Scientists unwrap the elements of life

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Researchers at Newcastle University have taken a step forward in our understanding of how the fundamental building blocks of life are put together.

In a paper published today in *Nature*, the team led by Professor Nigel Robinson have revealed a mechanism that ensures the right metal goes to the right protein. Proteins are essential and involved in just about every process in living cells.

Life, microbe, plant or human, is a painstaking assembly of trillions of atoms. The atoms include metals such as copper and manganese which act as catalysts in proteins. The proteins wrap around the metal atoms.

The research team has shown that to ensure a copper and a manganese protein wrap around the correct metal atoms they do this in different parts of the cell, in zones which contain different metals. Therefore, which protein attaches to which metal is determined by where the folding action takes place in the cell.

Previously, a common view was that the right metals were simply those which were most attracted to the protein, but in this work that is not the case.

Professor Nigel Robinson at Newcastle University who led the research says: "This has taken us one step closer to understanding why metals and proteins assemble in the ways they do."

"One motive behind the work is pure curiosity, but as so many proteins need metals this type of work has many potential uses - for example, in synthetic biology which is striving to produce green power from bacteria by using energy from sunlight to produce hydrogen gas, a process which needs nickel and iron.

"It may also help in diseases such as Alzheimers where there are unexplained links to proteins binding metals such as copper. There's also application in controlling infections by Staphylococcus aureus; a bacterium which our bodies defences succeed - or sometimes fail - in killing by removing manganese and zinc from abscesses."

The researchers have shown that the way the metals attach is identical for a protein that binds manganese to one that binds copper. In both cases the metals bind inside protein barrels with the same type of metal-attractions.

Carrying out the work in a blue-green algae, a cyanobacterium, the team has been able to show that a protein requiring copper transports to the periplasm, the outer area of the cell, where it then folds around the available metal, which is copper.

Conversely, manganese but not copper atoms are found in the cytosol, in the middle of the cell. The team has demonstrated that a protein requiring manganese folds in the cytosol. The manganese protein is then transported to the periplasm having first trapped its manganese.

The cyanobacterium organism was chosen because it has a high demand for these two metals which are required for proteins involved in photosynthesis. These metals were chosen because they lie towards opposite ends of a chemical series called the Irving-Williams series, such that selecting these metals for proteins should be especially demanding.

In the work funded by the BBSRC, the Newcastle University team first developed a new approach to discover metal-binding proteins. This is now being swiftly applied to lots of other types of living cells and other essential metals (zinc, nickel, cobalt, iron). Unexpectedly, x-ray crystal structures showed that the identified proteins, MncA for manganese and CucA for copper, were both cupins (Latin for barrels) with identical sets of atoms for binding to the metals. Consistent with the chemical series, a ten-thousand times excess of manganese over copper was needed to fill the MncA barrel with manganese when folding is done in the laboratory.

Once folded, the manganese site is buried, the metal trapped inside the protein, and so the manganese protein can subsequently co-exist with the copper protein because its' metal becomes impervious to replacement by metals further up the Irving-Williams series.

The work exemplifies a cell overcoming the metal binding preferences of proteins.

The new discipline of synthetic biology aims to engineer cells to carry out useful tasks, for example to generate valuable compounds. Because metals are the catalysts for so much of biology, knowing how to engineer a supply of the right metals to the right proteins will be important to the success of these ventures.

Reference: Protein-folding location can regulate manganese-binding versus copper- or zinc-binding. Steve Tottey, Kevin J. Waldron, Susan J. Firbank, Brian Reale, Conrad Bessant, Katsuko Sato, Timothy R. Cheek, Joe Gray, Mark J. Banfield, Christopher Dennison & Nigel J. Robinson; Published in: *Nature*

Source: Newcastle University