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miRNA targeting in host-virus interaction: inter-strain comparison in Pseudorabies Virus

Marie-Laure Endale Ahanda^{1, 2, 3}, Thomas Letellier^{1, 2, 3}, Elisabetta Giuffra^{1, 2, 3}

¹INRA, UMR1313 Génétique Animale et Biologie Intégrative, F-78350 Jouy-en-Josas, France

²AgroParisTech, UMR 1313 Génétique Animale et Biologie Intégrative, 16 rue Claude Bernard, F-75231 Paris, France

³CEA, DSV, IRCM, SREIT, Laboratoire de Radiobiologie et Etude du Génome, F-78350 Jouy-en-Josas, France

Background

During a viral infection an intricate interaction takes place between a virus and its host. MiRNAs, a class of small regulatory molecules, have been shown to be major actors in this process. Several host miRNAs are essential to immune response, with few of them proposed to directly target viral genes and to inhibit viral replication. This is illustrated by the example of human miR-199a* overexpression leading to reduced Hepatitis C virus replication activity [1].

On the other side, viruses are able to use the miRNA-induced gene-silencing pathway to mediate immune evasion by modulating host and viral transcripts expression, and many herpesviruses including the Pseudorabies Virus (PrV) are known to encode multiple miRNAs. Herpesvirus miRNAs have been described to manipulate host response to enhance viral pathogenesis-and to promote the establishment of a reservoir of latently infected cells [2].

Aims

- ⇒ To identify viral miRNAs targeting viral transcripts > Deciphering the role of miRNAs in viral pathogenesis and immune evasion
- ⇒ To predict host miRNAs regulating viral transcripts > Discovering host antiviral miRNAs, or > host miRNAs exploited by the virus to its own benefit

Updating of the current pig miRNA catalog

257 porcine miRNAs _ miRBase release 18 (Nov. 2011)

Literature : small RNA sequencing

Mapping

Secondary structure inference

+

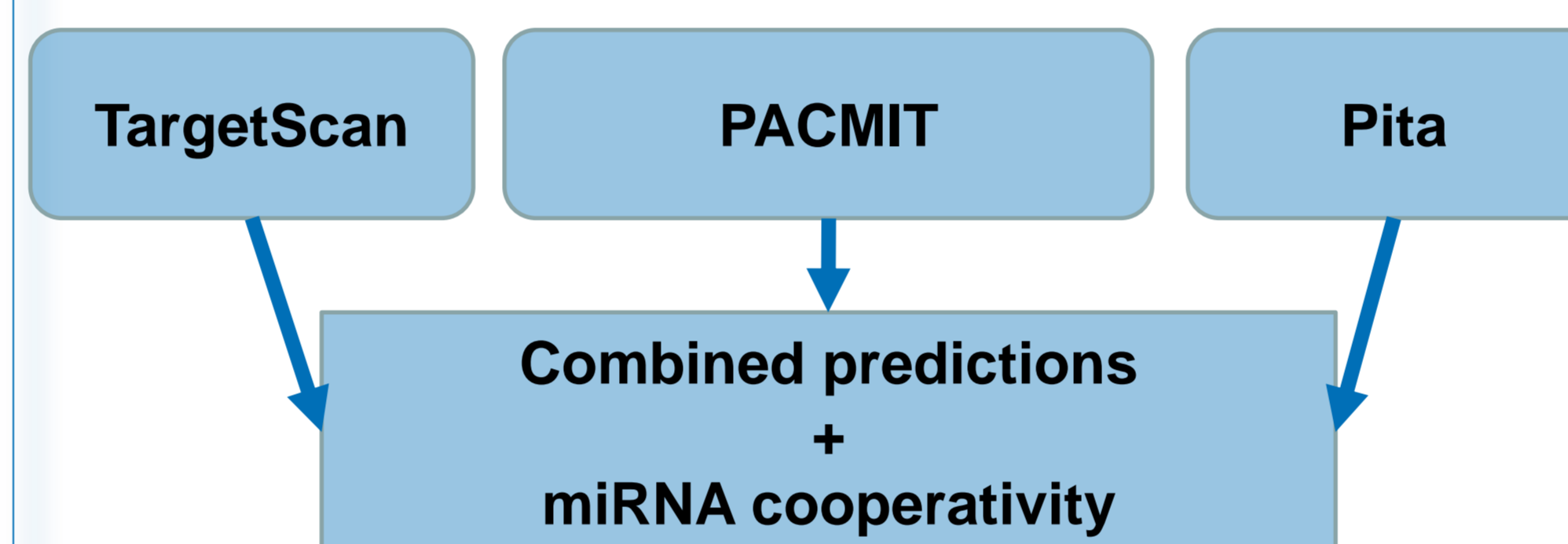
Compatibility of mature miRNA position in the stem-loop

