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Folliculogenesis and oogenesis: from basic science to the clinic

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From germ cell to fertilizable oocyte is a journey that captures the essence of *MHR*: a quest to understand the basic science of reproductive medicine. In view of the rapid developments in molecular biology and genetics, a major goal of ESHRE in recent years has been to provide clinicians, counsellors, embryologists and the public with novel research findings of relevance to assisted reproduction technologies (ART). In this spirit, the ESHRE Campus workshop in Potsdam in October 2009 on 'Mammalian Folliculogenesis and Oogenesis: from basic science to the clinic' was dedicated to fundamental research in an area that is increasingly affecting clinical practice. The meeting was well attended (Fig. 1) and eight invited speakers submitted manuscripts for peer review and collation into this thematic issue of *MHR*, the key messages of which are highlighted below.

Møllgård *et al.* (2010) open with a novel perspective on how human primordial germ cells (PGCs) first visible in the wall of the embryonic yolk sac might migrate to the hindgut and the primitive gonads. On the basis of an elegant series of immunocytochemical and electron microscopic observations, they posit that a majority of PGCs remain at the proximal end of the yolk sac, which becomes part of the wall of the hind- and midgut close to where the gonads develop. PGCs do not therefore have to move very far in order to reach the gonadal ridges. The idea is that PGCs migrate from there to the primitive gonad by tracking autonomic nerve fibres and Schwann cells extending across the dorsal mesentery to the gonadal ridge. The invoked pathfinder function of these cells might be explained by their release of chemo-attractants and/or transmit survival signals that may support and guide PGC migration from the hindgut to the gonads.

De Felici (2010) revisits the controversial issue of mammalian neo-oogenesis, speculating how germ stem cells (GSCs) found in the ovary after birth might be derived from somatic cells, PGCs or PGC-derived GSCs formed before birth. Such cells that commence—but do not complete—programming into germ cells during early embryogenesis may be retained into adulthood, providing precursors for 'neo-oogenesis' under certain (e.g. stress-related) conditions later on. However, as De Felici (2010) concedes, crucial evidence for the progression of such stem cells to fully competent oocytes in an adult ovary is absent. Moreover, there is still no compelling evidence that neo-oogenesis occurs naturally or is inducible in mammals.

Turning to the initiation of follicular growth, Nielsen *et al.* (2010) spotlight the TGF-beta superfamily member Anti-Müllerian Hormone (AMH), which is produced by follicular epithelial (granulosa) cells. They report that AMH concentration in follicular fluid and granulosa cell mRNA expression of CYP19 (encoding the aromatase enzyme essential for estrogen synthesis) are negatively correlated in human small antral follicles, consistent with a suppressive paracrine effect of AMH on follicular development. However, since AMH receptor2 (AMH-r2), follicle-stimulating hormone receptor 2 (FSH-r) and CYP19 mRNA are all positively associated, the role of AMH in follicular development and steroidogenesis remains enigmatic.

Folliculogenesis is a protracted process in humans requiring several months from primordial follicle recruitment to large antral follicle formation and ovulation. Activin, another member of the TGF-beta family of growth factors produced by granulosa cells, is known to modulate FSH action during pre-antral follicle development. McLaughlin *et al.* (2010) investigate the interaction of activin and FSH on bovine cultured pre-antral follicles as a model for humans. They provide evidence that activin treatment alone or with FSH promotes oocyte growth, through increasing connexin 43 gap junctional expression in a polarized fashion (i.e. at the oocyte/granulosa cell interface and at the follicular periphery); thereby activin supports granulosa cell anchorage to the follicle wall (basement membrane) as well as the zona pellucida of the oocyte. This previously unknown property of activin could have translational implications for the improvement of clinical *in vitro* maturation culture protocols.

The final step in follicular maturation leading to release of a fertilizable oocyte depends on the ovulation-inducing Luteinising Hormone (LH) surge. The mini-review by Solc *et al.* (2010) surveys the signalling pathways through which LH triggers meiotic resumption. These involve paracrine signalling via epidermal growth factor (EGF)-like proteins produced in mural granulosa cells should lead to reduced cGMP formation in cumulus cells. Since cGMP inactivates phosphodiesterase 3a (PDE3a) in the oocyte the reduction in cGMP in turn causes PDE3a activation and cAMP decrease. The attendant cAMP decrease orchestrates the downstream signalling network that switches on the CDK1/CyclinB (MPF) 'master switch', to resume meiosis.

