LABORATORY OF

EPIGENETIC REGULATIONS

Oocyte-to-embryo transition, RNAi, miRNA, piRNA retrotransposon

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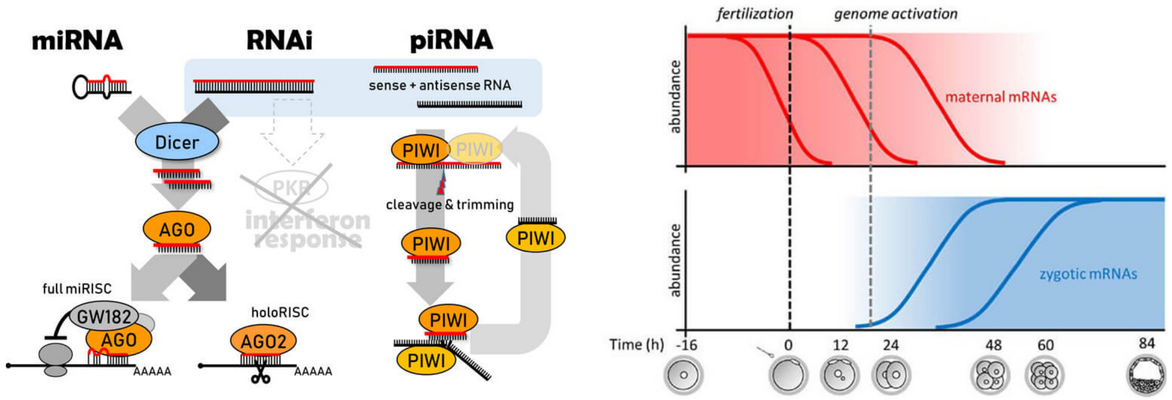
In the picture: 1. Florian Joseph Diego André | 2. Pasulka Josef | 3. Svoboda Petr | 4. Roos Kulmann Marcos Iuri | 5. Buccheri Valeria | 6. Kubíček Karel | 7. Ber Tobiáš | 8. Malík Radek

Despite the group's name, epigenetics is not its primary research area; the group owes its name to its early years, when ambitions to study epigenetic mechanisms were crushed by the lack of success to obtain funding for studying chromatin during mammalian oocyte-to-embryo transition. Nowadays, the group studies evolution of genes and their regulations, particularly post-transcriptional regulations, mainly in the context of the female germline in mice. However, there have been occasional detours into other research areas and model systems, such as oocytes of other mammals, zygotes, spermatogenesis, soma, and elsewhere. The major research theme during the recent years have been mammalian small RNA pathways (Fig. 1). The laboratory explored their functions and co-existence in mammalian germlines. We have found that these pathways dynamically evolved in mouse oocytes and we have been able to characterize some of the principles underlying function of small RNA pathways in oocytes and other cell types. We have explained how miRNAs loose activity in growing mammalian oocytes through dilution of the cytoplasmic content, which, at the same time, made oocytes permissive to canonical RNA interference (RNAi), which evolved there in rodents. The evolution has been accompanied by truncating Dicer, the key enzyme producing small RNAs. Mouse oocytes express high levels of a Dicer variant (Dicer^{0}), which is essential for development of meiotically and developmentally competent oocytes. It appears that the piRNA pathway has adapted along with RNAi, such that RNAi is dominant and essential in mouse females but not the piRNA, which is omissible there. In contrast, hamster oocytes require the piRNA pathway for developmental competence while RNAi pathway does not seem to be highly active. Lately, we have been trying to adapt RNA interference into an antiviral mechanism in vivo in mammals. We have been able to genetically engineer mice with somatic expression of Dicer^{0}, which have enhanced RNAi activity in soma, and with variable success we are analyzing antiviral effects of such a genetic modification. Additional research areas investigated in the lab recently include gene expression during mouse oocyte-to-embryo transition (Fig. 2) and long non-coding RNAs in mouse oocytes and zygotes.



Left: Overview of three mammalian small RNA pathways studied in the laboratory. Right: Oocyte-to-embryo-transition in mice | Oocyte-to-embryo transition has two major components: (I) maternal mRNA degradation, which erases oocyte's identity, and (II) zygotic genome activation, which drives establishment of zygote's new identity. In mice, the major zygotic genome activation takes place at the 2-cell stage. By that time, 75% of maternal mRNAs have been degraded.

Selected publications:

1. Ganesh S, Horvat F, Drutovic D, Efenberkova M, Pinkas D, Jindrova A, Pasulka J, Iyyappan R, Malik R, Susor A, Vlahovicek K, Solc P, Svoboda P*. The most abundant maternal lncRNA Sirena1 acts post-transcriptionally and impacts mitochondrial distribution. Nucleic Acids Res 2020. 48(6):3211-3227
2. Kataruka S, Modrak M, Kinterova V, Malik R, Zeitler DM, Horvat F, Kanka J, Meister G, Svoboda P*. MicroRNA dilution during oocyte growth disables the microRNA pathway in mammalian oocytes. Nucleic Acids Res 2020 48(14):8050-8062
3. Loubalova Z, Fulka H, Horvat F, Pasulka J, Malik R, Hirose M, Ogura A*, Svoboda P*. Formation of spermatogonia and fertile oocytes in golden hamsters requires piRNAs. Nat Cell Biol 2022 23(9):992-1001
4. Kataruka S, Kinterova V, Horvat F, Kulmann MIR, Kanka J, Svoboda P*. Physiologically relevant miRNAs in mammalian oocytes are rare and highly abundant. EMBO Rep 2022 ;23(2):e53514..
5. Zapletal D, Taborska E, Pasulka J, Malik R, Kubicek K, Zanova M, Much Ch, Sebesta M, Buccheri V, Horvat F, Jenickova I, Prochazkova M, Prochazka J, Pinkas M, Novacek J, Joseph DF, Sedlacek R, Bernecky C, O'Carroll D, Stefl R*, Svoboda P*. Structural and functional basis of mammalian microRNA biogenesis by Dicer. Mol Cell 2022 82(29)