394 new porcine miRNAs

Prediction of miRNA targets

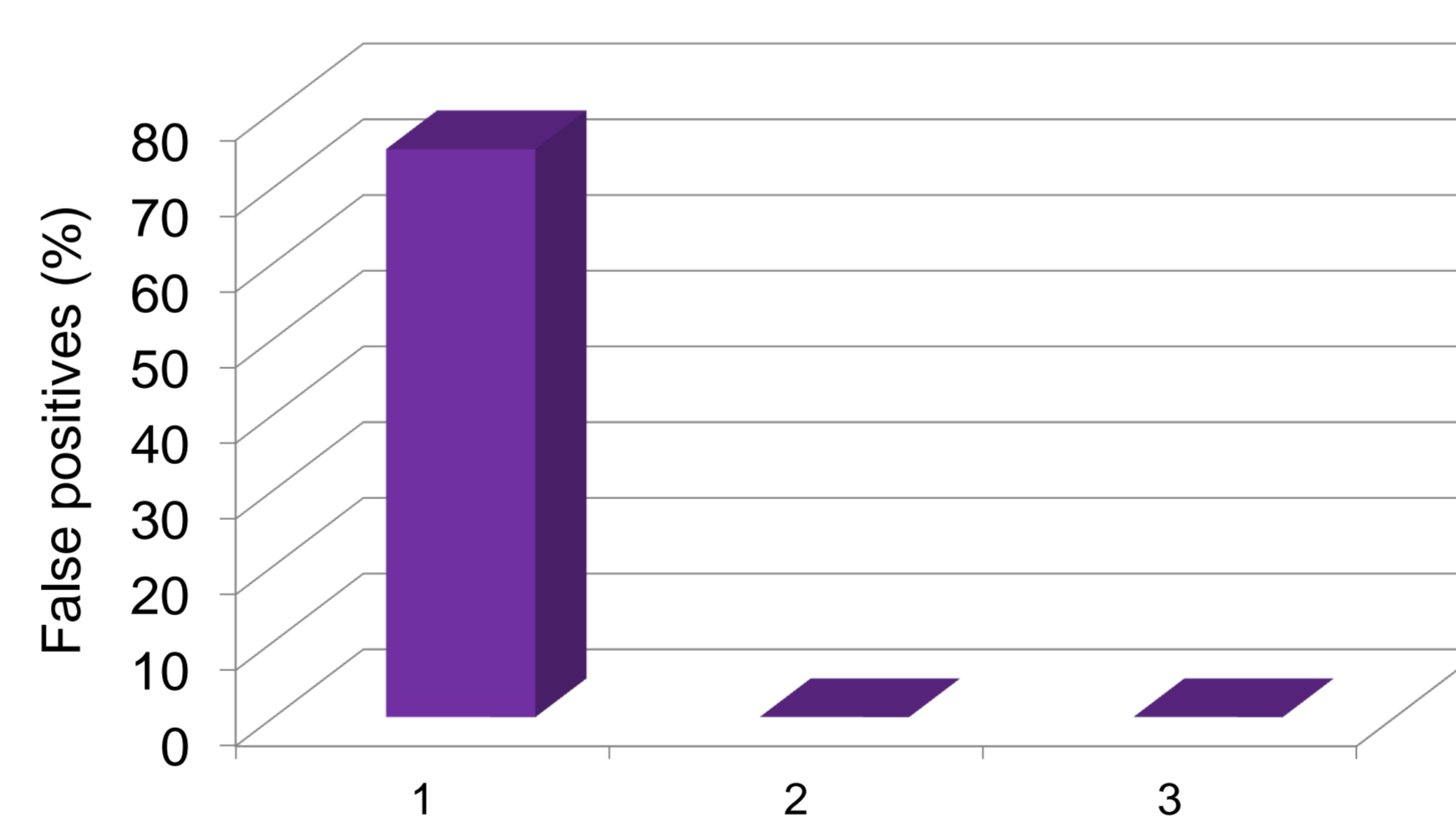
Creation of a pipeline combining three computational methods based on complementary criteria of target recognition

