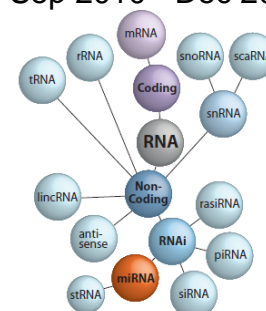


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The effects of negative energy balance (NEB) on microRNA regulation of liver gene expression in the postpartum cow



RNA world (©Todd M. Smith, Geospiza, Inc.)

Key external stakeholders:

Dairy and beef cattle breeders, ICBF, veterinary diagnostic companies, scientific community.

Practical implications for stakeholders:

The main findings from this research show that NEB affects hepatic microRNA (miRNA) expression in the early postpartum period. Changes in miRNA expression were also linked to changes in gene expression previously reported in the same liver tissue. One of these miRNAs was shown to be capable of suppressing a gene *FADS2* that is critical in fatty acid metabolism. SNPs in the miRNA or in its gene targets are likely candidates to eliminate or ameliorate the effects on NEB in the early postpartum period in cows.

Main results:

- This study shows that NEB affects miRNA expression in the liver and that this in turn may be responsible for the effects of severe NEB (SNEB) on liver gene expression previously reported.
- This study shows for the first time that *FADS2* the most highly down-regulated hepatic gene associated with SNEB can be functionally regulated by miR-2885, one of the most up-regulated miRNA.
- Dysregulation of the miRNA-target gene relationship of miR-2885 and *FADS2* could be a likely mechanism to ameliorate or eliminate the negative impact of SNEB in the postpartum dairy cow.

Opportunity / Benefit:

The primary stakeholders for this research are ICBF, the veterinary diagnostic companies and the scientific community. The benefits of the project will be realised in a commercial setting by incorporating the findings of this project into the next generation of genomic evaluations where prior information of associations, and more importantly the interactions between genes and regulatory elements, may be utilised to better reflect the complexity of biological systems.

Collaborating Institutions:

NUIG, Galway

Teagasc project team: Dr. Dermot Morris, Athenry

External collaborators: Prof. Cathal Seoighe, NUIG

1. Project background:

Emerging research has indicated the importance of miRNA regulation of gene expression in many areas of economic importance in livestock, including reproduction, immunology, feed efficiency and milk production (Fatima and Morris, 2013). In fact, recent large scale genome-wide studies have identified that differences in complex traits in many species (such as production traits in livestock) are mainly associated with regulatory elements within genomes rather than protein coding genes as traditionally perceived. A number of bioinformatics-based projects are currently underway in Teagasc, with the aim of understanding the extent of association between allelic variants of miRNA (and their mRNA targets) and economically important traits such as growth rate, fertility, milk production and disease resistance in dairy and beef cattle. NEB is a key factor affecting the health and fertility of dairy and beef cows in the postpartum period. This study set out to examine the association between miRNA and gene expression in an animal model of postpartum NEB on gene expression seen in different tissues (Morris et al., 2009; Wathes et al., 2009; McCarthy et al., 2010) and how this information may be used in a breeding programme to reduce the prevalence of NEB or to identify animals at risk.

2. Questions addressed by the project:

The major questions addressed by this research were

- What is the miRNA profile of the bovine liver in postpartum cows?
- What is the effect of SNEB on miRNA expression in the liver?
- What is the relationship between miRNA and mRNA expression?
- Can miRNAs inhibition be used to modify gene expression

3. The experimental studies:

The miRNA of liver from two groups of Holstein Friesian dairy cows 14 days postpartum with mild (MNEB) and SNEB energy balance was profiled using both a microarray and a miRNA-seq approach. A suite of bioinformatic tools, custom scripts and biological databases were used to determine the identity of the differentially expressed miRNAs and their putative gene targets. The effect of one of the most up-regulated miRNAs on a critic gene involved in fatty acid metabolism was validated in a loss-of-function *in vitro* study.

4. Main results:

This study shows that 10 miRNAs represent over 95% of the miRNAs expressed in the liver with one miRNA representing over 70%.

This study shows for the first time that SNEB affects miRNA expression in the liver and these miRNAs are in turn associated with changes in hepatic gene expression previously reported in these animals.

This study also shows for the first time that *FADS2* the most highly down-regulated hepatic gene under severe NEB can be functionally regulated by miR-2885 one of the most up-regulated miRNA in this study and suggests that dysregulation of this relationship could be a likely mechanism to ameliorate or eliminate the negative impact of SNEB in the postpartum dairy cow.

5. Opportunity/Benefit:

Identifying SNP polymorphisms in miRNAs or in their 3'UTR targets and investigation of the association between these and economically important traits in beef and dairy cattle will increase

our understanding of the complex molecular interactions that are responsible for these traits. These data could then be incorporated into the next generation of genomic evaluations where prior information of associations and, more importantly, the interactions between genes and regulatory elements, may be utilised to better reflect the complexity of biological systems.

6. Dissemination:

Main publications:

Fatima, A., Waters, S., O'Boyle, P., Seoighe, C. and Morris, D.G. (2014). Alterations in hepatic miRNA expression during negative energy balance in postpartum dairy cattle. *BMC Genomics*, 15 (1), 28.

Fatima, A. and Morris, D.G. (2013). Review: MicroRNAs in domestic livestock. *Physiological Genomics*, 45: 685-696.

Fatima, A., Seoighe, C., O'Boyle, P. and Morris, D.G. (2012). Negative energy balance alters hepatic miRNA expression in dairy cows during the early postpartum period. In: *Agricultural Research Forum*, Tullamore, Co. Offaly, Ireland, 12-Mar-2012, p18.

Popular publications:

A Fatima and D Morris (2011) MicroRNAs—a quantum leap for biology. *TResearch* 6(1), 24-25.

Compiled by: Dr Dermot Morris
