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Aberrant appendages

Having a second pair of hands might seem like an advantage but animals born with extra limbs, because of changes in their DNA, generally do not fair well. For more than 25 years, scientists have known about the existence of a mutation in a fruit fly gene that causes just such aberrant appendages, yet the identity of this gene remained a mystery.

That is until developmental biologist Jürg Müller and his team at EMBL Heidelberg set out to find the gene responsible. By comparing the DNA of mutant and normal flies, Jürg's group pinpointed the mutation and found that it disrupts the genetic code for the protein Ogt, an enzyme that sticks sugar molecules to the outside of proteins.

"Ogt is atypical because, unlike other enzymes that add sugars to proteins that eventually reside on the cell's surface or are secreted by the cell, Ogt adds a sugar to proteins in the cell's nucleus and cytoplasm," says Jürg.

"The sugar modification added by Ogt has been found on hundreds of other proteins, and so it was a little unexpected that removing this one protein would cause such profound developmental defects," explains Maria Cristina Gambetta, the PhD student who carried out this work in Jürg's lab. For this reason, Ogt was the last gene on a shortlist of 11 candidate genes that the group examined.

Because flies lacking Ogt show dramatic changes in their head-to-tail body patterning, the researchers suspected that the Ogt protein adds a sugar to a family of proteins that regulate the genes required for normal patterning. These proteins – called Polycomb proteins – do this by remodelling the DNA into compact structures called chromatin. By sitting on the chromatin, the proteins condense the DNA, making it inaccessible to the cellular machinery that would transform the genetic code into active proteins.

To confirm Ogt's role in adding a sugar to the Polycomb proteins, the next step for Jürg's group was to look whether the sugar and Polycomb proteins typically sit together on the chromatin. By tagging the proteins and sugars, they found that they were bound together in regions that are important for controlling whether genes are turned on or off. These findings hinted that the sugar was somehow needed for Polycomb proteins to silence the genes involved in building the fruit fly's body plan.

Jürg's team went on to show that the sugar was attached to just one member of the Polycomb protein family – a protein called Ph. "We don't know why adding a sugar to Ph is important for its function, but this is what we hope to investigate next," says Jürg. "But what we have found so far is a novel and unexpected role for the sugar added by Ogt; the fact that fruit flies that lack this sugar show compromised Polycomb silencing but no other obvious defects is remarkable." Ogt is likely to fulfil a similar role in humans, and so it could determine the positioning and number of our own arms, legs, ribs and, well, everything.

Gambetta MC, Oktaba K, Müller J (2009) Essential Role of the Glycosyltransferase Sxc/Ogt in Polycomb Repression. *Science* **325**: 93 - 96