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unfurling our heritage

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Our most precious things are kept where they meet the least damage. Out of reach on a shelf, in the depths of a drawer, deposited in a bank or perhaps parked in the garage. Frequently, too, a layer of protection is added by wrapping the valuable item in cloth or placing it in a padded box. Nature does exactly the same with one of its most treasured commodities: DNA. In eukaryotes, not only is our genetic heritage tucked away in the fortress-like nucleus of cells but it is also swathed in numerous molecules to form what is known as 'chromatin'. Protecting DNA is paramount, for obvious reasons. However, to survive, cells must have access to the genes their DNA carries in order to express them. This implies that cells need to dismantle the chromatin barrier, at different locations and at any given time. It's not so much dismantling chromatin, really, as remodelling it in such a way that genes are sporadically laid bare and thus open to transcription. One of the numerous proteins involved in chromatin remodelling is ATRX, so called because it is found on the X chromosome of mammals. An intriguing fact: in marsupials, ATRX is also found on their Y chromosome.

Woman Winding Yarn (1885)

Vincent van Gogh (1853-1890)

The recipes used to create and sustain life are held within an organism's DNA. Though life has benefitted hugely from mutations since its emergence on Earth four billion years ago, DNA needs to be preserved from damage and looked after with great care. In eukaryotes, DNA is folded into chromatin – from the Greek 'chroma' for 'colour' because, in the 19th century, new synthetic dyes revealed the characteristic architecture under the microscope. Chromatin is, in majority, a mixture of DNA and protein. It is a way of compacting very long strands of DNA which, otherwise, would not fit in the cell nucleus. It also protects DNA from harm and, in so doing, regulates gene expression. How? Chromatin is a dynamic system that, under given circumstances, can open up or close down regions on DNA thus giving access (or not) to genes and hence allowing (or not) gene expression and, ultimately, protein synthesis.

Though, under the microscope, chromatin may look like a scruffy ball of wool, it is in fact a very organised structure, with several built-in levels – each of which provides an extra level of protection. First, you have the nucleosomes. These are structured assemblies of histone proteins, which act like spools around which the thread-like DNA winds. Like beads on a string, long strands of DNA twist around nucleosomes at regular intervals. Second, you get chromatin loops, which allow distant chromatin regions to make contact. Third, sets of chromatin loops come together to form Topologically Associating Domains, or TADs, thus allowing further contacts that could not occur otherwise. Then you get chromatin compartments and finally chromosomal territories – and you have the geopolitics of chromatin.

In short, chromatin forms the basis of an on/off switch for gene expression. Tightly packed, like an overgrown hedge, the genes are hidden deep inside, i.e. protected but silenced because unreachable. It is only by clearing the shrubbery, so to speak, by unfurling and teasing apart portions of chromatin that the genes become

accessible. This unfurling and teasing apart is called chromatin remodelling, which is performed by different chromatin remodelling complexes (CRCs) themselves composed of widely varied proteins that, together, carry out many different tasks. One of these proteins is the ATPase ATRX.

ATRX stands for **A**lpha-**T**halassemia/Mental **R**etardation **X**-linked. This is because it was discovered whilst studying a rare genetic disease, now known as ATR-X syndrome, where patients specifically suffer from mental retardation and a blood disorder, alpha thalassemia, that reduces the production of haemoglobin. ATRX belongs to the SWI/SNF2 family of proteins that form chromatin remodelling complexes in eukaryotes. CRCs' main task is to rearrange nucleosomes – by either ejecting them or pushing them aside – so as to expose naked DNA and provide access to transcription factors for gene expression (or repression).

ATRX is found exclusively in the nucleus of cells, and is present in all tissues, as would be expected. In humans, ATRX is a very long protein – almost 2,500 amino acids long – and carries two conserved SWI/SNF2 domains, namely an ATPase domain and a domain which mediates histone-binding. ATRX is an integral and crucial part of many CRCs where it acts as an ATPase, splitting ATP to ADP to produce energy, like a tiny molecular motor. Because it is an integral part of so many different CRCs, ATRX is involved in a wide variety of functions such as transcriptional repression, DNA repair, replication fork restart, telomere cohesion, X-chromosome inactivation, homologous recombination, telomere maintenance... As a consequence, it is a key protein in biological processes as fundamental as embryonic development, sexual differentiation and brain development.

In placental mammals, ATRX is located exclusively on the sex-determining X chromosome. In marsupials, however, ATRX is located both on the X chromosome and on the sex-determining Y chromosome (where the ATPase is also known as ATRY). This came as a surprise. Why would marsupials have two copies of ATRX? Since, in females (XX), one X chromosome is always inactivated to keep things levelled with their male counterparts (XY), how can an extra ATRX on Y be explained?

The marsupial expression pattern of ATRX and ATRY turns out to be complementary: ATRX is expressed in all tissues save the testis, while ATRY is only expressed in the testis. In placental mammals, ATRX is expressed everywhere. The primary sex-determining event in an embryo is, precisely, the development of the testis. Once this has occurred, further masculinization hormones are expressed. In humans, protein SRY (*see PS issues 80 & 201*) is responsible for the development of the testis. Could ATRY then be the ancestral SRY? Did placental mammals (eutherians) lose ATRY and replace it by SRY? Possibly. In eutherians, the Y chromosome has undergone drastic degradation down the years and ATRY – like so many other genes – may well have been lost in the process. In marsupials, the same happened to the Y chromosome, naturally, but for some reason ATRY was retained (as other genes have been retained too).

What has been described above may give the impression that ATRX only belongs to humans and wallabies. This is far from the truth. ATRX belongs to all eukaryotes, from boletes and bluebells to bumblebees and bats. The way Nature has perfected intricate ways of preserving what is most precious to life and, likewise, subtle ways of lifting the veil of protection when it is necessary is awe-inspiring. So much is going on and so much can go wrong. Usually it works, sometimes it doesn't and, with such a central protein, this can have serious consequences. As an example, ATRX is likely to be essential for brain development, and mutations can bring about varying degrees of intellectual disability, which has led scientists to believe that ATRX may also have a role in neurodegenerative disorders. It could be the case but, like so many proteins, ATRX does not act on its own. It is part of a far larger complex, the CRC, and therapeutic developments would have to take this into account. The path from knowledge to therapy is always a long and windy one.

Cross-references to UniProt

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