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Identification and Functional Characterization of the Neuronal Piwi/PiRNA Complex in the Central Nervous System of Aplysia Californica

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In both vertebrates and invertebrates, the expression of the ribonucleoprotein (RNP) complex formed by the RNA-binding protein Piwi and its associated small noncoding RNAs, called Piwi-interacting RNAs (piRNAs), has been generally accepted to be restricted to germ cells, where the Piwi/piRNA complex is involved in epigenetic and posttranscriptional silencing of transposable elements (TEs).

In this study, the discovery of neuronal piRNAs in the CNS of the mollusk Aplysia californica is reported. Those neuronal piRNAs are abundantly expressed, selectively enriched in the CNS and exhibit all characteristic features of piRNA, including their typical length of 26-33 nt, a strong 5'-Uridine bias, genomic clustering, 2'-O-methylation at their 3'-end and - most importantly - specific association with Piwi proteins. Further experiments revealed that the neuronally expressed Piwi protein and its associated piRNA fraction are both predominantly localized in the nucleus of Aplysia neurons. Hence, it was tempting to speculate that the neuronal Piwi/piRNA complex occupies a nuclear role, which might be entirely different from the role the Piwi/piRNA complex has in the germline. Subsequent functional analysis indeed suggested a role for the neuronal Piwi/piRNA complex in synaptic plasticity through epigenetic regulation of the transcription factor CREB2. At this, the study shows that serotonin (5HT), a neuromodulator important for learning and memory, upregulates Piwi and a subset of neuronal piRNAs. The complex formed by Piwi and a specific upregulated piRNA, piR-F, hereupon mediates increased DNA methyltransferase (DNMT)-dependent methylation of the CREB2 promoter, which entails decreased CREB2 expression and facilitates LTP.

The study has the potential to significantly impact out understanding of the Piwi/piRNA complex and the molecular biological mechanisms it employs as well as to increase our knowledge on how transient neuronal stimuli can be converted into stable memory traces. First, the previously prevailing paradigm that Piwi/piRNA expression is germline-specific is shaken and needs to be revised. In fact, several other findings have been published in the aftermath of the study that also question the germline-specificity of the Piwi/piRNA complex and suggest a broader role for this relatively young and exciting ribonucleoprotein complex. Second, the study demonstrates that dynamic methylation of a gene promoter as epigenetic regulatory mechanism can have long-term affects on synaptic strength, which constitutes an exciting new way for neurons to store memory. Although this hypothesis awaits further validation, a molecular mechanism is proposed in which the Piwi/piRNA complex binds the nascent transcript through sequence complementarity of piR-F and the originating mRNA to subsequently recruit DNMT to the CREB2 promoter and hence mediate its methylation.