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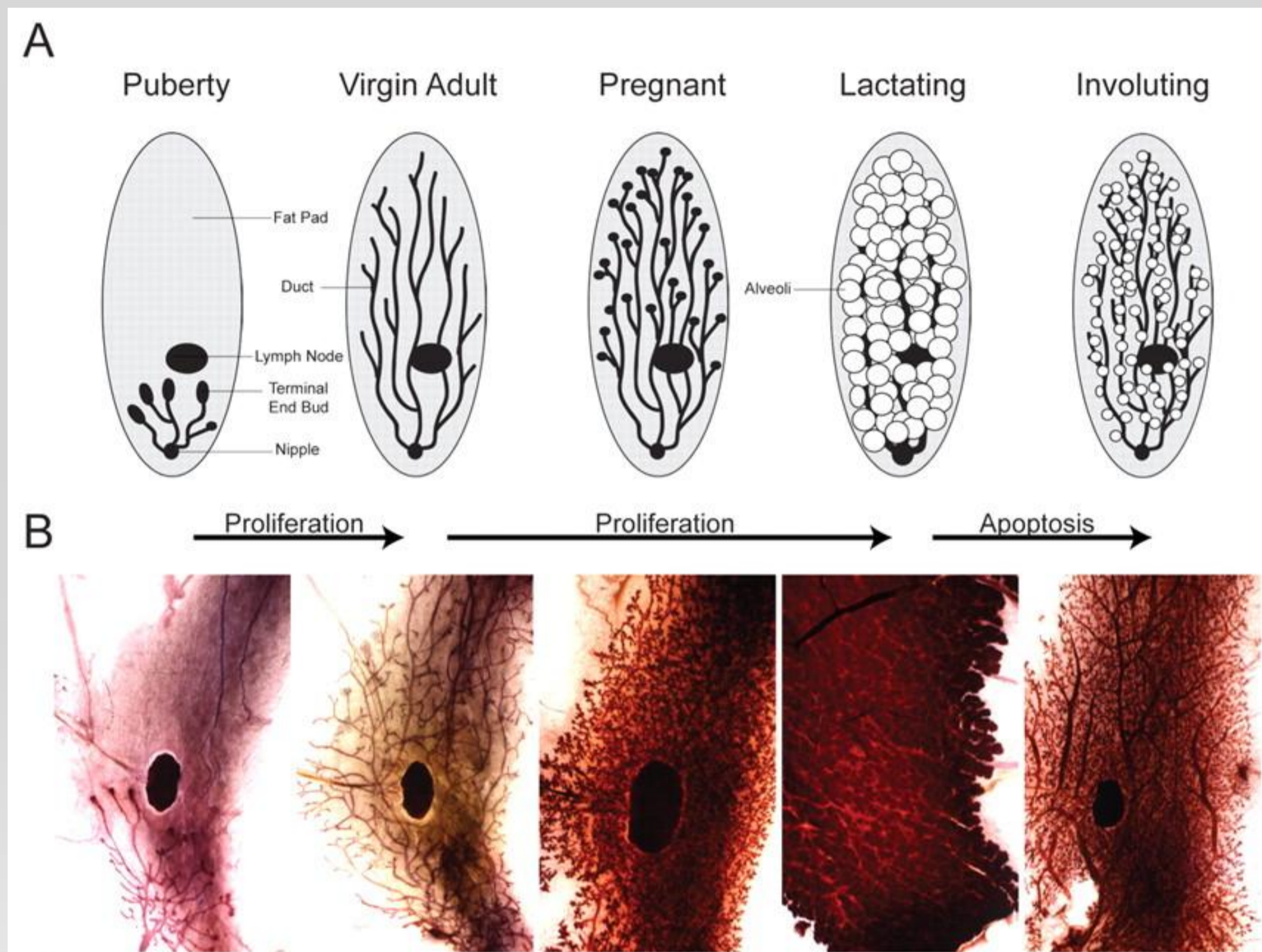
Involvement of microRNAs in the mouse mammary gland development

