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### Divisions asymétriques ovocytaires / *Asymmetric divisions in oocytes*

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## DIVISIONS ASYMÉTRIQUES OVOCYTAIRES / ASYMMETRIC DIVISIONS IN OOCYTES

Responsable : Marie-Hélène VERLHAC

### RECHERCHE

We study the last stages of murine oogenesis, a process that terminates with the production of functional female gametes required for sexual reproduction. The last step of oogenesis, named meiotic maturation, corresponds to two successive asymmetric divisions without intervening DNA replication. Mammalian meiotic maturation takes place at puberty under periodical hormonal influence. It can be reproduced and followed *in vitro* on synchronized population of cells. Oocytes are gigantic cells, up to 1000 times larger than most somatic cells, neuron excepted. Oocyte meiotic divisions are extremely asymmetric in size of the daughter cells, which allows the preservation of maternal stores required for embryo development. Oocytes have thus to accomplish two opposite tasks: segregate their chromosomes equally while partitioning their cytoplasm unequally. Furthermore this tour de force is challenged by the lack of canonical centres of microtubule nucleation, namely centrosomes containing a pair of centrioles. Canonical centrosomes of mitotic cells organize spindle as well as astral microtubules at spindle poles, mediating spindle positioning. We have identified mechanisms regulating the positioning of meiotic chromosomes in the absence of canonical centrosomes, processes that might have their share in the innate susceptibility of the female gamete to produce errors in chromosome segregation.

#### 1) A pressure gradient to position the nucleus

The position of the nucleus in a cell can instruct morphogenesis, conveying spatial and temporal information and abnormal nuclear positioning can lead to disease. In oocytes from many species, nucleus position regulates embryo development and in *Drosophila* it defines the future dorso-ventral axis of the embryo and of the adult. However, in mammals, the oocyte nucleus is centrally located and does not instruct any future embryo axis. Yet an off-centre nucleus correlates with poor outcome for mouse and human oocyte development, arguing that central positioning is important for later embryo development. This is surprising since oocytes further undergo two extremely asymmetric divisions in terms of the size of the daughter cells (enabling polar body extrusion), requiring an off-centring of their chromosomes. Thanks to a multidisciplinary approach, we discovered how the nucleus robustly localizes in a unique manner at the centre of mouse oocytes (Almonacid, 2015). We showed that the motion of the nucleus from the periphery to the centre depends on a gradient of pressure coming from a slight bias in the speed and the directionality of actin-positive vesicles toward the cortex. This gradient of pressure would propel large objects towards the oocyte centre in a non-specific manner. We also demonstrated that these actin-positive vesicles promote the fluidization of the whole cytoplasm essential to favour the movement of the nucleus, a very large object (30  $\mu\text{m}$  wide), from the periphery to the centre of the oocyte. We are currently investigating how the gradient of pressure impact on gene expression.

## 2) Cortex softening promotes asymmetry in oocytes, while cortex stiffening promotes symmetry in embryos

Mouse oocytes lack true centrosomes and their associated astral microtubules, their spindle positioning depends only on microfilaments whose nucleation is regulated by the spatial location of F-actin nucleators as well as force generating elements (Myosin-II). More precisely, meiotic spindle off-centering depends on F-actin, organized in two networks: a cytoplasmic one and a cortical one. Each network is required for spindle migration since when one is missing spindle motion is abolished (Verlhac, 2000; Dumont, 2007; Azoury, 2008; Schuh & Ellenberg, 2008; Chaigne, 2013). We have discovered a cortical F-actin thickening nucleated by the Arp2/3 complex, a branched actin nucleator. Using multidisciplinary approaches, we showed that the nucleation of the cortical F-actin thickening excludes Myosin-II from the cortex, decreasing cortical tension (Chaigne, 2013; Chaigne, 2015). This change in cortex mechanics amplifies an initial imbalance of pulling forces exerted by Myosin-II at the poles of the meiotic spindle, the forces being stronger at the pole closest to the cortex because of the initial slight asymmetry of nuclear position. The motion is very slow but is amplified by the deformation of the cortex, which is rendered possible by the lowering of cortical tension, allowing recruitment of more filaments between the cortex and the spindle and therefore amplifying the initial forces. Although the drop in cortical tension is required for spindle migration in oocytes, as artificially stiffening the cortex impairs spindle off-centering, spindle migration is also prevented by a too low tension. Thus the geometry of the division of mouse oocytes depends on a narrow window of cortical tension, regulated by Myosin-II cortical localization, itself fine-tuned by actin nucleation. Importantly, cortex softening favors asymmetry of spindle positioning, whereas we could demonstrate that cortex stiffening in early zygotes, after fertilization promotes symmetry of the division with spindle centration (Chaigne, 2016). The abrupt change in cortex properties between oocyte and early zygote is essential for the meiotic to mitotic transition and appears conserved in humans (Yanez, 2016).