Vogt *et al.* (2010) focus on the M-phase to anaphase I transition during meiotic maturation. Their work emphasizes Aurora kinase B



Figure 1 (A) Some of the participants at the visit to castle Sanssouci.

and the mitotic centromere-associated kinesin (MCAK), which is a microtubule depolymerase that affects chromosome behaviour and corrects microtubule attachment during mitosis. Prompted by the evidence that oocytic abundance of both mRNAs alters with aging, they analyse the distribution and possible function of MCAK in maturing mouse oocytes. They report MCAK protein enrichment at centromeres and centrosomes at the spindle poles and presence of the protein at the central spindle and in the midbody, as assessed by immunocytochemistry and overexpression of a MCAK-EGFP fusion protein. This pattern of distribution resembles that seen in somatic cells. However, MCAK is also enriched in multiple centrosomes at acentriolar spindle poles and at centromeres of homologous chromosomes at prometaphase and metaphase I oocytes, consistent with a unique meiotic function of MCAK, possibly through modulating microtubule dynamics and preventing precocious chiasma resolution. The take-home message here is that alterations in MCAK abundance or activity such as in ageing oocytes may contribute to errors in chromosome segregation and aneuploidy.

Attention then switches to telomere dynamics in oogenesis and embryogenesis. Building on evidence that short telomeres are

associated with infertility in mice, [Turner *et al.* \(2010\)](#) use quantitative fluorescence microscopy to analyse telomeres in nuclei of human GV-stage oocytes up to cleavage stage embryos, and blastocysts. Their data imply that telomeres shorten in length during the GV-to-cleavage stage of oogenesis. However, telomere length appears to vary greatly within blastomeres of an individual embryo and within patient groups, and there are dynamic, stage-specific changes in telomere length according to the stage of preimplantation development. More research is clearly warranted to determine if this level of control meaningfully impacts the clinical outcome.

Finally, two papers consider oocyte and embryo 'quality' in relation to genome stability and epigenesis. [Li \(2010\)](#) reviews evidence that a maternal zygotic effect gene coding for a zinc-finger protein (ZFP57) is involved in stabilization of differential DNA methylation marks at imprinted regions of many mammalian genes. Unlike the reported knockouts of other maternal effect genes, there is an unexpectedly late (mid-gestation) embryonic lethal phenotype in the ZFP57 knockout, possibly due to accumulated imprint defects during early preimplantation development. Thus oocyte-derived factors can affect epigenetic events in embryos, and mutations or epimutations during



Figure 1 (B) Workshop participants from left to right: Jan Motlik, Marco Conti, Helen Picton, Outi Hovatta, Marie Grondahl, Evely Telfer, Andrew Childs, Cristina Magli, Thomas Haaf, Johan Smitz, Xiajun Li, Karine Reynaud, Nadine Binard, Stephen Hillier, JoAnne Richards, Ursula Eichenlaub-Ritter, Richard Anderson, Stephen Viville, Claus Yding Andersen, Beatrice Mandon-Pepin, Georg Griesinger, Carlos Plancha, Geraldine Heartshorne, Robert Gilchrist, Martin Matzuk, Ellen Ankaert. Unfortunately our honorary guest speaker, Anne Grete Bysov and the following people from faculty are not included: Peter de Boer, Stephan Brunet, John Carroll, Giovanni Coticchio, Georg Griesinger, Ilpo Huhtaniemi, Misao Fukuda, Cornelis Lambalk.

oogenesis may have potentially damaging consequences for embryonic development and 'wellbeing'.

Concerns persist that hormonal stimulation or handling and culture of oocytes and embryos might be responsible for epigenetic abnormalities in the children conceived by ART. Zechner *et al.* (2010) describe the methylation patterns at differentially methylated regions of a number of imprinted genes as well as in promoter regions of a pluripotency and a tumour suppressor gene in chorionic villus samples of spontaneous miscarriages or stillbirths obtained after ART or spontaneous conception. Unexpectedly, rates of extreme methylation values and epigenetic imprinting defects, which might cause reprogramming defects, were lower in the villi of samples from ART cycles compared with the spontaneous conception cases. Furthermore, there was no evidence for differences in methylation patterns between ICSI and IVF-derived cases. These data reinforce other evidence that ART techniques *per se* do not increase imprint errors. However, it remains likely that methylation abnormalities contribute to characteristically high rates of human pregnancy loss, whether conception be natural or clinically contrived.

Overall this thematic *MHR* issue testifies to the importance of development/cell/pathway biology approaches to understanding female gametogenesis and gonadal formation, and how they might translate to reproductive health. We hope readers enjoy the papers and sense the spirit of the workshop, which truly captured the relevance of basic research to the clinical practice of reproductive medicine.

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