ABSTRACT

Nonretroviral RNA viruses (NRVs) are RNA viruses that do not code for an integrase or a reverse-transcriptase. Surprisingly, sequences from NRVs are not uncommonly integrated into the genomes of eukaryotes. These integrated viral sequences are called Nonretroviral Integrated RNA Virus Sequence (NIRVS). NRV comprise arboviruses (arthropod-borne viruses) and insect-specific viruses (ISVs). ISVs are viruses that infect exclusively insects, whereas arboviruses are viruses transmitted from arthropods to vertebrates, including humans. The Yellow fever mosquito, *Aedes aegypti*, and the Asian tiger mosquito, *Aedes albopictus,* are primary vectors for many epidemiologically relevant arboviruses including Dengue viruses (DENVs), Zika and Chikungunya virus (CHIKV). Previous studies of my own laboratory identified an enrichment of NIRVS of the *Flaviviridae* and *Rhabdoviridae* families in *Aedes* spp. mosquitoes with respect to other culicine, including *Anophelinae*, which are primarily parasitic vectors. The mechanism through which the integration event occurs and the NIRVS biological role are still poorly understood. In both *Aedes* spp. species, NIRVS are embedded within transposable element (TE) sequences, are enriched in piRNA clusters and produce piRNAs. The similarities observed between the way TEs and NIRVS are organized in piRNA clusters suggests that these viral integrations could be markers of past infections and have a role in antiviral immunity against cognate viruses. A corollary of this hypothesis is that NIRVS landscape should depend on the mosquito viral exposure, thus be different across wild mosquito populations.

On this basis, I combined bioinformatic and molecular approaches to the discover novel NIRVS (i.e. NIRVS not present in the annotated genome of each species) in wild collected samples and study their widespread distribution. In my thesis, I contributed to the development of a bioinformatic pipeline, named NovelViR, to identify novel viral integrations in the genomes of non-model organisms, such as those of *Aedes* spp. mosquitoes. NovelViR solves the dispersion of the information caused by repeated elements in the genome and generates hypothesis of integration events. Using this pipeline, I identified and then validate novel NIRVS in wild-collected samples of both mosquito species. Once novel NIRVS were molecularly validated, I also designed specific PCR primers to test their distribution across different geographic populations. Results showed that NIRVS distribution patter is concordant with the different *Ae. aegypti* and *Ae. albopictus* origin and invasion history.

This work lays the foundations for future functional studies to shed light on the biological role of NIRVSs in mosquito immunity.