Dr. James is an Emeritus Distinguished University Professor in the Biochemistry Department, University of Alberta in Edmonton, Alberta, Canada. His research career extends over 47 years at the University of Alberta. He is one of the founding members of the longstanding, celebrated MRC (now CIHR) Group in Protein Structure and Function at the University of Alberta. Dr. James is a structural biologist who uses macromolecular X-ray crystallography as his primary research tool. His major areas of research interest currently are: proteolytic enzymes and their protein inhibitors; glycolytic hydrolases and the enzymic mechanisms of carbohydrate hydrolysis; and the development of antiviral agents. In addition, Dr. James' group is involved in the Structural Genomics Consortium on Myobacterium tuberculosis. With the worldwide upsurge of antibiotic resistance to the isolates of this organism (MDR TB and XDR TB), the identification of new targets for antibiotic design against this diabolical organism is of paramount importance.

In the field of the glycosyl hydrolases, the James' laboratory has turned their interest to lysosomal storage diseases. In particular the group has determined the structures of β-hexosaminidases A and B, the two enzymes in which mutations are behind the genetic diseases, Tay-Sachs disease and Sandhoff Disease, respectively. More recently the group has determined the structure of α-L-iduronidase the mutants of which are the cause of Mucopolysaccharidosis type I. Not only did this research determine the native structure, but also the structure of α-L-iduronidase in the presence of several different iduronyl derivatives has allowed for the determination of the enzymatic mechanism of α-L-iduronidase.

Dr. James was elected a Fellow of the Royal Society of London in 1989 and a Fellow of the Royal Society of Canada in 1985. He earned his doctorate in 1966 from Oxford University where he studied under the guidance of the late Nobel Laureate Professor Dorothy Hodgkin, O.M., F.R.S.

Abstract

The Structure of Alpha-L-Iduronidase and its role in Mucopolysaccharidosis-I

Lysosomal storage diseases (LSDs) are a broad class of devastating genetic diseases that collectively represent over 50 disorders. These diseases are progressive in nature as the affected individual is unable to degrade certain macromolecules. The mucopolysaccharidoses (MPSs) are adiverse group representing 11 separate genetic disorders each caused by a deficiency of a specific lysosomal hydrolase involved in the stepwise degradation of glycosaminoglycans (GAGs). As a consequence, GAGs accumulate within the lysosomes of all cells and ultimately, through mechanisms that are poorly understood, lead to progressive and debilitating symptoms. One of the MPSs, MPS I, is a rare (~1.05/100,000 births), autosomal, recessive lysosomal storage disease caused by a deficiency of lysosomalα-L-iduronidase (IDUA). The mutations in α-L-iduronidase that result in MPS I likely fall into the category of misfolding and as a result there is defective transport of IDUA out of the ER into the Golgi. Our laboratory, along with the labs of Dr. Allison Kermode at Simon Fraser University and that of Dr. Steve Withers at UBC have determined the 3D structure of human IDUA. We have also determined the structures of several inhibitors bound to hIDUA and from those data have been able to interpret a reasonable enzymatic mechanism for hIDUA. Our work has also shed light on many of the misfolding mutations that are the cause of the disease. Unexpectedly we have also observed that the glycan bound to Asn372 plays a major role in the catalytic mechanism of hIDUA.