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▶ To cite this version:

Sandrine Le Guillou, Johann J. Laubier, Nezha N. Sdassi, Johan J. Castille, Jean-Luc Vilotte, et al.. Involvement of microRNAs in the mouse mammary gland development. Approches bioinformatiques pour décrypter la régulation des génomes, Centre National de la Recherche Scientifique (CNRS). FRA., Oct 2011, Bordeaux, France. pp.1. hal-01001042

HAL Id: hal-01001042 https://hal.science/hal-01001042

Submitted on 5 Jun2020

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Involvement of microRNAs in the mouse mammary gland development

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MicroRNAs (miRNAs) are a family of small noncoding RNAs involved in the negative regulation of target genes expression, by binding to mRNA complementary sites leading to their translational repression or degradation.



Mouse mammary gland development. (A) Schematic illustrating the development of the mouse mammary gland. Each stage of the schematic is accompanied by (B) matched time points of mammary glands in whole mount preparations. Andrechek et al., 2008

MicroRNA biosynthesis pathway. From http://www.wako-chem.co.jp/english/labchem/article/microRNA.htm

Until now, available data mainly report the identification of miRNA in tumoral mammary gland where aberrant expressions of miRNA have been demonstrated to be associated with cancer.

However, data about their involvement in normal mammary gland are still scarce even though this organ provides a very relevant model to study the involvement of miRNA in the control of different biological processes.

The characterization of miRNA expression in post-natal mouse mammary gland development is beginning to be documented:

- Avril-Sassen et al. (2009) data have been obtained by miRNA microarray hybridization on a chip exhibiting just over three hundred different miRNA. However, this microarray approach does not allow the identification of all miRNA expressed in the gland and specially the new miRNA. - We have performed a cloning approach to detect new miRNA, some of which are mouse-specific (Sdassi *et al.*, 2009). Despite the fact that we have obtained a limited number of clones, these results emphasized the need for a global approach to characterize miRNA expression such as the deep sequencing.

MiRNA-mediated gene regulation is a key component of a wide range of biological processes such as stem cell maintenance, development, morphogenesis, cell differentiation and proliferation, apoptosis, metabolism and is involved in several diseases including cancer. The function of most miRNA is still unknown and has become an **important topic of investigation**.

The identification of miRNA targets is an important step towards a better understanding of their function and different kinds of methods have been developed :

computational > New **experimental methods** to > Numerous generate miRNA better identify and validate miRNA methods to target predictions, based on targets: high-throughput to sequencing of RNAs isolated by complementarity sequence target sites (ex: TargetScan, cross-linking immuno-precipitation ((HITS-CLIP) or RNA-Induced PicTar, DIANA-microT). Complex (RISC) Silencing immuno-precipitation) (Nelson et al., 2007; Beitzinger et al., 2007; Chi *et al*;, 2009).

Mammary miRNome & miRISC description

Mammary miR-30b direct targets in vivo

We have performed the whole miRNome of a lactating mammary gland using high throughput sequencing to allow an exhaustive description of miRNA and to highlight some new and maybe mammary specific miRNA.

We compared it with its **RISC complex associated counterpart**, **miRISC**, in order to differentiate the subpopulation of active miRNAs at this stage.



We have established a transgenic mouse model that overexpressed one miRNA, miR-30b, in the mammary gland. These transgenic mice exhibit a defect in alveolar structure during lactation and a delayed involution.

To identify miR-30b direct targets in mammary gland and to evaluate the biological functions and pathways it controls, we developed a RNA-seq approach to compare mRNA present in the **RISC complex in control and transgenic mice.**





Our results should allow us to investigate miR-regulated biological functions and reveal pathways of regulations related to the identified targets by using adapted **bioinformatics approaches**.

