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## Species comparison of lactating mammary gland miRNomes: to the identification of conserved lactation-related microRNA

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## INTRODUCTION

The mammary gland is a dynamic organ that undergoes important physiological changes during the reproductive cycles, where the epithelial cells proliferate, differentiate so as to synthesize and secrete milk components and dedifferentiate successively. One of our interests is to understand the involvement of microRNA in the mechanisms regulating these stages. Until now, data relating to the identification of microRNA and their role in mammary gland are still scarce and mainly focused on their abnormal expression in breast cancer.



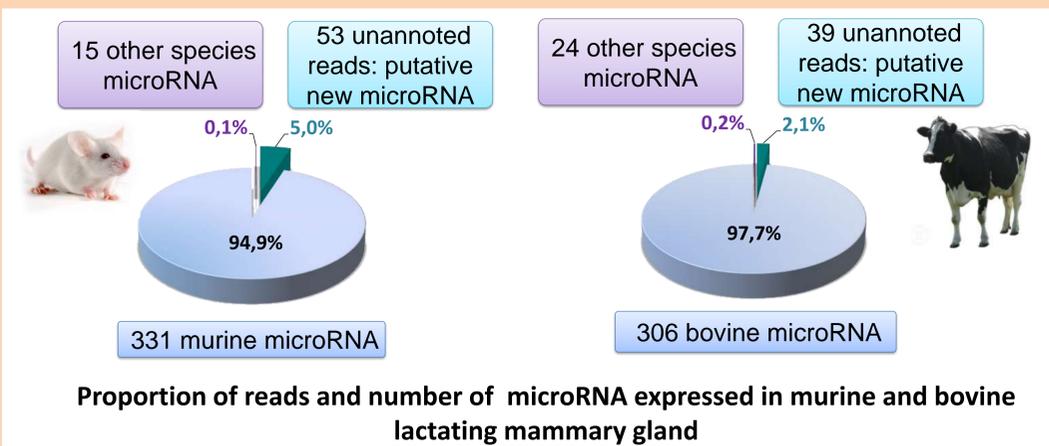
**Objectives:** describing the microRNA involved in lactation, a stage at which mammary epithelial cells are highly differentiated, by performing the identification and comparison of the exhaustive repertoire of expressed microRNA in the murine and bovine mammary gland during established lactation.

## MATERIAL

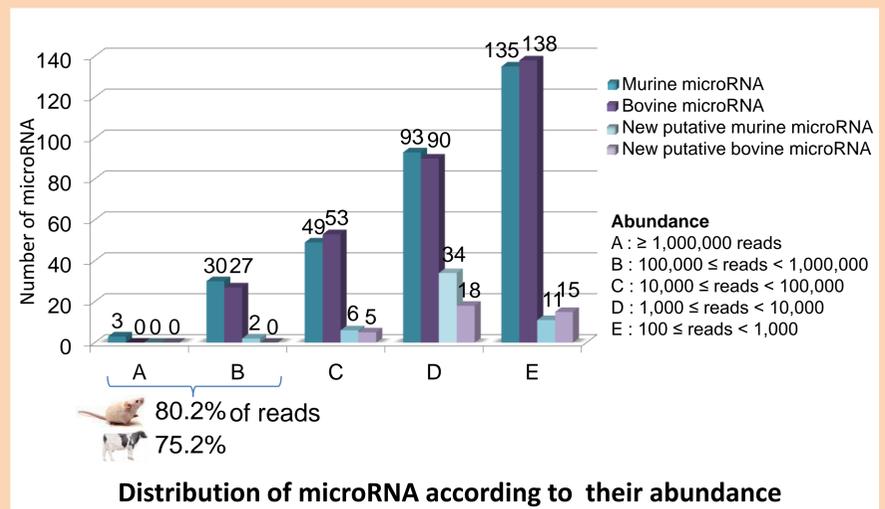
These analyses have been performed on mammary tissue samples collected from established lactating Holstein cows (2 pools of 2) and FVB/N mice (2). Total RNA were extracted from each sample and microRNA were sequenced using high-throughput technology. Cleaned reads were mapped on specific genomes and their annotation was expanded with the whole database miRBase (v.18.0). Statistical analysis were performed with the R/Bioconductor package DESeq.

## MICE & BOVINE LACTATING MAMMARY GLAND MIRNOMES

11 millions reads were obtained on average of the four libraries. After cleaning (adapters removing, 15-28 nt sizing) and filtering (rRNA, tRNA, snRNA, snoRNA, mRNA excepted them which contained microRNA annotation in an exon), a mean of 9.4 and 8.9 millions sequences were annotated in mouse and bovine, respectively, and allocated as follows:



The abundance of the microRNA expression level is highly divergent, however a high correlation (0.73) between the two species is observed:



An important part of these microRNA (213 known and 31 new) are conserved between the two species. However some species-specific expression have observed, including 4 significantly more strongly expressed in mouse (*miR-146b-5p*, *miR-378a-3p*, *miR-181b-5p*, *miR-451-5p*).

