


In Vitro Hypersensitivity to Oxygen of Fanconi Anemia (FA) Cells Is Linked to Ex Vivo Evidence for Oxidative Stress in FA Homozygotes and Heterozygotes

To the Editor:

The report by Whitney et al1 provides a brief mention of a phenotypic feature of Fanconi anemia (FA) cells related to oxygen hypersensitivity. However, one2 of the two citations used may lead the reader to overlook the in vivo relevance of this phenomenon, as the investigators attributed a ‘secondary’ role for oxygen sensitivity in FA cells. A previous report by Liu et al3 devoted a section to the abnormalities of oxygen metabolism in FA cells; however, no clear distinction was made between the results of in vitro studies versus the ex vivo data as reported by Korkina et al.4 Therefore, it is worthwhile to consider the subject of oxidative stress in FA with a reappraisal of the consistency between in vitro and ex vivo evidence.

An involvement of oxidative stress in FA has long been suspected, starting from the pioneering study by Norden, who reported an improvement of chromosomal instability following addition of catalase or Cu,Zn superoxide dismutase (Cu,ZnSOD) to cell cultures. Further studies pointed to analogous results by exposing FA cells to low-molecular-weight antioxidants or to a decreased oxygen level.5-9 Schindler and Hoehn10 showed a G2 cell-cycle delay in FA cells, which was counteracted by culturing cells in 5% O₂, and a recent report from the same group suggested a major role for free iron, and not for superoxide- or H₂O₂-forming systems in inducing G2 arrest in FA cells.11 Overall, the information available from in vitro studies suggested excess O₂ (Fe²⁺) sensitivity of FA cells, although some studies led to controversial conclusions, eg, reporting the lack of oxygen effect following viral transfection2 or on FAC gene expression.12 However, these data may have been biased by virus-induced cell immortalization.13

A series of ex vivo studies provided evidence that an abnormality in O₂ metabolism is not merely a cell culture artifact. Rumyantsev et al13 first reported that freshly drawn white blood cells (WBCs) from FA patients and from their parents produced excess reactive oxygen species (ROS) as detected by luminol-dependent chemiluminescence (LDCL). These data were confirmed on an expanded set of Italian FA families,4 mostly belonging to the FA(A) group.14 Subsequent studies corroborated those early reports:

1. Circulating WBCs from FA(A) patients displayed excess levels of the oxidative DNA damage, 8-hydroxy-2′-deoxyguanosine (8OHdG), correlated with LDCL activity as well as with chromosomal instability.15 These data were consistent with the observation of excess 8OHdG formation in FA(A) cell lines submitted to H₂O₂ stress.16 Thus, both ex vivo and in vitro evidence pointed to a direct link between ROS formation, oxidative DNA damage, and chromosomal breakages in FA.

2. Clastogenic factor (CF) was detected in plasma from FA(A) patients, and their siblings and parents.17 CF was obtained by plasma ultrafiltration, increasing the frequencies of chromosomal breakages in cells from healthy donors. The loss of clastogenic activity by SOD or low-molecular-weight scavengers suggested that plasma CF in FA homozygotes and heterozygotes could be related to the occurrence of in vivo oxidative stress. (3) Tumor necrosis factor-α (TNF-α) was found to be significantly increased in FA patients versus control plasma.18 Because TNF-α is a recognized effector of ROS release from phagocytes, its elevated levels may be associated with phagocyte activation. Which relationship, if any, exists between TNF-α and CF is a question deserving further investigation. However, the present data suggest that FA patients have a ‘prooxidant plasma,’ possibly arising from activated phagocytes.

Lastly, the observation of erythropagocytosis in bone marrow from early stage FA patients19 can be viewed as an in vivo condition consistent with a chronic activation of phagocytes.

One limitation in the above data is that studies have been conducted so far either on FA(A) cells2,14-16 or plasma,17 or on cells with unknown FA gene defects.19,20 Therefore, further ex vivo studies are required to ascertain any differences in oxidative activity as related to the other FA subtypes.

Notwithstanding the above limitation, the available evidence points to oxidative stress as a major phenotypic hallmark in FA that cannot be overlooked in FA clinical history. The major role for neutrophils in ROS formation, their enhanced depletion in FA progression, as well as the multiple cellular interactions of neutrophils (with, eg, platelets, endothelium, and chondrocytes), altogether make the neutrophil a prime candidate as the affected cell in FA. Ongoing investigations on the roles for FA neutrophils are expected to provide relevant information on the pathogenesis of this disorder.

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Platelet Antibody Testing in Idiopathic Thrombocytopenic Purpura

To the Editor:

Although it has been accepted for decades that most cases of idiopathic thrombocytopenic purpura (ITP) are caused by autoantibodies against platelets, the clinical utility of serologic testing in ITP never has been established. A recent report by Brighton et al analyzed predictive characteristics of direct and indirect tests for platelet-associated IgG (PAIgG) and an antigen capture test (MAIPA) designed to detect autoantibodies specific for platelet glycoproteins IIb/IIIa or Ib/IX. It was concluded that the MAIPA was better than tests for PAIgG in discriminating immune from nonimmune thrombocytopenia.

We recently analyzed the clinical utility in ITP of a commercially available serologic test for PAIgG, the Capture-P designed to detect autoantibodies specific for platelet glycoproteins IIb/IIIa or Ib/IX. It was concluded that the MAIPA was better than tests for PAIgG in discriminating immune from nonimmune thrombocytopenia.

We analyzed the predictive characteristics of the Capture-P for the clinical diagnosis of ITP and found that the MAIPA was better than tests for PAIgG in discriminating immune from nonimmune thrombocytopenia.

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