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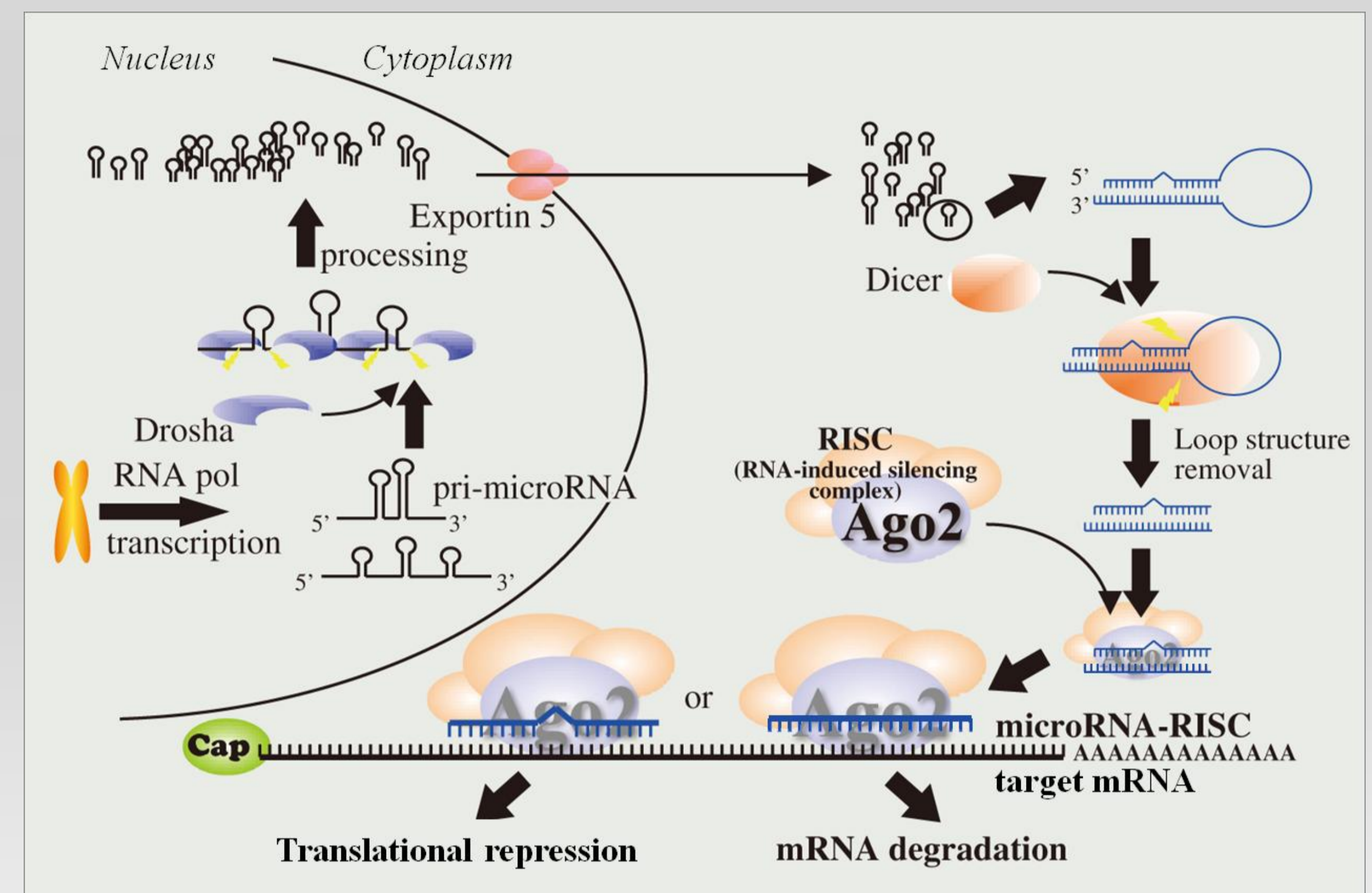


The **mammary gland** is a **dynamic organ** with successive physiological stages which are characterized by **proliferation, differentiation and apoptosis**.

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**.

