The fight against genome parasites

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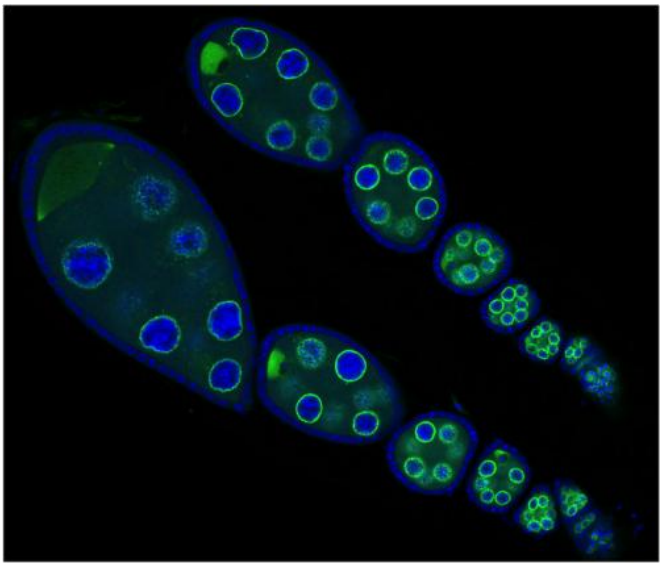

Drosophila Ovaries.

In the gonads of animals, genome parasites such as transposons pose a serious threat to evolutionary fitness. With their ability to bounce around in the genome, they often cause dangerous mutations. To protect genomic integrity, animals evolved a sophisticated mechanism – the so called piRNA pathway – to silence the deleterious transposons. Not much is known about the molecular processes and the involved factors that constitute the piRNA pathway. Researchers at the Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences (ÖAW) in Vienna have now identified ~50 genes, that play important roles in the piRNA pathway of the fruitfly Drosophila melanogaster.

With roughly 50%, the human genome is densely populated with genome parasites, and so is the DNA of other animals, plants and fungi. Many of these selfish DNA elements are able to freely move around in the host's genetic material. They are referred to as transposons and their mobility causes DNA breaks and mutations that can lead to severe genome damage.

Although they are harmful, most organisms do not specifically eliminate transposons from their DNA. Such a massive intervention might bear too much of a risk for germ cell genomes and hence a species reproductive fitness. To deal with the potential dangers, plants and animals possess defense systems – also seen as sort of a 'genome immune system'. In all cases, these are based on small RNA silencing mechanisms and hence date probably back to the early days of eukaryotic evolution. The ancient silencing systems are able to selectively interfere with transposon expression preventing them from causing damage.

In animals, the most prominent of these silencing pathways is the so-called piRNA pathway. At its core act so-called RNA induced silencing complexes (RISC) that are composed of PIWI proteins bound to 22-30nt long piRNAs. Via the small RNA, PIWI complexes recognize transposon RNAs and this induces degradation of the transposon RNA and feeds back negatively on the encoding locus on the host DNA to inhibit transposon transcription.

Pioneering spirit at IMBA

The field of piRNA research is relatively young and only a handful of experts exist worldwide. One of them is the molecular biologist Julius Brennecke. Since 7 years the IMBA group leader is investigating transposon control mechanisms in Drosophila gonads. The fruitfly is one of the genetic workhorses of molecular geneticists and many aspects of piRNA biology have been pioneered in this model system. Brennecke's fascination for this system arose during his postdoctoral studies in the US: "This is one of the most ancient host-parasite conflicts and to understand it at the molecular and genetic level is simply fascinating".

With his transition to IMBA in Vienna, he managed to establish this highly competitive field in Austria. His work has a pioneering spirit, since the archaic

piRNA-signalling pathway and his underlying mechanisms are still poorly understood. "We really want to know in detail, how the fly manages to keep transposons in check", says Brennecke.

With their recent work, Brennecke and his team made a major step forward in the dissection of the piRNA pathway. With a mix of genetic, molecular and computational methods the team performed a screen in the Drosophila ovary for factors involved in the piRNA pathway. All in all they examined 7,000 different genes and manually inspected around 60.000 fruitflies for defects in transposon silencing.

Fly library as goldmine of knowledge

For their screen, Brennecke and his group took advantage of the Vienna Drosophila RNAi Center (VDRC) library, a collection of ~30.000 fly stocks each allowing the silencing of a specific gene in a desired cell type. The VDRC library was established at the IMBA/IMP campus under leadership of Barry Dickson and Krystyna Keleman and is now run by the Campus Support Facility (CSF). From there, flies are sent out to institutes and research centers all over the globe. "The Vienna fly library is a worldwide unique resource that allows systematic studies of gene function in virtually every aspect of fruitfly biology", compliments Brennecke.

In their two years of work, Brennecke and his group discovered around 50 genes that are important for a fully functional piRNA pathway. Dominik Handler, PhD student in Brennecke's lab and first author of the study, explains: "For many of the identified genes, orthologous genes can be identified in the human genome, too. Our results will therefore have a broad impact on the general understanding of this transposon silencing system." Some of the identified genes are required for the biogenesis of piRNAs, but others connect the defense system to basic processes such as mitochondria-metabolism, RNA transport, transcription or chromatin-biology.

Signalling-pathway with great potential

The obtained results set the stage for multiple lines of future investigations, underlines Brennecke. The identified factors will play key roles in understanding the mechanistic framework of the pathway, but they will also be unique entry points into understanding how this silencing system is embedded into the general process of oogenesis. Key question along those lines are how piRNAs are passed from generation to generation and what evolutionary benefit the host might have from transposons. Brennecke is fascinated by the close interplay between possible advantages and dangers that transposons and other repetitive sequences have for host genome regulation. He is confident: "Core concepts of the piRNA pathway are highly conserved amongst organisms. I have no doubt, that our results will have far reaching implications for the understanding of genome evolution and possibly even aspects of human medicine."

More information: The Genetic Makeup of the Drosophila piRNA Pathway, *Molecular Cell*, Doi: 10.1016/j.molcel.2013.04.031

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