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taming genes

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Some mistakes turn out to be beneficial. And life, or its survival, has always thrived on them. Add a few mutations to a genome, drench it in time, and you have the driving force of evolution. Transposons – these bits of DNA that are able to skip along genomes – are just one kind of mutation that has contributed hugely towards life's unfolding. Not so long ago, researchers discovered remnants of a well-known transposon, made up of so-called *mariner* elements, glued aside another gene whose product is a histone methyltransferase. This chimeric gene, baptised SETMAR, expresses a product whose roles are similar to both of its parts. But with a little twist. A twist which, in the past 50 million years, has contributed to human evolution, and is due to the protein it expresses: histone-lysine N-methyltransferase SETMAR.

Collage by Koji Nagai, Japan 2015

Courtesy of the artist

What exactly are transposons? These lonely but very independent stretches of DNA seem to exist with the sole aim of being utterly self-centred. Once inserted into a genome – by way of a virus for instance – transposons are able to replicate, and their copy can then hop onto another part of the genome, squeeze itself between two nucleotides and continue the process. It is not difficult to see that depending on where a transposon lands in the genome, it can cause havoc. But, by a happy stroke of luck, it can also end up by being beneficial to an organism, with a little help from time. For this to happen, however, at one point the transposon has to slip into the organism's germ line for it to be inherited by downstream generations.

This is probably what happened to the *mariner* transposon and its companion the histone methyltransferase gene. Scientists believe that a *mariner* transposon must have wedged itself into a part of our ancestors' genome about 50 million years ago, and then spent the following 20 million years leaping from one part of it to another, leaving in its wake about 7000 transposon imprints. Imprints which can be found in today's anthropoid genomes, ours included. Then one day, one *mariner* transposon slipped in beside a histone methyltransferase gene. And, unknown to either of them at the time, this companionship would prove to be successful and became SETMAR, a protein only expressed in humans, apes and New World monkeys today.

What is the point of clinging onto a transposon you might ask? Why would a gene bother to trail another bit of DNA along with it? Moorings may be the answer. The 7000 or so transposon imprints that were planted along the anthropoid genome over a period of 20 million years constitute as many DNA binding sites for SETMAR by way of its transposase domain. It's a little like having 7000 private harbours built just for you along a very wide stretch of coast.

This means that the histone methyltransferase domain has numerous places spread across the genome to which it can dock and from where it can act. In this light, you begin to grasp the advantage of dragging transposon remnants along with you.

What advantage is there in having so many docking sites? Histone methyltransferase catalyses histone methylation, which is used to regulate all sorts of essential chromatin functions such as transcription, DNA repair, DNA replication, DNA integration and X chromosome inactivation, besides jump-starting replication forks when they stall. These are crucial functions and need to be fulfilled throughout the genome. What the transposase domain of SETMAR ensures is the ability to dock SETMAR'S methyltransferase to any of the thousands of docking sites scattered across the genome. Once docked, other proteins join to form complexes which carry out the various functions.

So here we have a chimeric protein that has ensured itself multiple moorings along the human genome, from where it can carry out crucial functions. But Nature has achieved a little more by actually taming the role of the initial transposase which was able to excise and ligate DNA to insert itself into other parts of the genome. SETMAR cannot do this anymore; all it has preserved is its DNA binding capacity. But it has gained something else: DNA repair. So here is a wonderful example of a gene which, over millions of years, has been tamed by Nature to keep its DNA-binding activity, lose its catalytic activity and gain DNA repair activity.

None of this would be possible without the dimerization of SETMAR, which has created a catalytic site that is flexible and necessary not only for DNA-binding but also for histone methylation, suppression of chromosomal translocation activities, DNA double-strand break repair and hence DNA stability.

About 50 genes present in the human genome today are the result of transposons that have been domesticated in much the same way. SETMAR is found in a region of the genome that is linked to a number of diseases – such as non-Hodgkin's lymphoma, acute leukemia, hereditary prostate cancer, myeloma and myelodysplastic syndromes – and has subsequently become a choice area of study. SETMAR also happens to enhance resistance to cancer chemotherapeutics and promote HIV integration so it is important to develop SETMAR inhibitors. Here is a relatively recent gene addition to the anthropoid genome which has been house-trained to promote DNA repair instead of predisposition to malignancy and genome instability. This particular transposon system is an ideal tool for genome manipulations, besides investigating the dynamics of a transposon and how these discreet stretches of DNA have sculpted primate evolution.

Cross-references to UniProt

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