The Physical Chemistry of Sickle Cell Anemia

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Sickle cell anemia is a deadly inherited disease. Every year, about 500,000 children are born with this disease, mostly in the poorest countries of equatorial Africa and the inland regions of India. The sickle cell gene leads to the expression of a mutant hemoglobin, HbS, which induces two main pathological sequences: (i) HbS forms polymers which stretch and rigidify the erythrocytes. (ii) HbS is unstable to autoxidation and hence to release of its hemes. The released heme oxidizes to hematin, which, among other pathological consequences, is known to damages the erythrocyte membranes, and enhance their adhesion to the endothelial walls. Both of these sequences lead to blood flow obstruction, organ damage, and death. We study the interactions between the two consequences of the sickle cell gene. We show that the concentration of free heme in HbS solutions typically used in the laboratory is 0.02 - 0.05 mole heme/mole HbS. We show that dialysis of small molecules out of HbS arrests HbS polymerization. The addition of 100 - 260 uM of free heme to dialyzed HbS solutions leads to rates of nucleation and polymer fiber growth faster by two orders of magnitude than prior to dialysis. Towards an understanding of the mechanism of nucleation enhancement by heme, we show that free heme increases by two orders of magnitude the volume of the metastable clusters of dense HbS liquid, the locations where HbS polymer nuclei form. These results suggest that free heme in the erythrocytes of sickle cell anemia patients may be a major factor for the puzzling complexity of the clinical manifestations of sickle cell anemia. The prevention of free heme accumulation in the erythrocyte cytosol may be a novel avenue to sickle cell therapy.