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> ONE MONTH, ONE PROTEIN <

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on mar and motion

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Movement is what sustains life. Organisms need to move to find food, seek shelter and to reproduce. Mobility is also essential inside organisms where cells are continuously dividing and migrating. There is also unceasing movement inside every cell where myriads of molecules are being trafficked, and cellular compartments of all shapes and sizes shifted. What keeps things moving? Years ago, scientists discovered a protein they coined actin. Actin is a small globular protein that has many different roles in eukaryotic cells. One characteristic feature is its capacity to polymerize into microfilaments that stretch from one end of a cell to another to form the cell's cytoskeleton – which speaks for itself. Though the formation of a cell's cytoskeleton is perhaps considered as actin's fundamental role in the cytoplasm, the protein is also involved in many other activities, one of which is mobility. Actin is also present in the nucleus but, until recently, scientists believed that microfilaments did not form there. It turns out that they do: damaged DNA seems to be oriented towards repair centres thanks to actin microfilaments whose growth is prompted by a protein complex known as Arp2/3.

watercolour by Giorgiana Houghton (ca 1868)

We tend to think of cells as entities with many compartments and macromolecules floating in a biological fluid, and navigation from A to B – if necessary – is merely a question of swimming there. But it is not so. As for all vehicles, energy is required to create motion, and this is what actin provides. A cell's nucleus is characterised by its DNA, usually stored in the form of chromosomes. There are also hosts of proteins that fold the DNA, protect it, transcribe it, translate it, replicate it and so on. DNA repair is also an important task that occurs in the nucleus. Damage occurs to an organism's DNA all the time, which is why cells must have repair mechanisms. Small 'point' mutations are the most frequent type of damage, but greater damage can occur when the DNA double helix snaps altogether and some bits may even get lost in the process. The cell has two ways of repairing this: either it simply sticks the loose ends back together or, first, it fills in what may have gone amiss, and then joins the ends. It is this second kind of repair that demands more craft, and where nuclear actin microfilaments are involved.

Actin is one of the most versatile proteins in eukaryotes. Its sequence has changed very little over the course of evolution and it is found in organisms as diverse as algae and humans – as a consequence, scientists consider its structure optimised. Its fundamental role is to hydrolyse ATP – the biological currency of energy – thereby releasing power. It is hardly surprising, then, that it is involved in so many different activities in the cell, i.e. cell shape, cell robustness, cell plasticity, cell adhesion, cell division and tissue stabilisation. It is also part of many cell-signalling pathways while providing a scaffold for transport inside the cell and a means to organize the cell's contents in space. Actin also belongs to more specialised structures such as flagella and cilia, and is an integral part of muscle contraction.

Actin is a small globular protein that can polymerise and depolymerise at a surprising pace. In doing so, it creates dynamic structures known as microfilaments of varying lengths and durability – it all depends on the microfilaments' function, where they are

necessary in the cell and when. Actin is also active in the nucleus where it is involved in DNA transcription and gene expression for instance. However, no one had observed nuclear actin microfilaments, and the ongoing belief was that actin acted only in its monomeric form in this part of the cell. Until recently, when researchers noticed that bits of damaged DNA were relocated to distinct parts of the nucleus for repair – and relocation was achieved by way of actin microfilaments.

Arp2/3 is an actin nucleation factor, and its presence is necessary to initiate the growth of actin microfilaments both in the cell's cytoplasm and in its nucleus. Arp2/3 is a complex of seven protein subunits, all of which have specific roles in keeping the complex together, increasing nucleation efficiency, tethering one subunit to another and so on. Phosphorylation may also be a way of fine-tuning Arp2/3 activity, and the concept of multiple versions of Arp2/3 that coexist in a cell is beginning to emerge, as opposed to only one as has been thought for the past 20 years. Arp2 and Arp3, in particular, have been dubbed "unconventional actins" because they adopt the same three-dimensional fold and form the first two subunits of a nascent microfilament.

As mentioned above, there are two ways of repairing damaged DNA, and these are non-homologous end joining (NHEJ) or homology-directed repair (HDR). NHEJ is the most straightforward and widespread way of repairing DNA: the broken ends of both DNA strands are 'simply' stuck back together. In the process, however, little bits may have fallen off the part that snapped and the repaired DNA is not identical to what it was before damage. Try snapping a chocolate bar in half and look at all the crumbs that fall to the ground. As for HDR, the nucleus makes sure that all the missing parts are added before the DNA double strands are joined together again. In this way, not only is the DNA break repaired but no information is lost either. Actin microfilaments seem to grow in the nucleus especially for HDR. Though very little is yet known on the molecular level, it could be that the HDR machinery stimulates actin polymerization, and DNA double strand breaks are hurried to the "repair centre" – although who stimulates what is difficult to unjumble.

The British physiologist W.D. Haliburton discovered actin experimentally in 1887. It took another half century for the laboratory of the Hungarian biochemist Albert Szent-Györgyi to extract pure actin from muscle in 1942. Ever since, actin has been studied extensively, yet it has taken a further 80 years to realise that actin microfilaments also exist in the nucleus. In a way, this shouldn't be surprising. Why would a protein as versatile as actin not polymerize in the nucleus too? Why would microfilaments be specific only to the cytoplasm? Is movement not as fundamental to the nucleus as it is to the cytoplasm? Why would Nature imagine a different system between two cellular compartments when it has used the same system throughout eukaryotes? Actin certainly seems to share its secrets sparingly. Or perhaps the obvious is sometimes difficult to see.

Cross-references to UniProt

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Actin-related protein 3, *Homo sapiens* (Human): P61158
Actin, cytoplasmic 1, *Homo sapiens* (Human): P60709

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