Molecular monkey arranges X-chromosome activation

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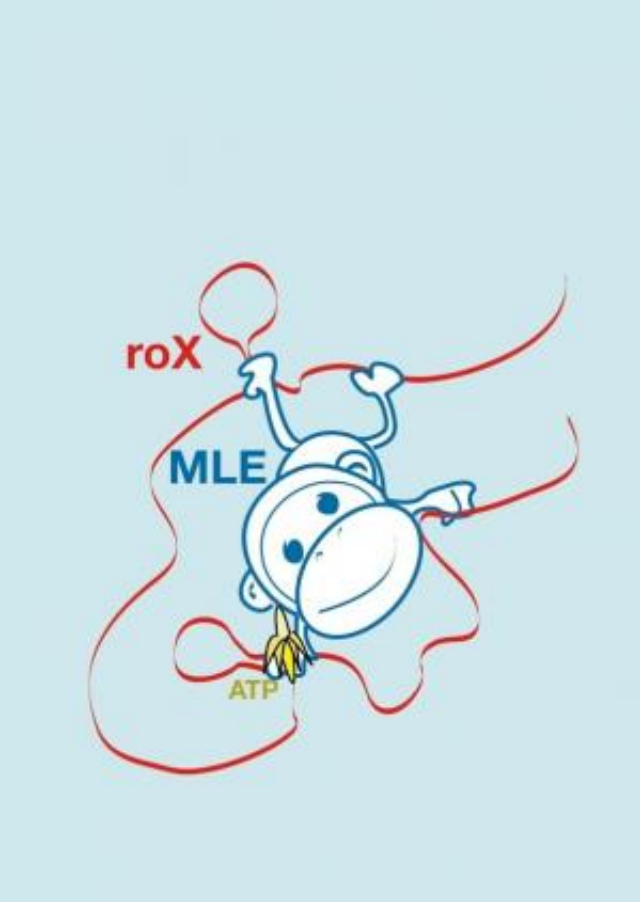

The protein MLE grabs the RNA strand like a monkey grabs a liana. One site serves as a simple anchor (feet), while the other is able to mould the strand. This consumes energy (banana). The moulded RNA allows other proteins to bind and thus to activate the X chromosome in male flies. Credit: MPI of Immunobiology and Epigenetics Ibrahim Ilik, Tugce Aktas

X chromosomes are very special genetic material. They differ in number between men and women. To achieve equality between sexes, one out of two X chromosomes in women is silenced. In flies, the opposite happens: in male flies, the only available X chromosome is highly activated, to compensate for the absence of the second X-chromosome. Researchers from the Max Planck Institute of Immunobiology and Epigenetics (MPI-IE) in Freiburg have now shown how the RNA molecules and proteins involved in the activation find and stick to each other. Similar to a monkey that grabs a liana with hands and feet, one of the proteins holds on to the RNA. Then it moulds the molecular liana with its hands and thus generates a dynamic RNA - protein meeting place.

Just a few years ago, they were assumed to be genetic trash: DNA sequences that are not translated into proteins. But this has rapidly changed during the last years. Nowadays, it is widely known among scientists that much of the DNA is transcribed into RNA that, in turn, can act as gene regulator and structural element. Also in the regulation of sex chromosomes, RNA plays a central role. In both female humans and male flies one X chromosome is covered by a protein-RNA complex. In humans, this leads to chromosome silencing, while in flies it results in a double activation of the chromosome. Misregulation is lethal. Although known for many years, the interaction between the central proteins and the distinct role of the RNA strand was unclear.

Asifa Akhtar of the MPI-IE and her team now unravelled the function of the RNA and the interaction of the proteins. The protein MLE that is known to be a central player in X chromosome activation binds to the RNA in a very special manner. Like a monkey that grabs a liana with hands and feet, the protein grabs the RNA in two different ways. While one site is a simple anchor (the feet), the other (the hands) changes the form of the RNA. "The protein MLE moulds the RNA strand. This allows MLE to bind the RNA in a dynamic manner", says Asifa Akhtar, head of the study. Like one monkey helping the other to catch the liana

MLE could thus help other proteins to grab the RNA strand. Thus, the whole X chromosome can be covered by the RNA-protein complex.

During his PhD work, first author Ibrahim Ilik investigated why MLE was found at the same places on the X chromosome but did not directly interact with other proteins. "The biochemical and the biological results seemed to point in different directions in the beginning", says Ilik. "But when we realised that the proteins bind highly specifically to certain regions of the very long RNA, this was a very exciting moment."

The researchers also found that individual mutations in the RNA hardly harm the protein-RNA binding. Only multiple mutations lead to a non-functional RNA and thus to lethality of male flies. "The system is very robust for evolutionary influences. This shows how important it is for the survival of the animals. In this, RNA could provide the necessary plasticity", says Akhtar. The scientists now want to explore the evolutionary conservation of the RNA-protein system and its equivalent in mammals.

Scientists at the Max Planck Institute of Immunobiology and Epigenetics (MPI-IE) in Freiburg investigate the development of the immune system over the course of evolution and during lifetime. They analyse genes and molecules that are important for immune cells maturation and activation. Researchers in the field of epigenetics investigate the inheritance of traits that are not caused by changes in the DNA sequence. Epigenetic research is expected to lead to a better understanding of many complex diseases, such as cancer and metabolic disorders.

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