RNA-mediated epigenetic inheritance

The central dogma of molecular biology, which is still largely considered one of the most core fundamental concepts in the field, states that DNA is transcribed to RNA, which is then translated into protein. Although this statement is true, it may be an oversimplification because over the years we have discovered many novel roles of players in this pathway, including the very diverse functionality of different classes of RNAs and also the structure of the underlying DNA itself. In the age of next-generation sequencing, where entire sequenced genomes are available to the public, much attention has shifted from analysis of the genomic sequences themselves to epigenetics, which involves how the structure of DNA, or how it is packaged within the cell, affects how it behaves (i.e. which genes are physically accessible for expression at a given time, differential gene expression among cells of the same organism, etc.) Taking this concept one step further, we may define the term transgenerational epigenetic inheritance as heritable changes to the state of DNA, without changing the underlying sequence, which may be passed to subsequent generations. An interesting theme that has been emerging in the field of transgenerational epigenetic inheritance more recently, is that RNAs, once thought to be simply an intermediate by which genes are expressed, play a significant role in affecting the chromatin states of subsequent generations in some of the model systems investigated. Here we will focus on two of the most well studied examples of RNA-mediated transgenerational inheritance, which are the ciliates and flowering plants. These examples make it clear that not only is the actual sequence of DNA important for biological functions, but the way RNA and proteins interact with it to modify the way it is expressed is just as fundamentally important.

Ciliates are large, unicellular eukaryotic protists that can be found in both fresh and salt water environments across the planet. Although very diverse, all ciliates share a common characteristic called nuclear dimorphism, in which two different types of nuclei exist in each single cell. The germline nucleus, or micronucleus (MIC), is similar to a typical eukaryotic nucleus and contains the entire genome on long chromosomes, but is transcriptionally silent. The macronucleus (MAC) however provides all the necessary transcription for vegetative growth of the cells and is considered the somatic nucleus. One major difference between the two nuclei, is that while the MIC contains large amounts of “junk” DNA, including transposable elements, microsatellite repeats and internally eliminated sequences (IESs) that interrupt coding genes, the MAC is devoid of these sequences and the genes have been processed so that they may be properly transcribed. During each sexual cycle, the parental MAC provides genetic information for the formation of a new macronucleus from a micronuclear precursor, in the form of transported small RNAs (sRNAs). Not only are sRNAs involved in marking which regions of the genome are to be retained and eliminated during development, but long noncoding RNAs have also been implicated in specifying how retained genomic sequences are then stitched back together in the proper functional order.

Epigenetic inheritance has also been extensively studied in flowering plants, with *Arabidopsis thaliana* being one of the best examples. In these types of plants, epigenetic inheritance most often comes in the form of RNA-directed DNA methylation (RdDM), which helps to target and suppress the expression of transposable elements and other repetitive DNA sequences. sRNAs derived from these specific regions along with the help of other protein complexes, lead to methylation of the DNA template and gene silencing by changing the structure of the DNA itself. The repressive histone modifications generally associated with RdDM, lead to establishment of a heterochromatic state, inhibiting the transcriptional activity in the region. These methylation patterns that are established across these repetitive DNA sequences are then passed from parent to offspring upon fertilization, with particular methylation patterns being simultaneously reestablished during development.

Zachary T. Neeb, Mariusz Nowacki
Institute for Cell Biology, University of Bern, Baltzerstrasse 4 3012 Bern, Switzerland

Publication

RNA-mediated transgenerational inheritance in ciliates and plants.
Neeb ZT, Nowacki M
Chromosoma. 2018 Mar