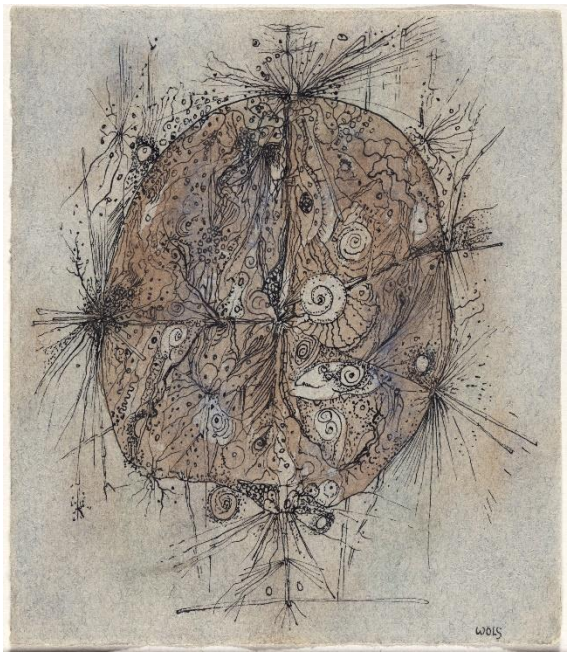
proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 235, April 2021
www.proteinspotlight.org

catalysis

Vivienne Baillie Gerritsen

Sometimes, it takes very little to change the course of things. Though frequently it may require the presence of another. Take two people who become lovers and whose destinies change after having met by chance at a friend's house. Or two artists who recognise in each other a similar understanding of things and whose meeting causes something very different to emerge– take Georges Braque and Pablo Picasso, Lee Krasner and Jackson Pollock, or Elaine and Willem de Kooning for instance. Or two scientists, for that matter. James Watson and Francis Crick will have no doubt fed on each other's enthusiasm to elucidate the structure of DNA. The same occurs in the world of proteins. It is no secret that proteins frequently work in twos – or indeed threes or more – by binding to one another to perform an overall function. Each individual protein, however, usually has a very distinctive part to play. On more rare occasions, bonding can influence a protein to act differently. This is what happens when two proteins, known as HPF1 and PARP1 (or 2), meet. PARP1/2 is known to act in one way, but when HPF1 binds to it, like two pieces of a jigsaw puzzle that lock to become a different shape, their active sites add up to create a novel one and, in so doing, PARP1/2 behaves differently.



Mollusks

Wols (A.O.Wolfgang Schulze), 1944

Poly (ADP-ribose) polymerases 1 or 2, which we will call PARP1/2, and histone PARylation factor 1, or HPF1, are involved in post-translational modifications. These are chemical modifications made to proteins once they have been synthesized, and which confer specific functions to them. PTMs can be compared to a set of tools you would hand to someone – a hammer, a saw, a chisel or a screwdriver – to perform different actions depending on what needs to be fixed. PTMs are a world of their own and paramount to faithful cellular function – and, so, to life as well. Consequently, one gene gives rise not to one but frequently to many proteins, each with a potentially different function depending on the post-translational modification (PTM) that has been added to it. To date, thousands of different PTMs have been characterised – which all fall into about 200 different types. These may include small chemical modifications such as phosphorylation, glycosylation or acetylation for example, or even the addition of complete proteins, as in ubiquitylation.

PTMs are a wonderful energy-saving answer to protein diversity, function diversity and environmental changes. Cells do not necessarily need to transcribe new genes if they need a new protein; all they have to do is pop a PTM onto an existing one. Despite the apparent simplicity, the world of PTMs is highly regulated and can only occur at specific sites on chosen proteins. All sorts of enzymes are responsible for PTMs, as they add chemical compounds onto a protein's surface – or indeed remove them. Like setting off a firework, other proteins will recognise these PTMs, bind to them and trigger off downstream cellular processes. The whole point of PTMs, then, is to influence the properties of proteins – by altering

their activity for example, prompting their interactions with other proteins and perhaps even making them shift from one part of the cell to another. Have PTMs always existed? Most probably, researchers think. They are spread across all domains of life, so must have been around for a long time, and there is reason to believe that PTMs such as phosphorylation, acetylation and glycosylation were already used in the last universal common ancestor, LUCA.

