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Increased Activity of Glutathione S-Transferase and Fast Decay of Reduced Glutathione in Fanconi's Anemia Erythrocytes

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Fanconi's anemia (FA) is an autosomal recessive disease characterized by pancytopenia, abnormally high levels of chromosome aberrations and increased susceptibility to leukemia and cancer. The molecular defect of FA cells is still unknown. However, several evidences suggest that the primary defect is to be expected in a very specific DNA damage or repair mechanism [1]. On the other hand, the in vitro correction of FA chromosome breakage following the addition of superoxide dismutase (SOD) and catalase [2], the demonstration of decreased RBC SOD activity [3] and the oxygene dependence of chromosome breakage rates [4] point to a defect in the detoxification of active oxygen species.

To test the latter hypothesis, different red cells oxidation-reduction reactions have been investigated in 6 FA patients. Clinical, hematological and cytogenet-ic details have been reported elsewhere [5].

The activities of catalase, SOD, glutathione per-oxidase, glutathione reductase, the reduced glutathione (GSH) stability test, together with the amount of glucose utilized in the hexose monophosphate shunt, in the presence of increasing concentrations of methylene blue, were in the normal range.

These data, in agreement with previous evidences [1], do not support the idea that the free-radicals scavenging system is defective in FA cells.

Since GSH has been shown to protect DNA against many carcinogens and mutagens [6], we also have assayed the GSH content [7] and the activity of glutathione S-transferase [8], which is known to be responsible for the elimination of electrophilic foreign compounds, by conjugation with GSH.

No significant difference in the GSH levels has been found in the patients, as compared to 20 matched, unrelated controls. However, a fast GSH decay was consistently observed in FA erythrocytes during 36 h of incubation at 4°C.

Furthermore, the glutathione S-transferase activity was increased from 3.82 ± 0.67 U/g Hb (range 3.0–4.10) in controls to 6.04 ± 1.40 U/g Hb (range 4.68–8.10) in the patients. The activities of glyoxalase I and II were normal.

The present results, together with the evidence provided by the in vitro chromosome breakage enhancement by glutathione S-transferase substrates, like diepoxybutane, suggest that the increased activity of glutathione S-transferase could be responsible of the faster depletion of cellular GSH. This, in turn, would explain the increased susceptibility of FA cells to mutagens and carcinogens and also might be a critical parameter for endogenous chromosome breakage in these patients.

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