## SPECIES CONSERVED MICRORNA HIGHLY EXPRESSED IN LACTATING MAMMARY GLAND

To identify highly expressed microRNA in the mammary gland, we have compared our mouse and bovine data with recently published microRNA expression profiles of mammary gland in several species, obtained by the same next-generation sequencing technology:

- [1] Bovine lactating and non-lactating mammary gland (Li *et al*, BMC Genomics 2012);
- [2] Goat mammary gland during early lactation (Ji *et al*, Mol.Biol.Rep. 2012);
- [3] Goat mammary gland during peak and late lactation (Ji *et al*, PLoS One 2012);
- [4] Goat mammary gland during dry period and peak lactation (Li *et al*, PLoS One 2012);
- [5] Human non-lactating mammary gland (Farazi *et al*, Cancer Res. 2011);
- [6] Bovine milk (Chen *et al*, Cell Res. 2012).

⇒ Among the thirty most expressed microRNA in all studies, 8 are common in all lactating mammary gland samples:

Study [ref]	Lactation								Non-lactation			Milk
	[1]	[2]	[3]	[4]	[3]	[1]	[4]	[5]	[6]			
microRNA												
		Early	Peak	Peak	Late							
<i>miR-143-3p</i>	4 <sup>th</sup>	4 <sup>th</sup>	21 <sup>th</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	13 <sup>th</sup>	2 <sup>nd</sup>	31 <sup>th</sup>	7 <sup>th</sup>	3 <sup>rd</sup>	115 <sup>th</sup>	
<i>miR-103-3p</i>	12 <sup>th</sup>	27 <sup>th</sup>	5 <sup>th</sup>	11 <sup>th</sup>	22 <sup>th</sup>	6 <sup>th</sup>	20 <sup>th</sup>	12 <sup>th</sup>	3 <sup>rd</sup>	51 <sup>th</sup>	16 <sup>th</sup>	
<i>let-7f-2-5p</i>	14 <sup>th</sup>	16 <sup>th</sup>	3 <sup>th</sup>	6 <sup>th</sup>	13 <sup>th</sup>	1 <sup>st</sup>	10 <sup>th</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	15 <sup>th</sup>	4 <sup>th</sup>	
<i>let-7c-5p</i>	15 <sup>th</sup>	28 <sup>th</sup>	6 <sup>th</sup>	8 <sup>th</sup>	23 <sup>th</sup>	4 <sup>th</sup>	28 <sup>th</sup>	5 <sup>th</sup>	16 <sup>th</sup>	23 <sup>th</sup>	3 <sup>e</sup>	
<i>miR-30a-5p</i>	16 <sup>th</sup>	24 <sup>th</sup>	4 <sup>th</sup>	7 <sup>th</sup>	8 <sup>th</sup>	19 <sup>th</sup>	15 <sup>th</sup>	14 <sup>th</sup>	15 <sup>th</sup>	30 <sup>th</sup>	5 <sup>e</sup>	
<i>let-7a-5p</i>	18 <sup>th</sup>	3 <sup>th</sup>	1 <sup>st</sup>	3 <sup>rd</sup>	4 <sup>th</sup>	2 <sup>nd</sup>	7 <sup>th</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	19 <sup>th</sup>	2 <sup>e</sup>	
<i>miR-21-5p</i>	27 <sup>th</sup>	5 <sup>th</sup>	9 <sup>th</sup>	10 <sup>th</sup>	15 <sup>th</sup>	8 <sup>th</sup>	13 <sup>th</sup>	6 <sup>th</sup>	12 <sup>th</sup>	7 <sup>th</sup>	6 <sup>e</sup>	
<i>let-7b-5p</i>	28 <sup>th</sup>	6 <sup>th</sup>	2 <sup>nd</sup>	2 <sup>nd</sup>	6 <sup>th</sup>	3 <sup>rd</sup>	9 <sup>th</sup>	3 <sup>rd</sup>	13 <sup>st</sup>	4 <sup>th</sup>	1 <sup>er</sup>	

**The eight mostly expressed microRNA in multiple species and their rank of expression**  
 (Cells in gray: microRNA that do not belong in the top 30 of the species studied)

## AGO2-LOADED MICRORNA

In order to provide new information on microRNA loading in the RNA-induced silencing complex (RISC), we have compared the miRNome of the whole cell to the one associated with Ago2-RISC in mouse lactating mammary gland:

⇒ All microRNA are found in both samples, however some of them show dissimilar abundances, indicating different levels of use according to microRNA.

## CONCLUSION

**This study provides the first report of multi-species (murine and bovine) mammary miRNome during lactation and the identification of some species-conserved microRNA in this fundamental biological function.**

