Heightened DNA damage response impairs hematopoiesis in Fanconi anemia

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Since its first description by Guido Fanconi in 1927,[1] Fanconi anemia (FA) has become one of the best characterized inherited bone marrow failure syndromes.[2-3] Numerous studies over the years have documented its clinical and biological features. It is recognized as being clinically heterogeneous and patients can have a wide range of developmental abnormalities. Many patients develop progressive bone marrow failure and there is a high predisposition to cancer. FA cells characteristically display a high frequency of spontaneous chromosomal breakage and hypersensitivity to DNA cross-linking agents[4] such as mitomycin C and diepoxybutane. This *FA cell hallmark* has facilitated diagnosis in the clinic and scientific advances in the laboratory.

FA is now known to be caused by biallelic mutations in one of 15 genes, the products of which interact in the *FA/BRCA pathway* in response to cellular stress and DNA damage to maintain genomic stability.[5] FA can, therefore, be regarded as an inherited DNA repair disorder. Despite these advances, the precise pathophysiology of the bone marrow failure in FA has remained elusive.

A recent international study by Ceccaldi and colleagues[6] now provides new insights into the pathogenesis of bone marrow failure in FA. They analyzed bone marrow samples from a large number of FA patients and controls. By undertaking quantitative and qualitative assessment of hematopoietic function they established that FA patients have a significant impairment of hematopoiesis that begins early and is progressive throughout life. In view of the DNA repair defect that has been observed in FA cells, together with the observation that p53 plays an important role in the response to DNA damage, Ceccaldi and colleagues[6] decided to analyze p53. They found strong basal and mitomycin C-induced p53 expression in primary cells from FA patients and in bone marrow cells of FA mouse (*Fancg*$^{-/-}$ and *Fancd2*$^{-/-}$) models. To confirm that the p53 induction was directly related to the FA/BRCA pathway defect they knocked down FANCD2 (a key target of the FA pathway) in a human cell line (293T cells) and observed that p53, as well as p21, was induced in these cells. To mimic the response of FA cells to endogenous DNA damage, and to determine the link to the progressive cell impairment observed in patients, they exposed EBV-immortalized FA cells to interstrand cross-linking agents and studied the cellular response at several time points. These EBV-immortalized FA cells displayed the classic excess G2 arrest at 24 h; however, at later time points the G2 arrest resolved and the cells shifted to G0/G1 cell cycle arrest. Interestingly, in p53-silenced FA cells, p21 induction and G0/G1 accumulation were less marked. Complementary studies in FA mice showed that p53 impairs the hematopoietic and mitotic potential of *Fanc*-deficient murine hematopoietic stem and progenitor cells. Additional studies (including on bone marrow from young FA patients and fetal liver of FA patients) demonstrated constitutive activation of p53 and p21 as well as G0/G1 cell cycle arrest in hematopoietic progenitor cells *in vivo*.

In conclusion, this study identifies an exacerbated p53/p21 DNA damage response as an important factor in the progressive impairment of hematopoiesis in FA; this begins prenatally and typically results in overt bone marrow failure in childhood. These new observations have important implications for the management of FA patients.

References

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