Tagging the tail on the histone

Nearly 60 years ago, Pamela Lewis, a geneticist at the California Institute of Technology in Pasadena, noticed that some of the flies she was experimenting on had tiny comb-like structures on their second and third pairs of legs, and not just the first pair as is usual. Lewis called these structures 'sex-combs' because males use them to grasp females during mating and she went on to discover the first *Polycomb* gene, one of many such genes now known to encode proteins that disrupt head-to-tail body patterning in a variety of animals, ranging from humans to fruit flies to worms.

Christoph Müller and Jürg Müller

When these genes are mutated, structures in one part of the animal are transformed into structures normally found in another part of the body. Developmental biologist Jürg Müller, a group leader who studies Polycomb group proteins (see page 80) in EMBL Heidelberg's Genome Biology Unit, explains that these proteins are responsible for turning off genes in the body regions where their products don't belong. This suppression is usually permanent: the genes remain silenced even after the cell divides. Polycomb proteins do this by tagging histones – spool-like structures around which DNA is wound – causing them to become compacted to the point that genes on the DNA itself become inaccessible to the cellular machinery.

But how these silencing proteins choose which histones to tag and how this tagging leads to the silencing of nearby genes remains a mystery. To investigate this puzzle, Jürg teamed up with structural biologist Christoph Müller, joint head of the Structural and Computational Biology Unit at EMBL Heidelberg, to study how one Polycomb group protein complex known as PhoRC binds to the flexible tails of histones.

The researchers had previously found that PhoRC is made up of two parts: the first part, Pho, contains a DNA-binding site, whereas the second, dSfmbt, recognises a molecular tag that is attached to a region of the histone tail. This arrangement helps dSfmbt find the DNA regions to be silenced, Christoph explains. "dSfmbt is very selective about which tag it binds to, preferring to bind only to a certain kind of tag, while other, very similar, tags are not recognised," he says. "But we were surprised that dSfmbt is less specific about which region of the histone tail it binds." Combining biophysical analysis and crystallography, the researchers examined the structure of the bound dSfmbt at high resolution and to their surprise, they saw that this region of the dSfmbt protein possessed four similar cage-like structures, only one of which secured the histone tag.

Jürg, Christoph and their groups also found that dSfmbt binds to another protein, called Scm. The researchers found that Scm uses similar cage-like structures to bind the same tags on histones. The researchers suspect that when these two histone-tethered proteins bind to each other they act as a bridge between neighbouring histones that helps to keep the DNA tightly coiled. Through their combined efforts, these two proteins switch off the genes that are meant to be inactive in a particular part of the developing fruit fly.

But many questions still remain. "What we still don't fully understand is how PhoRC helps to recruit other Polycomb proteins that go on to ensure that the nearby genes are silenced," explains Jürg. He and his group would also like to pinpoint what stops Polycomb proteins from silencing genes in all cells, allowing these genes to remain 'on' in regions of the body where their activity is needed to produce the fly's normal body pattern.

Grimm C, Matos R, Ly-Hartig N, Steuerwald N, Lindner D, Rybin V, Müller J, Müller C (2009) Molecular recognition of histone lysine methylation by the Polycomb group repressor dSfmbt. *EMBO J* **28**: 1965-1977