

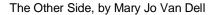
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## best left unsaid

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There are times in life when things are best left unsaid. So you bite your tongue or someone bites it for you. Either way, you are silenced and no – or less – harm is done. Nature also has its techniques for muffling genes whose products are not necessary at a given time, or that are perhaps harmful once expressed. One technique, which seems to have been with us for a very long time, is DNA methylation. DNA methylation is like locking a door with a key that you promptly throw away: you're making things difficult for someone to open it and see what's on the other side. In the same vein, DNA methylation has the capacity to keep a gene in a locked – or silent – state, thus hindering the production of an undesirable protein and a probable adverse downstream metabolic pathway. DNA methyltransferase 3C is one of the many enzymes able to gag a gene. Although not any old gene: DNA methyltransferase 3C seems to silence specifically retrotransposons.





Courtesy of the artist

The American cytogeneticist Barbara McClintock was the first to suggest, in the 1940s, the existence of transposons – which she referred to as jumping genes – whose mobility, she noticed, had an effect on other genes. At the time, her research met with skepticism more than understanding, and she finally put a halt to publishing her data in 1953. In the 1960s and 70s, however, other scientists began not only to confirm the existence of jumping genes or "transposons" as they called them, but also to grasp the role they could have in genetic change

and regulation – and not merely damage. This demonstrates yet again how scientific beliefs are sometimes hard to shake. McClintock actually went on to receive the Nobel Prize in Physiology or Medicine in 1983 for the discovery of genetic transposition.

Retrotransposons are a particular type of transposon: before leaping to another part of the genome, transposons are transcribed into RNA and then "retro" transcribed by an enzyme, known as reverse transcriptase, into DNA. It is this copy that is inserted into another part of the genome. This results in the duplication of a portion of the genome which occurs via an intermediary RNA copy of the fragment that is transcribed back - hence the "retro" - into its DNA version before being inserted elsewhere into the genome. Astonishingly, half the mammalian genome is composed of retrotransposons! What sounds instinctively like a biological error – something of a certain kind of gross mutation – has in fact become part of the general function and evolution of our genome. However, like all active parts of the genome, retrotransposons are under tight regulation, and some have to be permanently silenced.

DNA methyltransferase 3C specifically regulates retrotransposons in male rodent germ cells and has a role in male fertility. The enzyme belongs the very large family of DNA to methyltransferases that methylate their substrates - in this case: retrotransposons. DNA methylation can be a powerful transcriptional

repressor and is a mechanism of choice when transposons need to be silenced on a lasting basis. Certainly, DNA methylation is not as finetuned and sophisticated as many other mechanisms used for gene regulation but its stability is perfect to repress the expression of transposons. Scientists believe that transposon regulation is actually one of the most ancient roles of DNA methylation, which is indeed shared by plants, animals and many protists. DNA methylation, some say, may even have evolved just for this purpose.

How exactly does DNA methyltransferase 3C repress the expression of a retrotransposon? Transposons are portions of genomic DNA that may include more than one gene; each has its particular landscape, flanked by a promoter region. In rodent male germ cells, DNA methyltransferase 3C focalizes on the promoter regions of retrotransposons during spermatogenesis. Methylation affects transcription in two ways: either it prevents transcriptional proteins from binding to the promoter region, or it can act as a signal for recruiting proteins that will render the transposon inactive by compacting its DNA.

DNA methylation is a very widespread and very old biological phenomenon, both necessary and vital for an organism's development. It occurs in waves during a lifetime – DNA methylation and demethylation are unceasing – and the particular patterns are usually erased and then reestablished in the future generation. This state of things flirts with the very intriguing world of epigenetics and the possibility of non-genetic modifications that may occur in a parent but are not erased for some reason, and can therefore be passed down to progeny, or to the progeny's progeny. What if certain life events experienced by a parent are reflected one way or another in their DNA methylation patterns, and what if some of this information is not erased but passed on? Would it have an effect of some kind on the parent's descendants? Or none at all? Could DNA methyltransferases have this tantalizing role of passing on something that is barely tangible?

Scientists first thought that what is now known as DNA methyltransferase 3C was in fact a pseudogene, i.e. a sort of "has been" gene that has lost much, if not all, of its functional capacity. However, a bit like McClintock's jumping genes, it has turned out to be a fullyfledged gene with an important role in cell development and male fertility - at least in rodents. It does not work on its own but is part of a quintet which is probably representative of all mammalian DNA methylation protagonists. Naturally, as for all entities that regulate gene DNA methyltransferases expression, are involved in diseases. Anomalous methylation is associated with Rett syndrome for instance - a rare genetic mutation that affects brain development in girls - or certain forms of cancer where hypermethylation can cause the inactivation of tumour suppressor genes. DNA methylation is a bit of a dark horse – apparently lacking complexity, it seems to be an essential part of what is driving life.

## **Cross-references to UniProt**

DNA (cytosine-5)-methyltransferase 3C, Mus musculus (Mouse) : P0DOY1

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