The evolutionary cauldron of Nidovirales

Positive RNA viruses are forced to protect their genome. To do so, they use enzymes that will modify the RNA to ensure stability and escape from the immune system. In this article, published in the journal *Nucleic Acids Research*, scientists characterize one of these enzymes in a family of viruses related to Coronavirus. The emergence of the latter shows that the function is critical and that its evolution is not linear.

The *Nidovirales* constitute a viral order that groups together various families of viruses, notably the *Coronaviridae*, whose particularity is to possess large RNA genomes. Generally speaking, the genomic organization of the *Nidovirales* presents two large open reading frames (ORF1a and ORF1b). ORF1a encodes the scaffolding proteins of the replication complex (protein activator, and innate immune system antagonist enzymes) while ORF1b encodes RNA synthesis, editing or degradation enzymes, including all currently known methyltransferases. For the *Coronaviridae* (CoV) family, the N7 and 2'O cap methyltransferases protecting RNA from degradation have been well characterized, residing in nsp14 and nsp16, respectively, both in ORF1b.

In the case of *Tobaniviridae*, another family of *Nidovirales*, only the 2'O-methyltransferase, located at the end of ORF1b, could be easily identified, while the probable presence of an N7-methyltransferase in ORF1a, a strange location for this gene remained discussed. In this paper, the scientists demonstrate that this domain indeed harbors a specific N7-methyltransferase activity, which breaks with the common concept that Orf1b carries such RNA editing/replication enzymes. They present its structure at very high resolution, resolved by X-ray crystallography and the use of a remote structural model generated by Alphafold2. This structure shows a canonical folding MTase, despite a very limited sequence conservation with known N7-MTases. This ORF1a MTase from nidoviruses is thus remarkably different from nsp14 from CoVs.

This new structure and activity is essential to understand the different strategies developed by nidoviruses to cap their genomic RNA. It highlights how critical this methylation function is for the survival of these viruses, and also shows that in this order, different gene acquisition events have taken place, raising the question of the evolutionary advantages of such an appearance at this unexpected location in the genome in viruses infecting cold-blooded animals. Finally, this seemingly insignificant virus, like other poorly understood viruses, could provide biotechnological tools for stabilizing RNA therapeutics such as mRNA vaccines.

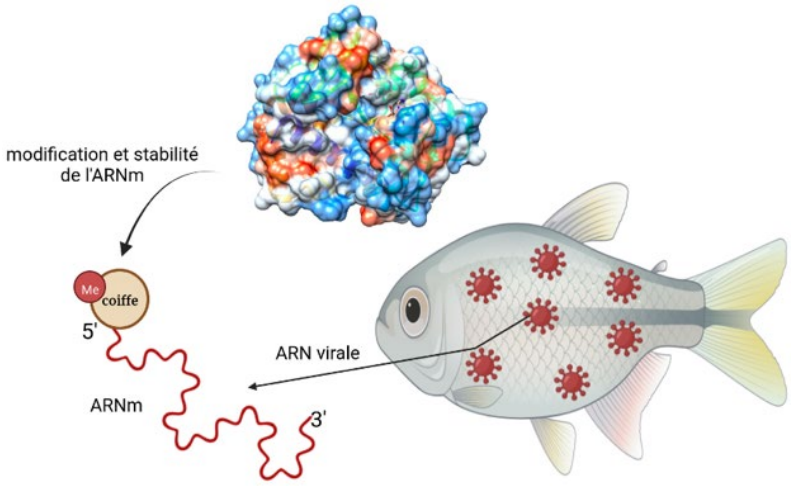

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Figure: Tobanivirus genome encodes a N7-specific Methyltransferase that aims to protect the genomic RNA and to avoid innate immunity. The structure is the first of its kind in a positive stranded RNA virus.

To know more:

A second type of N7-guanine RNA cap methyltransferase in an unusual locus of a large RNA virus genome

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