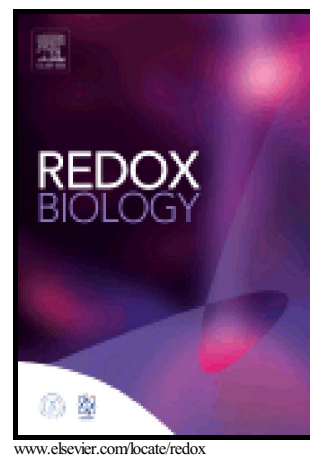


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Site-directed mutagenesis of cysteine residues alters oxidative stability of fetal hemoglobin^{*}

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Abstract

Redox active cysteine residues including β Cys93 are part of hemoglobin's "oxidation hotspot". Irreversible oxidation of β Cys93 ultimately leads to the collapse of the hemoglobin structure and release of heme. Human fetal hemoglobin (HbF), similarly to the adult hemoglobin (HbA), carries redox active γ Cys93 in the vicinity of the heme pocket. Site-directed mutagenesis has been used in this study to examine the impact of removal and/or addition of cysteine residues in HbF. The redox activities of the recombinant mutants were examined by determining the spontaneous autoxidation rate, the hydrogen peroxide induced ferric to ferryl oxidation rate, and irreversible oxidation of cysteine by quantitative mass spectrometry. We found that substitution of γ Cys93Ala resulted in oxidative instability characterized by increased oxidation rates. Moreover, the addition of a cysteine residue at α 19 on the exposed surface of the α -chain altered the regular electron transfer pathway within the protein by forming an alternative oxidative site. This may also create an accessible site for di-sulfide bonding between Hb subunits.

^{*} This article reflects the views of the authors and should not be construed to represent FDA's

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