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Heavy metal

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Our grandmothers used to make jam in huge copper pans. The same copper pans that you would see hanging over the stove, with that distinctive green patina lining the inside. The same green patina that children instinctively knew was poisonous. And yet copper is essential to life. Without traces of this heavy metal in most living beings, a lot can go wrong because many enzymes depend on it to carry out their function. As a result, an organism must know how to keep copper at a healthy level – neither too high, nor too low. And this is achieved by way of transmembrane pumps which taxi copper in and out of cells. One such copper pump is known as the Menkes disease-associated protein because an American neurologist, John Menkes, first described an illness associated with this pump. Indeed, when the protein is deficient, it creates havoc.

Copper is not only important for electromagnets, dinnerware or cymbals but it is also needed to sustain life. The importance of copper in our system was perhaps first brought to light when – in the 1930s – an Australian vet described poor neurodevelopment in the lambs of sheep that had grazed in copper-deficient pastures during their pregnancy. Besides poor brain development, the lambs' wool was unusually brittle.

'Fruit and copper pan' by Owen Rohu

Oisìn Gallery, Dublin, Ireland

In the 1970s, David Danks, a British pediatrician, described the same kind of phenotype in infants who presented a neurological disease and associated his findings with those made on the Australian lambs – and hence copper deficiency. In between times, John Menkes had meticulously described an inherited X-linked disease in the male infants of one family where what he depicted as 'kinky hair' was one of the distinctive features. It was only in the 1990s however, that the gene was tracked down and the protein's sequence unveiled.

Menkes protein turned out to be a copper-transporting ATPase and acts as a pump which shuttles copper through plasma membranes. It is found in every tissue save the liver where a fellow copper pump does the job. Surprisingly, Menkes protein is found both in the intracellular and the cellular plasma membranes, where it keeps a keen eye on copper levels in the cell's cytosol.

When the level of copper is normal, Menkes protein is found within the intracellular membranes of the Golgi system where it distributes copper to enzymes whose function depends on the heavy metal. It is thought that the binding of copper to Menkes protein brings on a change in its 3D structure thereby reorienting the molecule in the membrane and creating a channel ready for copper transport. The enzymes armed with their copper ions are then secreted, ready for action.

When copper levels are too high in the cell cytosol, Menkes protein is then translocated to the cell's plasma membrane – probably by way of intracellular vacuoles and exocytosis – where it proceeds to get rid of excess copper by transferring from the inside of the cell to the

outside. Once the cell's level of copper is back to normal, Menkes protein is then retranslocated to the Golgi system. This was an astonishing discovery since other organisms frequently have two different pumps to carry out these two different shuttling processes. As a consequence, Menkes protein is most certainly at the very heart of copper homeostasis in mammals.

Save for the liver, Menkes protein is distributed throughout mammalian tissue and, besides supervising copper trafficking within the cells themselves, on a more global scale, it also makes sure that copper is taxied from the gastrointestinal tract into the bloodstream, and then from the bloodstream into the brain. It is hardly surprising then, that a deficiency in Menkes protein can cause chaos. If a mutation hits any part of the protein which affects copper transport – either because it cannot bind copper anymore or cannot function as a pump – then a battery of copper-dependent enzymes will also be affected. As a result, many different kinds of symptoms are observed. Menkes disease is an inherited disease and affects 1 out of 250 000 newborns who show specific phenotypes at birth: kinky hair, sagging skin, heavy jowls… Before long, it is apparent that they have profound neurological drawbacks accompanied by many other defects affecting numerous parts of their body. Most children die by the age of three.

There are some mild forms of Menkes disease, which can be overcome by injecting copper subcutaneously at a very early age. In some cases, the copper ions find their way to the enzymes that need them to function, and as a consequence brain development can be more or less normal. Gene therapy could also be an option although such a therapy brings about obvious ethical considerations. Certainly, getting more acquainted with Menkes protein on the molecular level – how it binds copper and how it folds to form a channel – is an obvious aim for drug design, especially for the less severe forms of the disease. In the meantime, you may be interested to discover another medical adventure, a thriller written by John Menkes himself: The Angry Puppet Syndrome.

Cross-references to Swiss-Prot

Menkes disease-associated protein, Homo sapiens (Human) : Q04656
Menkes disease-associated protein, Mus musculus (Mouse) : Q64430
Menkes disease-associated protein, Rattus norvegicus (Rat) : P70705

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