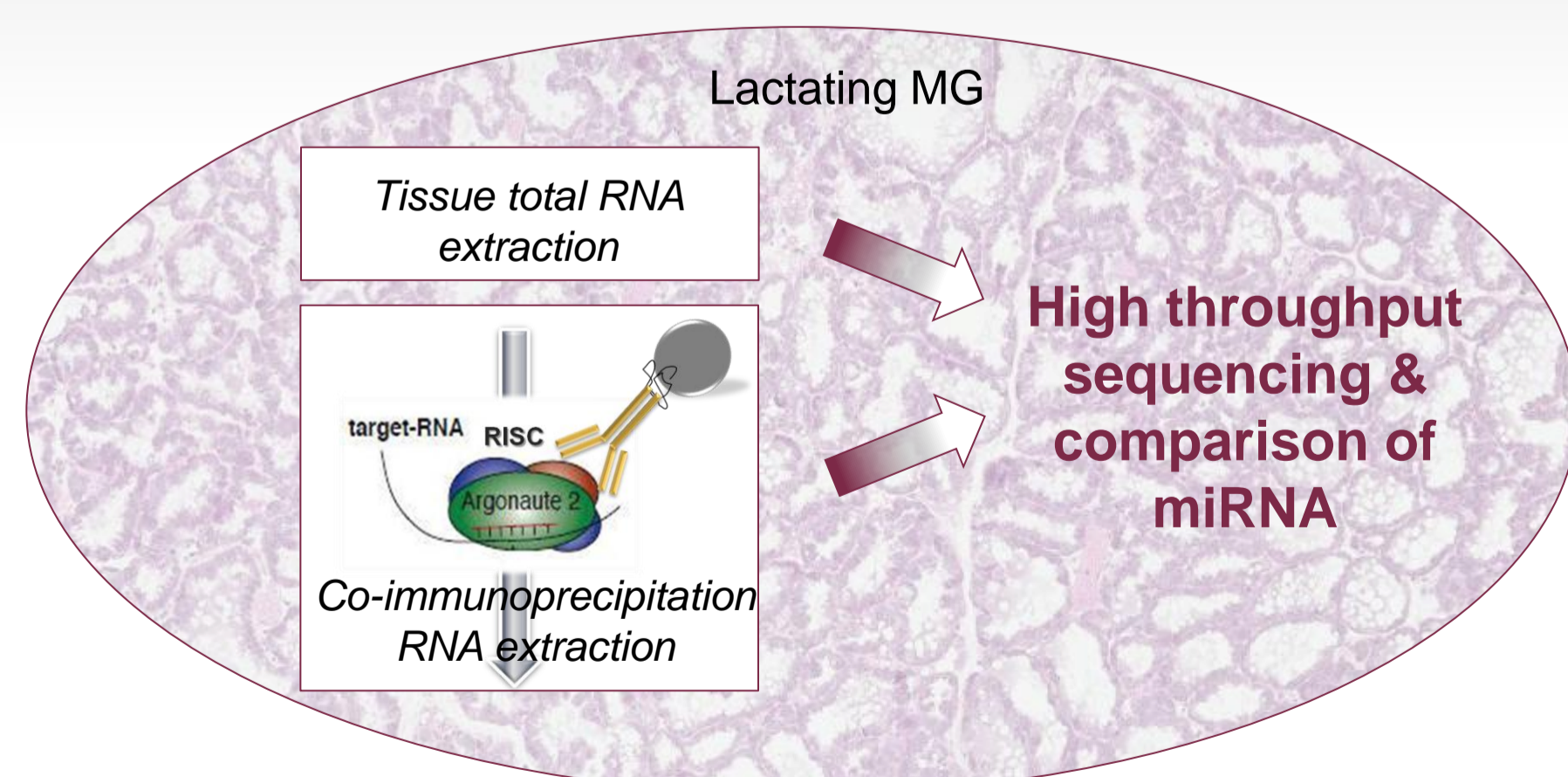
The **identification of miRNA targets is an important step towards a better understanding of their function** and different kinds of methods have been developed :

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

Mammary miRNome & miRISC description

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.

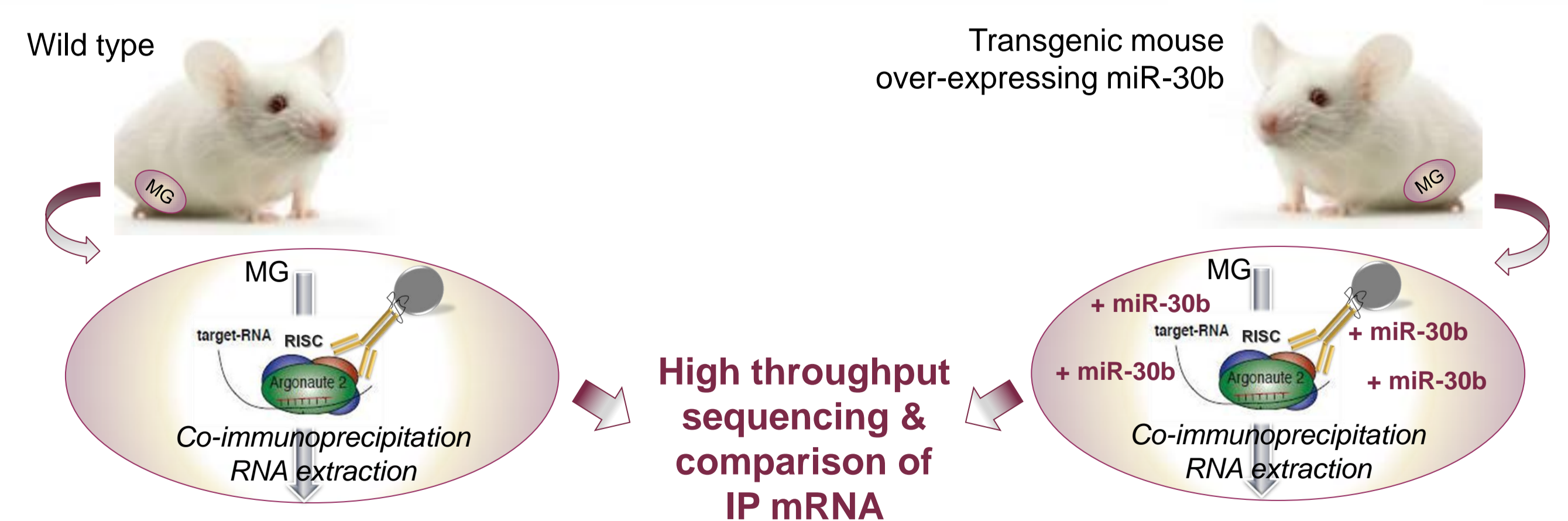
We compared it with its **RISC complex associated counterpart, miRISC**, in order to differentiate the subpopulation of active miRNAs at this stage.



Mammary miR-30b direct targets *in vivo*

We have established a **transgenic mouse model that over-expressed 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**.