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Commentary

Multifunctional Fanconi proteins, inflammation and the Fanconi phenotype

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The products of the 19 Fanconi anemia (FA) genes play important and often biochemically collaborative roles in the repair of DNA interstrand crosslinks and regulation of cellular responses to the genotoxic stress imposed by cellular replication. In response to exogenous and endogenous (e.g. aldehydes) cross-linking agents, large multimeric nuclear FA "core complex" proteins facilitate the monoubiquitinylation of FANCD2 and FANCI, post-translational changes required for resolution of stalled replication forks, removal of interstrand cross-links and promotion of homologous recombination. Other members of the FA family of proteins function "downstream" of FANCD2 and FANCI and also participate in other nuclear functions (e.g. promoting telomere maintenance) (Kim et al., 2013). Biallelelic inactivation of these genes results in the rare inherited disease, Fanconi anemia, a disorder characterized by various developmental anomalies, bone marrow failure, leukemia, and epithelial malignancies (Bogliolo and Surralles, 2015). In some cases (FANCD1, FANCJ, FANCM, FANCN, FANCO and FANCS) monoallelic inactivation predisposes individuals to breast and ovarian cancer. While the prevalence of Fanconi anemia is about 1–9 per million, the constellation of clinical findings and their apparently disparate pathophysiologies has permitted studies on this disease to inform the broad fields of hematopoiesis, development, and carcinogenesis. It is now clear that at least some of these proteins function to protect stem cells from damage imposed on them by inflammatory and oxidative stress and do so in ways that do not necessarily rely upon unique canonical nuclear functions (Sumpter et al., 2016).

FA hematopoietic stem and progenitor cells (HSPC) exhibit unique sensitivities to both oxidative stress and inflammatory cytokines (Haneline et al., 1998). Moreover, innate immune cells bearing FA mutations exhibit abnormal mitophagic and virophagic responses as well as abnormally robust responses to toll-like receptor activation all of which can result in the overproduction of precisely those cytokines to which FA HSPC are hypersensitive (Garbati et al., 2016; Sumpter et al., 2016). Murine models of FA did not initially demonstrate key features of the FA phenotype (marrow failure, spontaneous leukemia, and cancer) but once inflammatory stress was applied the phenotype of progressive and fatal bone marrow failure was provoked (Walter et al., 2015), and it became clear that the murine models will be enormously helpful in sorting out the heterogeneous features of the disease by linking them with particular functions of these multifunctional proteins.

Might nuclear functions of FA proteins contribute to extranuclear inflammatory processes? The work of Brégnard et al. in this issue of *EBioMedicine* (Brégnard et al., 2016) supports that notion. Because the FA phenotype involves both cytokine overproduction and a deficient DNA damage response, they reasoned that the damage response might result in excess nucleic acid loads in cellular compartments that permit recognition by proteins designed to recognize pathogen associated molecular patterns. Indeed, they found that loss of the FANCP or FANCD2 genes results in the accumulation of cytoplasmic DNA which then triggers the cGAS-STING pathway and interferon production. Interestingly, this phenomenon has been likewise reported in the inherited disease Ataxia Telangiectasia, a cancer predisposition syndrome characterized by heterogeneous inflammatory manifestations. In cells from patients and from $Atm^{-/-}$ mice, unrepaired DNA lesions induce type I interferons (IFNs). Activation of the type I interferon system involved accumulation of cytoplasmic DNA where it activates the STING-mediated pathway, and activates expression of RIG-I-like receptors and Toll-like receptors (Hartlova et al., 2015). Both of these studies provide a potential mechanistic link between the inflammatory phenotype of AT and FA patients and the DNA damage phenotype. It should be mentioned that the inflammatory process incited in these studies by cytoplasmic DNA can play an important role in cancer progression (Krelin et al., 2007).

Brégnard et al. also discovered that some of the cytoplasmic DNA resulted from enhanced LINE-1 retrotransposition, a phenomenon others have associated with inflammatory diseases (Volkman and Stetson, 2014). That inhibitors of reverse transcription diminished cytokine production in the FA cells is compatible with the view that these FA proteins function in some way to constrain endogenous reverse transcriptase activities, preventing accumulation of cytoplasmic nucleic acids thereby suppressing the activation of cytokine gene transcription. Therefore, this new pathway by which the inflammatory response participates in the Fanconi anemia phenotype may hold some therapeutic potential. While more work is required on the precise mechanisms by which FA proteins might constrain cytoplasmic accumulation of endogenous nucleic acids, and while the downsides of reverse transcriptase inhibitors need to be investigated carefully in primary FA cells, the possibility that such agents might inhibit aberrant constitutive activation of the inflammatory response is intriguing and, given the important role this response plays in disease pathogenesis, the use of such agents clinically may have some potential. Because inflammation can result in DNA damage and vice versa, the use of such inhibitors in preclinical models might also permit investigators in the field to sort out the order of events in Fanconi anemia pathogenesis.

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Conflicts of interest

None.

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