- TargetScan [3]: Inter-specific conservation
- PACMIT [4]: Site accessibility and over-representation
- Pita [5]: Site accessibility



Preliminary validation:

Positive and negative datasets (12+12 genes) extracted from an investigation of the global impact of miR-124 overexpression on protein output in human cells [6]



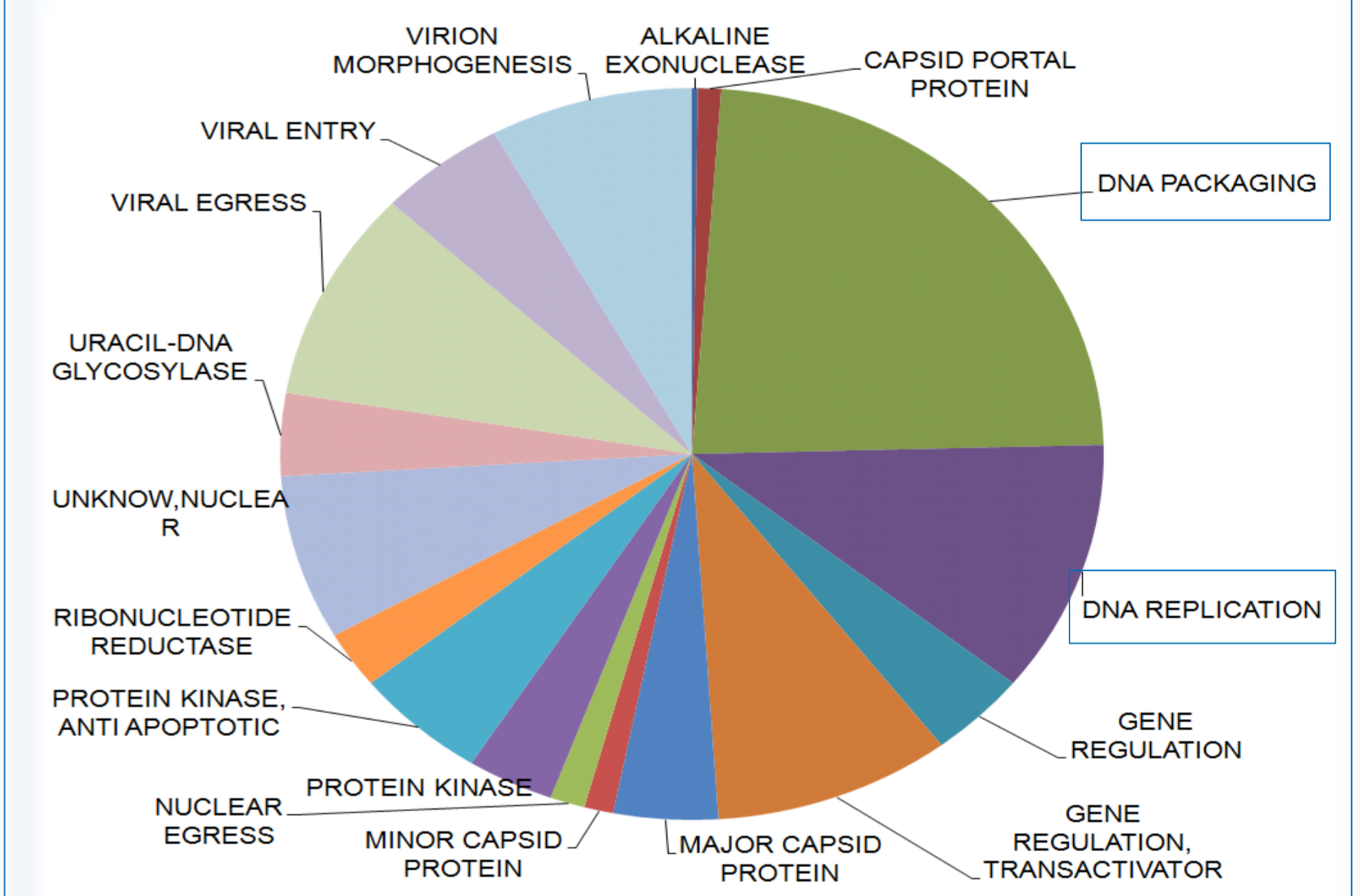
Combination of algorithms dramatically reduces the number of false positive

