Chromosome dynamics and integrity in mammalian oocytes and early embryos

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Correct chromosome segregation during oocyte meiosis and first cell divisions of embryos is critical for reproduction and healthy offspring. Defective chromosome segregation (aneuploidy) in oocytes and embryos leads to the developmental defects (e.g. Down syndrome) or infertility. Spindle apparatus is essential molecular machine ensuring normal chromosome segregation. In somatic mitotic cells bipolar spindle formation is supported by two centriole containing centrosomes. However, in oocytes multiple acentriolar microtubule organizing centers (MTOCs) facilitate spindle formation and finally MTOCs are sorted into the two spindle poles. We have identified signaling of three Aurora kinases (Aurora A, B, C) as crucial for effective spindle formation and normal chromosome segregation in mammalian oocytes. Now we would like to discover how these kinases cooperate with each other and also with chromosome associated RanGTP signaling during spindle formation and chromosome segregation in mammalian oocytes. Although early embryos are dividing by mitosis their spindles are still meiotic and they contain MTOCs rather than centrosomes. During preimplantation development from zygote (fertilized oocyte) to blastocyst spindle gradually shifts from meiotic to mitotic form and only in blastocyst cell division is supported by true mitotic spindle containing two classical centrosomes. Now, we would like to uncover how Aurora kinases participate in this step by step development from meiotic to mitotic spindles.

Recently it was shown that not only whole chromosome missegregation (aneuploidy) but also increased double strand DNA breaks in oocytes and embryos can account for infertility or health problems of offspring. Surprisingly, we have found that oocytes do not have DNA damage checkpoints preventing cell cycle progression in the presence of increased DSBs. On the other hand we have discovered that DSBs repair machinery work during meiotic maturation on already condensed chromosomes what is in strong contrast to somatic cells where DNA repair is suppressed in mitosis. Now, we would like to uncover how the absence of DNA damage checkpoints not only in oocyte but also in early embryos effects genome integrity in the beginning of the new life and why checkpoints are not working in this very important moment of our development.

We are using mouse genetic tools, combined with chemical biology approaches and advanced live cell imaging (both confocal and light sheet microscopy) and computer image analysis to uncover how chromosome segregation and integrity are ensured in mammalian oocytes and embryos. This project will bring important knowledge for human reproductive medicine and we plan that in the right moment we would like to move to human oocytes to see how does it work?

Further reading:

Nguyen AL, Drutovic D, Vazquez BN, El Yakoubi W, Gentilello AS, Malumbres M, **Solc P**, Schindler K. Genetic Interactions between the Aurora Kinases Reveal New Requirements for AURKB and AURKC during Oocyte Meiosis. Curr Biol. 2018 Nov 5;28(21):3458-3468.e5.

Balboula AZ, Nguyen AL, Gentilello AS, Quartuccio SM, Drutovic D, **Solc P**, Schindler K. Haspin kinase regulates microtubule-organizing center clustering and stability through Aurora kinase C in mouse oocytes. J Cell Sci. 2016 Oct 1;129(19):3648-3660.

Mayer A, Baran V, Sakakibara Y, Brzakova A, Ferencova I, Motlik J, Kitajima TS, Schultz RM, **Solc P**. DNA damage response during mouse oocyte maturation. Cell Cycle. 2016;15(4):546-58.

PhD study will be realized at Faculty of Science, Charles University.

We are offering part time job (0.8) at IAPG additional to stipend, possible accommodation in Libechov (for both single or double situation), work on the collaborative project with Rutgers University, USA (Dr. Karen Schindler).