### PUBLICATIONS

#### Original articles

FODOR É., AHMED W.W., ALMONACID M., BUSSONNIER M., GOV N.S., VERLHAC M.-H., BETZ T., VISCO P. et VAN WIJLAND F., « Nonequilibrium dissipation in living oocytes », *Europhysics Letters*, vol. 116, n° 3, 2016, DOI : 10.1209/0295-5075/116/30008.

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LI H., MOLL J., WINKLER A., FRAPPART L., BRUNET S., HAMANN J., KROLL T., VERLHAC M.-H., HEUER H., HERRLICH P. et PLOUBIDOU A., « RHAMM deficiency disrupts folliculogenesis resulting in female hypofertility », *Biology Open*, vol. 4, n° 4, 2015, p. 562-571, DOI : 10.1242/bio.201410892.

CHAIGNE A., CAMPILLO C., GOV N.S., VOITURIEZ R., SYKES C., VERLHAC M.H.\* et TERRET M.E.\*, « A narrow window of cortical tension guides asymmetric spindle positioning in the mouse oocyte », *Nature Communications*, vol. 6, n° 6027, 2015, DOI : 10.1038/ncomms7027 (\* co-senior authors).

### Invited reviews and book chapters

BENNABI I., TERRET M.-E. et VERLHAC M.-H., « Meiotic spindle assembly and chromosome segregation in oocytes », *J Cell Biol*, vol. 215, n° 5, 2016, p. 611-619, jcb.201607062, DOI : 10.1083/jcb.201607062.

CHAIGNE A., « Mécanique de la cellule et œuf mollet », *Pour la Science*, vol. 470, décembre 2016, p. 44-53.

TERRET M.-É. et VERLHAC M.-H., « Comment l'embryon se divise-t-il ? », *La Recherche*, vol. 518, décembre 2016, p. 42-46.

CHAIGNE A., TERRET M.-E. et VERLHAC M.-H., « Asymmetries and symmetries in the mouse oocyte and zygote », in J.-P. TASSAN et J.Z. KUBIAK (dir.), *Asymmetric Cell Division in Development, Differentiation and Cancer*, Springer, coll. « Results and Problems in Cell Differentiation », n° 61, 2017, p. 285-299, DOI : 10.1007/978-3-319-53150-2\_13.

VERLHAC M.-H., « Mother centrioles are kicked out so that starfish zygote can grow », *The Journal of Cell Biology*, vol. 212, n° 7, 2016, p. 759-761, DOI : 10.1083/jcb.201602053.

VERLHAC M.-H. et TERRET M.-E., « Oocyte maturation and development », *F1000Research*, vol. 5, n° 309, 2016, DOI : 10.12688/f1000research.7892.1.

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## HOMÉOPROTÉINES ET PLASTICITÉ CELLULAIRE / HOMEOPROTEINS AND CELL PLASTICITY

Responsables : Sophie VRIZ et Alain JOLIOT

### RECHERCHE

Cette année est marquée par la soutenance de thèse de Francesca Meda, « The role of ROS signaling in adult regeneration and development ». Nous avons par ailleurs obtenu des résultats significatifs pour les différents projets menés dans l'équipe.

#### 1) Mécanismes du transfert intercellulaire des homéoprotéines

Nos résultats antérieurs attribuent à la membrane plasmique un rôle central dans la régulation des échanges d'homéoprotéines entre milieux intérieur et extérieur,