Laboratory of Epigenetic Regulations

RNA degradation, dsRNA, RNAi, miRNA, chromatin

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We study mechanisms governing the gene expression control during mammalian oocyte-to-embryo transition (OET, Fig. 1). Mammalian OET is an orchestrated process where a highly specialized cell – the oocyte – is transformed into a cell that will develop into a new organism. Importantly, oocyte reprogramming is closely associated with producing the pluripotent nature of embryonic cells, i.e. their ability to differentiate into any body cell type. We currently work on three OET topics:

Maternal mRNA metabolism

OET relies on extensive post-transcriptional control of maternal mRNAs. Maternal mRNAs, which are no longer needed, are eliminated while mRNAs, whose products are needed for zygotic genome activation (ZGA), are maintained and translated (Fig. 2). We focus on the molecular foundations of selective mRNA degradation. While some maternal mRNAs are naturally unstable, others are relatively stable and their degradation occurs in waves triggered by three major developmental transitions: resumption of meiosis, fertilization, and ZGA. We aim to develop an integrated model based on the dynamics of mRNA degradation pathways, mRNA binding proteins, and combinatorial composition of 3'UTR motifs, which would explain the observed maternal mRNA behaviour.

Role of small RNAs during OET

We study the role of small RNAs (microRNAs (miRNAs), short interfering RNAs (siRNAs) and PIWI-associated RNAs (piRNAs)) in the mammalian female germline. Mouse oocytes offer a unique co-existence of all three classes of small RNAs. It was reported that miRNA activity is minimal and non-essential in mouse oocytes, while endogenous siRNAs are required for normal meiotic maturation. We discovered the cause of highly active RNAi in mouse oocytes – a unique truncated maternal isoform of Dicer, the key enzyme in siRNA biogenesis (Fig. 3). Such an isoform was not found in other mammals except rats. Our current research addresses endogenous RNAi-related questions: How do the small RNAs function in oocytes of other mammals? Which consequences would bring enhanced RNAi in somatic cells? Can we use chemical biology to modulate RNAi and miRNA pathways?

Role of long non-coding RNAs during OET

Long non-coding RNAs (lncRNAs) are a heterogeneous group of genome-encoded RNAs, many of which have important biological functions. In collaboration with the laboratory of Kristian Vlahovicek from the Zagreb University (bioinfo.hr), we explored microarray and next-generation sequencing datasets and generated a catalogue of lncRNAs expressed during OET. Remarkably, many of the identified lncRNAs are novel and have unique expression patterns. We currently work on functional analysis of selected candidates.

This research is supported by a Marie Curie Initial Training network, RNATRAIN.

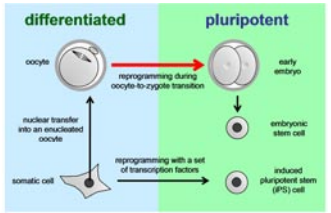
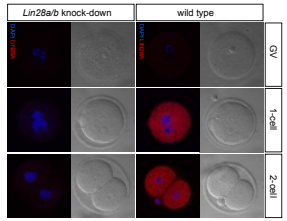


Fig. 1. Oocyte-to-zygote transition is a unique model for studying pluripotency. The mammalian oocyte is a highly specialized cell, whose cytoplasm is capable of reprogramming a genome to initiate development of a new organism. The blastomeres of the 2-cell embryo are totipotent as they can give rise to all embryonic and extraembryonic tissues. The pluripotent embryonic stem cells, which have potential to give rise to any body cell type, are derived from the blastocyst, the final preimplantation embryo stage carrying the first defined cell lineages.

Fig. 2. Lin28a dormancy. Lin28 mRNA stored in the oocyte is recruited for translation after fertilization



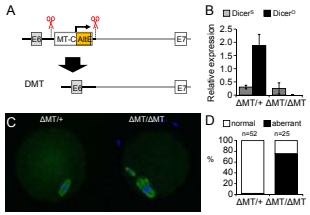


Fig. 3. Specific retrotransposon element deletion phenocopies conditional Dicer deletion in mouse oocytes. (A) Schematic depiction of cleavage sites for specific TAL effector nucleases (depicted as scissors) to generate the •MT allele. (B) Truncated Dicer (DicerO) isoform expression is absent in •MT/•MT oocytes. (C, D) Spindle defects frequently appear upon loss of DicerO.

- GACR, GBP305/12/G034 – Centre for RNA Biology, 2012-2018, D. Staněk, P. Svoboda
- ASCR, M200521202 – Integrative approach to understanding the mechanism of genome activation and natural occurrence of pluripotency in mammalian embryo, 2012-2015, P. Svoboda
- FP7 EU, 607720 RNATRAIN – The European non-coding RNA network, 2013-2017, P. Svoboda
- GACR, GA13-29531S – Development of chemical regulators of miRNA and RNAi pathways, 2013-2016, P. Svoboda
- MEYS, LH13084 LH - KONTAKT II – Post-transcriptional control of oocyte-to-zygote transition, 2013-2015, P. Svoboda
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From the left: Petr Svoboda, PhD / Head of Laboratory, Kateřina Chalupníková, PhD / Postdoc (maternity leave), Ondřej V. Šolc, Sravya Ganesh / PhD Student (since 2014), Radek Malík, MD, PhD / Postdoc, Eliška Svobodová, MSc / PhD Student (since 2013), Josefina A. "Shotgun" Šolcová, Radek Jankele / Diploma Student, Jana Faltýnková / Diploma Student, Kateřina Podolská, MSc / PhD Student (maternity leave), Jana Nejepínská, MSc / Postdoc, Michaela Vaškovičová/ Diploma Student

Not in the picture: Jan Petržílek, Meyer Lansky / Secretary, Claire Louise Ryan, MSc / PhD Student (until 2014)