How cells hack their own genes

August 24 2017

DNA in all organisms from yeast to humans encodes the genes that make it possible to live and reproduce. But these beneficial genes make up only 2 percent of our DNA. In fact, more than two-thirds of our genome is populated by selfish genes that only care about their own replication – so-called genetic parasites. Scattered throughout the genomes of plants, fungi, and animals, they can jump from one genomic location to another. Although they can be important for generating diversity in the genome, they can also cause lethal mutations or sterility. Just as bacteria use the CRISPR/Cas9 system to identify and cleave viruses invading their DNA, eukaryotic cells have developed various strategies to protect the genome and silence these selfish genetic parasites. Small regulatory RNAs govern many of these genome-defense mechanisms and have also yielded major biotechnological innovations.

Solving an evolutionary "chicken and egg" dilemma

One important pathway that maintains the genomic integrity of animals is the piRNA pathway. This system is active in germ cells and utilizes small snippets of RNA—so called piRNAs—which fit like mirror images onto the transcripts of selfish sequences and thereby initiate silencing with their associated Argonaut proteins. The Brennecke lab at IMBA has been rigorously exploring these RNA-based self-defense mechanisms in fruit flies, using cutting-edge next generation sequencing. The source of piRNAs is within silenced regions containing the selfish elements. This organization established an evolutionary "chicken and egg" dilemma: How could piRNAs be generated from the very regions that they silence? In their current *Nature* publication, Brennecke's lab not

only solve this enigma but also describe a completely new mechanism for gene-expression.

Moonshiner: There is always a way around

The newly discovered pathway is centered around a protein called moonshiner. Moonshiner is related to basal transcription factors, and interacts with Rhino, a protein bound to heterochromatin at the selfish genes. Rhino recruits Moonshiner to the heterochromatic region, and Moonshiner initiates assembly of the RNA polymerase II pre-initiation complex, that catalyzes the transcription. Therefore, gene expression is activated in an otherwise silent region via a different code embedded in histone marks rather than DNA sequence. The findings show that piRNAs are transcribed by bending the classical rules of gene activation, combining elements of standard gene activation with gene silencing. "The pathway, that is active in the piRNA clusters – where the piRNAs are born – literally hacks the gene machinery by combining two different systems, gene activation with gene silencing, just like furniture can be repurposed by IKEA hacking," illustrates Peter Andersen, Postdoc at IMBA and first author of the paper. The moonshiner pathway thus reveals how cells can utilize heterochromatin for transcription. "Cells have developed strategies to bypass conventional pathways. The current findings are not only essential to understand the arm´s race between useful genes and the selfish genes that have shaped and still drive evolutionary processes, they also contribute to understanding gene expression in a holistic way," says Julius Brennecke, IMBA group leader and last author.

More information: Peter Refsing Andersen et al. A heterochromatin-dependent transcription machinery drives piRNA expression, *Nature* (2017). DOI: 10.1038/nature23482

Provided by Institute of Molecular Biotechnology