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Recycler protein helps prevent disease

Researchers identify protein recycling mechanism that helps protect from genetic disorders

Heidelberg, 1 May 2009 - Recycling is important not only on a global scale, but also at the cellular level, since key molecules tend to be available in limited numbers. This means a cell needs to have efficient recycling mechanisms. Researchers at the European Molecular Biology Laboratory (EMBL) and Heidelberg University, Germany, have now uncovered the first step in the recycling of a crucial molecular tag which ensures the instructions encoded in our genes are correctly carried out. The study, published this week in the journal *Cell*, sheds new light on a proof-reading process that helps protect us from genetic diseases.

The translation of information from gene to protein in our cells is very important, but also error-prone. As errors can lead to diseases, several control mechanisms check for mistakes along the way. One such mechanism, called nonsense-mediated decay (NMD), is based on a molecular tag that is attached to messenger RNAs, an intermediate step in the translation from DNA to protein. The tag, called exon-junction complex (EJC), tells the NMD machinery if an RNA is faulty, potentially dangerous and should be degraded. Overall, a cell would need to mark around 400,000 sites with EJCs, but it only has 10,000 copies of one of the marker's components. This means EJCs must be broken down as soon as possible, so that their components can be re-used.

Researchers in the groups of Matthias Hentze, associate director of EMBL, and Andreas Kulozik at the University Clinic Heidelberg discovered that a protein called PYM is responsible for the disassembly and recycling of EJCs.

“Our results were very surprising,” says Niels Gehring, who carried out the research. “Everybody had assumed that ribosomes, the large structures that carry out protein assembly, simply iron out the EJCs as they pass. Now we see that this is not quite right, because without PYM EJC disassembly is impaired.”

Although PYM can be found on its own in the cell, it tends to associate with ribosomes. This explains why - and how - EJCs are removed when the ribosome goes by, and could also ensure that they are not removed too early. If that happened, NMD would be compromised, as the proofreading machinery would have no markers to guide it. This in turn could have wider consequences, as NMD influences how diseases such as thalassaemia, Duchenne's muscular dystrophy and cystic fibrosis manifest themselves.

“The new insights fill an important gap in the basic understanding of a vital cellular process,” says Hentze. “But they also have medical implications. Ultimately we would like to find ways to modulate NMD pharmacologically to influence the development and course of genetic diseases.”

The research was conducted in the joint Molecular Medicine Partnership Unit (MMPU), a collaboration between EMBL and Heidelberg University. “The MMPU bridges the gap between basic and clinical research. The constant cross-fertilisation between biologists and medical scientists guides our studies and often leads to discoveries that are applicable to medicine,” says Kulozik, medical director and professor of pediatrics at Heidelberg University. ●

Source Article

Gehring, N.H., Lamprinaki, S., Kulozik, A.E. & Hentze, M.W. Disassembly of Exon Junction Complexes by PYM. *Cell*, 1 May 2009

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