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MEETING REVIEW

The embryo reunited with its membranes in Göttingen

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ABSTRACT

An EMBO workshop entitled 'Embryonic-Extraembryonic Interfaces' took place in Göttingen, Germany, in May 2015. It showcased the enormous breadth of this area not only by touching on the molecular and cellular mechanisms of development, but also because of its coverage of particularly interesting evolutionary questions and of several medically related aspects. This Meeting Review discusses some highlights from the workshop and the emerging themes in the field.

KEY WORDS: Extraembryonic tissues, Placenta, Visceral endoderm

The legendary late Rosa Beddington certainly deserves the credit of reawakening interest in mammalian extraembryonic tissues. She made many realise for the first time that these are not boring sheets of cells with structural and nutritional roles for the rest of the embryo, but rather that some of these tissues, such as the visceral endoderm of the mouse, play crucial roles in directing cell fate allocation and morphogenesis of the embryo proper in a truly instructive manner. Despite this, I expect that many would still turn up their noses at a meeting entitled 'Embryonic-Extraembryonic Interfaces', expecting that it would be very mouse-centric and extremely specialised. Richard Gardner (University of York, UK) reminded me that before realising the instructive role of the primitive endoderm, Rosa herself called it the "yuk sac". Nothing could be further from what this meeting, held at the University of Göttingen, Germany on 6-9 May 2015, actually offered. The organisers, Karen Downs (University of Wisconsin, Madison, USA), Susana Chuva de Sousa Lopes (Leiden University Medical Center, The Netherlands) and Christoph Viebahn (University of Göttingen, Germany) did a fantastic job of putting together a diverse and yes, very exciting and unusual meeting. The meeting covered a huge range of model organisms – in addition to the mouse, many mammals were represented, including marsupials (Marilyn Renfree and Karen Hansen, both from the University of Melbourne, Australia), human (John Opitz from the University of Utah, USA, Peter Nichol from the University of Madison, Wisconsin, USA, Brian Cox from the University of Toronto, Canada, Hiroaki Okae from Tohoku University, Japan and Chuva de Sousa Lopes), rabbit (posters from the Viebahn group) and many other mammals (Anthony Carter, University of Southern Denmark). Among non-mammalian amniotes, the chick and reptiles (Federica Bertocchini, IBBTEC-University of Cantabria, Spain and Markus Lambertz, University of Bonn, Germany) were represented. But more surprising was the presence of teleost fish (Ekaterina Kondakova, Saint-Petersburg State University, Russia) and even insects (Kristen Panfilio, University of Cologne, Germany), generally assumed not to possess extraembryonic tissues.

For me, the comparative and evolutionary aspects were the main highlight of the meeting. We learnt about this from the palaeontology and phylogeny studies of Martin Sander (University of Bonn, Germany), who examined the deployment of different reproductive strategies in vertebrates and the evolution of viviparity, which seems to have arisen independently several times. David Haig (Harvard University, USA) argued that there is a conflict between the mother and the embryo so there is an evolutionary trade-off between producing many embryos at low 'cost' and few offspring at high cost, leading to different strategies that manifest themselves in highly variable arrangements of the maternal-fetal interface. Just how variable this is among the mammals was emphasized by Anthony Carter, who discussed how the yolk sac placenta (chorion, allantois, yolk sac and the arrangement of parietal and visceral endoderm) adopts many different configurations among species ranging from rodents to rabbits, hedgehogs, bats, marsupials and primates. Federica Bertocchini also presented cross-species comparisons of the site of gastrulation in chameleon, turtle and other reptiles with amphibians, fish and avian/mammalian models, arguing that reptile gastrulation occurs through a structure intermediate between an ancestral blastopore and the typical amniote primitive streak. Kristen Panfilio provided an unusual but particularly lucid analysis of the membranes surrounding the insect embryo, revealing that the similarity between insect and amniote extraembryonic tissues is not just superficial or morphological, but that there are also strong physiological and molecular parallels. Ekaterina Kondakova discussed how the yolk syncytial layer of teleost fish is often likened to amniote extraembryonic membranes and has a role in embryonic development (Ho et al., 1999), although the evidence for true homology in the evolutionary sense is still not clear-cut.

