymes such as Foxo3a, p50, p450.

(5) Application of antioxidants and free radical scavengers (quercetin and NAC) decreases ROS overproduction in such diseases as diabetes or hydrocephalus in FA patients.

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