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Review

Fanconi Anemia and Ubiquitination

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Abstract: Fanconi anemia (FA) is a rare recessive hereditary disease characterized clinically by congenital defects, progressive bone-marrow failure, and cancer predisposition. Cells from FA patients exhibit hypersensitivity to DNA cross-linking agents, such as mitomycin C (MMC). To date, at least 12 FA genes have been found deleted or mutated in FA cells, and 10 FA gene products form a core complex involved in FA/BRCA2 DNA repair pathway–FA pathway. The ubiquitin E3 ligase FANCL, an important factor of FA core complex, co-functions with a new ubiquitin conjugating enzyme UBE2T to catalyze the monoubiquitination of FANCD2. FANCD2-Ub binds BRCA2 to form a new complex located in chromatin foci and then take part in DNA repair process. The deubiquitylating enzyme USP1 removes the mono-ubiquitin from FANCD2-Ub following completion of the repair process, then restores the blocked cell cycle to normal order by shutting off the FA pathway. In a word, the FANCD2 activity adjusted exquisitely by ubiquitination and/or deubiquitination in vivo may co-regulate the FA pathway involving in variant DNA repair pathway.

Keywords: Fanconi anemia; FA pathway; ubiquitination; DNA repair

Fanconi anemia (FA) is a rare autosomal or X-linked recessive hereditary disorder characterized by congenital abnormality, progressive bone marrow failure, and cancer susceptibility[1−3]. Cells from FA patients exhibit spontaneous chromosomal instability and hypersensitivity to chromosomal breakage caused by cross-linking agents, such as mitomycin C (MMC) [4], diepoxybutane (DEB) [5], and cisplatin (CDDP) [6], a feature that is proposed as a diagnostic test for FA. Studies on this disease have revealed that FA is a kind of multi-gene related hereditary disorder and certain involved genes being found depleted or mutated in the lymphocyte of these patients. The depletion or mutation of these genes cause DNA repair defection and produce the typical phenotype of FA [7]. These gene products interact functionally with each other *in vivo* and form a common DNA repair pathway□FA pathway, which mediates DNA damage repair and maintains the chromosomal stabilization[8,9]. Ubiquitination is a universal manner of protein modification in organisms and plays important roles in many pathways [10, 11]. Recent studies have found that certain proteins in FA pathway are modified with ubiquitin and certain present ubiquitin enzyme activity, which play a key role in this pathway. Recent progresses on the function of ubiquitination in FA pathway were discussed in this review, particularly the complexity of regulatory mechanisms of ubiquitination and deubiquitination.

1 Fanconi Anemia and FA Pathway

Fanconi Anemia (FA), also named congenital aplastic anemia, was first diagnosed and reported in

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three siblings who exhibited congenital defects, aplastic anemia, and bone marrow pimelosis in 1927 and until now at least 1,000 cases have been reported [12]. FA is relatively rare compared with other hematological system diseases. The prevalence of FA is estimated to be only 1–5 per million and the children carrier frequency is estimated to be 1 in 360,000 [13, 14]. This disease has no race and region diversity, although patients can be found in one family. The typical clinical symptom of FA patients is progressive bone marrow failure and most children are characterized by complete blood cells reduction and aplastic anemia. The pre-hematopoietic cells maturation and differentiation defect caused by DNA damage, which is possibly the main mechanism of haematogenesis failure, will result in the death of FA patients with malignant hematopathy and malignant tumor syndrome [15]. Until now, there have been no other therapeutic options except for stem cell transplantation [16].

Hypersensitivity to DNA cross-linking agents, such as mitomycin C (MMC), has been exploited to assess genetic heterogeneity in FA patients through complementation analysis by correcting the cell MMC sensitivity. To date, at least 12 complementation groups of FA have been identified (A, B, C, D1/BRCA2, D2, E, F, G, I, J, L, and M) [3, 7, 17–25], 11 FA genes being cloned, and 10 FA gene products being confirmed to take part in a common cellular pathway□FA pathway [1, 26]. Any protein in this pathway if deleted or mutated will lead to a clinical symptom and FA cell phenotype.

FANCD2, a newly found member of FA family, can be monoubiquitinated at K561 by certain ubiquitin enzymes and play a key role in FA pathway [22, 26]. According to FANCD2 monoubiquitination, the FA pathway has been divided into two stages [27]: In the first stage, the FA complementation group proteins including A, B, C, E, F, G, M, and the E3 ligase FANCL interact with each other and form a multisubunit complex known as FA-core complex Ⅰ after being treated with DNA damage factors. The FA-core complex Ⅰ migrate from the cytoplasm into the nucleus and catalyze FANCD2 monoubiquitination using its E3 ligase activity. Given that the loss of any of the eight subunits disrupts the complex normal assemble and prevents nuclear foci formation, it is still unclear whether ubiquitination is the only function of complex Ⅰ. Recently, a component of FA core complex Ⅰ, FANCM had been identified as the ATP dependent helicase and DNA translocase. In chicken cells, Mosedale found that when the FA core complex is combined with the cross-linked DNA in the chromatin, it indicates that the core complex plays a key role not only in catalyzing ubiquitination, but also in sensing and detecting DNA cross-linking damages[25, 28]. At the second stage, the monoubiquitinated FANCD2 together with FANCD1/BRCA2 makes up for the second complex, called FA complex Ⅱ, to mediate the DNA homologous recombination (HR) repair and/or other repairs by recruiting different DNA-repair proteins including the breast and ovarian cancer suppressor protein 1 (BRCA1), RAD51, and proliferating cell nuclear antigen protein (PCNA) to localize in nuclear foci. Three respective groups had recently reported that FANCJ was the BRCA1-interacting DNA helicase and FA core complex formation and monoubiquitination of FANCD2 are normal in *FANCJ* deleted or mutated cells, suggesting that FANCJ acts downstream of FANCD2 in the FA pathway and may be one of the members of FA complex Ⅱ [29–31].

FANCD2 monoubiquitination is the key event connecting stage Ⅰ and stage Ⅱ and the key process of FA pathway involved in DNA repair. Any effects on disturbing FANCD2 monoubiquitination or FA complex Ⅱ formation will lead to the defect of DNA repair.

2 FANCL Is the Ubiquitin Ligase in FA Pathway (FA–E3)

Since the cloning and identification of *FANCD2* in 2001, the gene product has been found in two