Most target predictions are conserved in the 3 PrV strains

	# Total of predictions	# Predicted in all strains
Host miRNAs	581	512 (88 %)
Viral miRNAs	69	55 (80%)

Viral targets of viral and host miRNAs

Genes targeted by host miRNAs are involved in viral essential functions



Host miRNA/ PrV mRNA interactions may be conserved in alphaherpesviruses

6 miRNAs conserved in human and pig are predicted to target both Human Simplex Virus (HSV) and PrV.

Pseudorabies virus (PrV)

- Alpha-herpesvirus
- Pig is its only *natural host*
- It encodes 70 proteins and a large latency transcript (LLT), and
- 12 miRNA genes located in the intron of LLT
- 3 PrV strains recently sequenced by high-throughput sequencing:
 - Kaplan } virulent
 - Becker }
 - Bartha (vaccine) => 4 deleted proteins

Conclusions/Perspectives

- Using a combinatorial approach to predict miRNA targets allowed to expand the range of potential miRNA/ mRNA interactions and to increase accuracy.
- Predicted target sites tend to be conserved among viral strains.
 - 6 predicted interactions (6 miRNAs targeting 5 viral targets) are also conserved in HSV.
 - Moreover, overexpression of 3 of these miRNAs can impact on the replication of other herpesviruses [7].
- ➔ The viral functions predicted to be targeted by host miRNAs determine essential and highly conserved steps of viral replication [8].
- ➔ Indeed, host miRNAs are predicted to target the same processes than those inhibited by currently available antiviral drugs.
- We are currently performing further predictions of miRNAs targeting others herpesviruses and performing functional validations in vitro.

References

- [1] Murakami et al. 2008. J Hepatol 50: 453–460. ; [2] Cullen. 2011. Curr Opin Virol. 1:211-215. ; [3] Lewis et al. 2005. Cell. 2005 Jan 14;120(1):15-20. ; [4] Marin et al. 2011. Nucl. Acids Res. 39 (1): 19-29. ; [5] Kertesz et al. 2007. Nature Genetics 39, 1278 – 1284. ; [6] Baek et al. 2008. Nature 455: 64-71.; [7] Santhakumar et al. 2010. Proc. Natl. Acad. Sci. U. S. A. 107:13830–13835. ; [8] Baines. 2011. Trends Microbiol. 19 (12): 606-613.

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