Cystinosis research at IISER Mohali

FROM THE LAB

A WEEKLY UPDATE FROM INDIAN FINEST RESEARCH INSTITUTES

The unknown world of rare genetic disorders

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THE RESEARCH

Understanding the causes of cystinosis, a rare genetic disease, and studying its impact on the kidney

THERE ARE a number of 'rare' genetic disorders in human beings, classified as such because very few people are affected by them. Lysosomal storage disorders are prominent among those. Many of them have no cure because pharmaceutical companies have little interest in investing in developing drugs for these diseases. Government support for research in these diseases is also limited.

While the numbers of people suffering from any one of these lysosomal storage disorders is quite low, put together they account for a large number of patients. In India alone, millions of people are estimated to be suffering from these 'rare' diseases.

While working on sulphur metabolism in human cells, we were introduced to one such disease, called cystinosis, which has now become one of the prime focus of our research.

In normal human cells, proteins are broken down into amino acids inside lysosomes, one of the several sub-structures inside a cell, and then moved out with the help of specific transport proteins. Cystinosin is a transport protein that pumps out cystine (an oxidised form of the sulphur-containing amino acid 'cysteine') out of the lysosome into the cytoplasm.

Due to the inherited mutations, the cystinosin transport protein becomes non-functional in cystinosis, and thus the cystine can not move out and gets trapped inside the lysosome.

High concentration of cystine leads to its crystallisation within lysosome of every individual cell, affecting their normal function. This disorder manifests itself in stunted growth, loss of vision, and kidney malfunction.

The problem with this disorder, cystinosis, is that it does not get diagnosed early. Ideally, it should be diagnosed by the paediatrician when the parents first complain of lack of growth in the child. But these often, especially in our country, it does not get detected till the kidneys stop functioning. At that stage, the only remedy doctors can offer is a kidney transplant.

In cases of early detection, patients can be administered a drug called Cysteamine, but it has to be given every six hours. It is a painful treatment, costs about Rs 4 lakh per year in India and even then the patients do not live beyond 30-35 years, though much more normally than those who go on without the medicine.

In India, Dr Rajan Ravichandran, head of nephrology at the Madras Institute of Orthopaedics and Traumatology (MIOT), has done some groundbreaking work on this disease not just on its treatment but also on cataloguing and research.

He has formed a registry of cystinosis patients in India. This registry now has about 25 names. Through a Cystinosis chapter of India that he founded and a health foundation, he also supports the cost of treatment of many of the poor parents in India.

It is in close collaboration with Dr Ravichandran that we have been carrying on with our research on this disease and developing mutation maps associated with the Indian population.

We have been exploring multiple angles to understand the disease and its causes. One of them is to understand the initial biochemical consequences of cystine's inability to exit the lysosome. This biochemical understanding may help explain why primarily the kidney gets affected.

Our studies have allowed us to come up with a hypothesis to explain some of the events that follow cystine accumulation in the lysosome. That, we believe, can get us a good, and new, insight into the disease. We are also studying how the high cystine levels 'talk' to the cell. For this, we have been pumping in a lot of this amino acid from outside to see how the cell behaves.

For our experiments, funded by the Cystinosis Research Foundation, USA, we have been using the baker's yeast, the one that is used in wine-making and in baking, as our model organism. This unicellular yeast is quite different from the multi-cellular humans, and yeasts don't have kidneys and don't suffer from cystinosis. However, the key is that both organisms are "eukaryotes" and thus have similar intracellular structures and biochemical pathways. The critical aspect to using this model organism for studying cystinosin function, therefore, is to show that the human cystinosin protein when "put" into this organism, functions in a similar manner as its original form.

This successfully developed yeast model will further help us to understand the effect of the mutations on the functioning of this protein and biochemical base of this disorder.

For your research to be considered for this column, please write to Senior Editor Aniruddha Sinha at aniruddha.sinha@expressindia.com