Proteins in their natural habitat

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Illustration of lipid nanodiscs introduced in a nanoflow droplet. The image shows: Heads of the lipids at the top and bottom of the bilayers (magenta dots); the protein belt used to protect lipid tails from coming into contact with water (light blue); and the membrane protein encapsulated in the centre (red). The disc encased in a charged water droplet (left) undergoes evaporation to form the naked disc (right) which can then be studied in the mass spectrometer. Credit: Oxford University

Proteins which reside in the membrane of cells play a key role in many biological processes and provide targets for more than half of current drug treatments. These membrane proteins are notoriously difficult to

study in their natural environment, but scientists at the University of Oxford have now developed a technique to do just that, combining the use of sophisticated nanodiscs and mass spectrometers.

Mass spectrometry is a technique which allows scientists to probe molecular interactions. Using a high-tech 'nanoflow' system, molecules are transmitted into the instrument in charged water droplets, which then undergo evaporation releasing molecules into the gas phase of the mass spectrometer.

But membrane proteins are difficult to measure in this way, as they are hydrophobic: they don't dissolve in water. One way to overcome this problem is to mix them with detergents. Detergents work by surrounding insoluble substances with a water-friendly shell. Each detergent particle has two ends – the heads are attracted to water and the tails are attracted to insoluble regions of the membrane protein. The tails stick to the hydrophobic parts, leaving a shell of water-loving heads around the outside. The molecules can then easily dissolve in water.

Although detergents can be used to get membrane proteins to dissolve in water, these artificial chemicals can damage protein structures and do not faithfully mimic the natural environments in which they are normally found. The Oxford group, led by Professor Carol Robinson, has utilised a technique which allows them to study membrane protein structures by mass spectrometry from their natural environment. Their new method, published in *Nature Methods*, uses tiny disc-like structures made from molecules called lipids, as first author Dr Jonathan Hopper explains:

'Membrane proteins are naturally found in flat structures called lipid bilayers. Lipids are a bit like nature's detergents, in that they have water-loving heads and fat-loving tails. Lipid bilayers are made up of two sheets of lipids with their tails pointing inwards.

'The nanodiscs we use are made from lipids, the same material that membrane proteins occupy in the body. It's essentially as if you took a round cookie cutter to remove a section of the natural bilayer, so the conditions are just like they would be in the body. The discs are stabilised by wrapping a belt of proteins around them to keep the exposed lipid tails from the water.

'Aside from the nanodiscs, we actually got great results from 'bicelles', which are made in a similar way. The main difference is that instead of putting a belt of proteins around the edge, we plug the gap with short-chain lipids instead. This actually gives us much more control over the size and structure of the disc.'

These innovations enable researchers to study membrane protein structures using sophisticated mass spectrometry, in environments as close to the human body as possible.

'I am delighted that this has worked, it is completely unexpected given the difficulties we have had in the past in studying these complexes in lipidic environments,' says study leader Professor Carol Robinson. 'The breakthrough enables us to study membrane proteins in a natural environment for the first time. We believe this will have a great impact on structural biology approaches, and could in turn lead to better-designed drug treatments.'

More information: www.nature.com/nmeth/journal/v … full/nmeth.2691.html

Provided by Oxford University

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