ADP-ribosylation is one type of PTM. Though perhaps millions of years old, it was only discovered in the 1960s by the French geneticist and molecular biologist Pierre Chambon. ADP-ribosylation involves the addition of units of ADP-ribose to a protein. ADP-ribose is derived from NAD+ – or nicotinamide adenine dinucleotide – a compound which is essential to an organism's metabolism. PARP may add one unit of ADP-ribose (mono ADP-ribosylation) or more (poly ADP-ribosylation). Poly ADP-ribosylation is added as a linear sequence which – after a certain length – will begin to branch out. Though it was first thought to be a PTM involved only in gene regulation, it is now apparent that ADP-ribosylation initiates other vital processes, among them cell-signalling, apoptosis and DNA repair.

PARP1 and 2 are homologous enzymes, each involved in the ADP-ribosylation of many different proteins – in particular histones early in the response to DNA damage. When a lesion occurs in double-stranded DNA, either PARP1 or PARP2 is swiftly recruited, and binds to it – actually bridging the break and preparing the terrain for DNA repair by repair proteins. As PARP1/2 binds the nucleic acid, it undergoes a conformational change which concomitantly opens up a binding site for an effector protein while also prompting the binding of NAD+, necessary for ADP-ribosylation. It is in this particular 'PARP-NAD^+-effector protein' conformation that ADP-ribosylation on histones occurs, literally setting off the siren that will summon a DNA repair force.

But none of what is described above is really new. Many enzymes require effector proteins to get on with their jobs. However, in this instance, the effector protein in question – histone PARylation factor 1 (HPF1) – actually modifies the way PARP1/2 usually deals with ADP-ribosylation. In the absence of HPF1, ADP-ribosylation by PARP1/2 occurs on certain aspartate or glutamate residues of substrates. While with HPF1, ADP-ribosylation occurs on serine residues. This ADP-ribosylation residue shift seems to ensure that PARP1/2 is committed to DNA damage and to nothing else. How? When binding to PARP1/2, HPF1 also provides extra substrate-binding and catalytic residues, thus adding to the existing catalytic site. In this way, HPF1 seems to complete what has been considered by some as a 'half-finished' active site – although it may be a question of perspective.

The PARP1/2-HPF1 partnership provides cells with yet another means of inducing and regulating DNA repair – an event which is not infrequent and without which havoc would wreak. It may come as a surprise, but certain cancer treatments actually take advantage of such a process by inhibiting the action of PARP1 in the hope of enhancing DNA damage made to tumour cells caused by chemotherapy. It is like seducing the devil, only to push him over the top of a cliff. Such cancer treatments, however, have met with resistance mechanisms which may find their explanation in the newly discovered role played by HPF1 in modifying the active site. The molecular world is certainly a very crowded and a busy one. Lift one veil, and you are bound to find another underneath.

Cross-references to UniProt

Histone PARylation factor 1 (HPF1), *Homo sapiens* (Human): Q9NWY4
Poly [ADP-ribose] polymerase 1 (PARP1), *Homo sapiens* (Human): P09874
Poly [ADP-ribose] polymerase 2 (PARP2), *Homo sapiens* (Human): Q9UGN5

References

1. Suskiewicz M.J., Zobel F., Ogden T.E.H. et al.
   HPF1 completes the PARP active site for DNA damage-induced ADP-ribosylation
   Nature 579:598-602(2020)
   PMID: 32028527

2. Beltrao P., Bork P., Krogan N.J., van Noort V.
   Evolutional and functional cross-talk of protein post-translational modifications
   Molecular Systems Biology 9:714 (2013)
   PMID: 24366814

Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).