INTERNATIONAL SOLVAY INSTITUTES BRUSSELS

Solvay Colloquium

Professor Peter G. Vekilov

(University of Houston, USA)

The physical chemistry of sickle cell anemia

Sickle cell anemia is a debilitating genetic disease, which affects hundreds of thousands babies born each year worldwide. Its primary pathogenic event is the formation of long fibers (with 14 molecules in the cross section) of a mutant, sickle cell, hemoglobin (HbS). Fiber formation is a first order phase transition, and, thus, sickle cell anemia is one of a line of diseases (Alzheimer's, Huntington's, prion, etc.) in which nucleation initiates pathophysiology. I will summarize recent results, which show that the homogeneous nucleation of HbS polymers follows a two-step mechanism with metastable dense liquid clusters serving as precursor to the ordered nuclei of the HbS polymer. The evidence comes from data on: the rates of fiber nucleation and growth, and nucleation delay times; the interaction of fibers with polarized light; and mesoscopic metastable HbS clusters in solution. The presence of a precursor in the HbS nucleation mechanism potentially allows low-concentration solution components to strongly affect the kinetics of nucleation. We show that the free heme leads to orders of magnitude faster nucleation and that its removal prevent polymerization.

The presence of soluble heme in the erythrocytes has never been considered as a factor for the disease pathology, owing to its putative low concentration. We develop a sensitive method based on enzymatic catalysis and luminescence to determine the concentration of free heme in erythrocytes. We find that the average free heme concentration in sickle cell patients is 45±10 mM, in sickle-trait individuals, 33±4 mM, and in healthy adults, 21±2 mM, about 100´ higher than previously determined. We show that the release of heme from hemoglobin is autocatalytic, i.e., the presence of free heme induces stronger heme release. Free heme contributes to both polymerization-related and polymerization-independent mechanisms of sickle cell anemia; hence, the found high concentrations suggest that it may be an important factor for sickle cell pathology and the target of novel treatment strategies.

These findings suggest that variations of the concentrations of the components of the red cell cytosol, e.g., heme, in patients might account for the high variability of the disease in genetically identical patients. In addition, these components can potentially be utilized for control of HbS polymerization and treatment of the disease.

Tuesday 26 May 2015 at 4.00 P.M.

COFFEE AND TEA WILL BE SERVED AT 3.45 P.M. IN FRONT OF THE SOLVAY ROOM

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