It would have been nice to hear more about the possible role of retroviruses in the evolution of placentation, as it has been known for some time that retrovirus-derived proteins [such as Syncytin (Mi et al., 2000)] are very important for the origin of placentation, but one can't have everything. Only two talks touched on the topic: Marilyn Renfree mentioned that PEG10, a protein important for placentation in mammals, has a retroviral origin, and a wonderful talk about maternal and paternal imprinting by Davor Solter (A*STAR Institute of Medical Biology, Singapore and now also at Siriraj Hospital, Bangkok, Thailand) provided evidence that TRIM28 suppresses the activity of endogenous retroviruses (which may make up as much of 15% of the mouse oocyte genome!).

Also touching a very important evolutionary aspect, Elizabeth Radford (University of Cambridge, UK) illuminated us on the inheritance of epigenetic factors, exploring when methylation patterns are preserved or erased across successive generations. Other epigenetic aspects were discussed by Terry Magnuson and Karl Shpargel (both from the University of North Carolina, USA), Ali Rahjouei (from Michael Kessel's lab, Max Planck Institute, Göttingen, Germany), Hiroaki Okae, Rita Khoueiry (University of Leuven, Belgium) and, of course, Davor Solter, who was one of the first to recognise imprinting. However, one gets the feeling that the big stories in this area are only just starting to emerge.

One tantalising and clinically relevant topic is the influence of extrinsic, environmental factors during the *in utero* period acting

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through non-Mendelian mechanisms to increase the risk of metabolic disease dramatically in subsequent generations. Maternal protein malnutrition in the peri-implantation period, as discussed by Tom Fleming (University of Southampton, UK), significantly increases risk for common diseases (e.g. hypertension, diabetes and heart disease) affecting the next two generations. Late *in utero* undernourishment, as highlighted by Elizabeth Radford, also affects metabolism of the subsequent generation through the adult sperm methylome. Both of these observations could enable clinicians to reduce the incidence and cost of these chronic diseases through simple modifications in maternal prenatal nutrition. Other maternal influences appear to include the activation of Wnt signalling by the very early embryo that affects the allocation of cells to extraembryonic lineages, as presented by Monika Bialecka (University of Cambridge, UK).

Although the mouse has been by far the dominant model mammal in almost all fields of study, many of the speakers at this meeting highlighted that the early development of rodents is unusual. Their compact, cylindrical morphology with the endoderm facing outwards and especially the very close proximity of the prospective head and tail ends at the 'proximal' part of the egg cylinder (embryonic-extraembryonic junction) requires some variation in the mechanisms of axis development as compared with other amniotes. This might be part of the reason why mouse embryos do not tend to form monozygotic twins very frequently after the two-cell stage, as pointed out by Richard Gardner. There is obviously a need for more work using other mammalian species as models.

Ka Yi Ling and Adriana Rodriguez (both from the Downs lab), Anne Camus (Institut Jacques Monod, France), An Zwijsen (University of Leuven, Belgium), Jacqueline Deschamps (Hubrecht Institute, Utrecht, The Netherlands) and Lars Wittler (Max Planck Institute, Berlin, Germany) illuminated us on the complex relationships between tissues at this proximal embryonic-extraembryonic junction of the mouse, reminding us that the interactions are very much reciprocal. Likewise, the embryonic epiblast and the primitive endoderm also influence each other at the distal end of the cylinder, as reflected in talks by Elizabeth Lacy (Sloan-Kettering Memorial Institute, New York, USA), Shankar Srinivas (University of Oxford, UK), An Zwijsen and others, as Rosa Beddington had highlighted for the mouse (Thomas and Beddington, 1996) and C. H. Waddington for the chick several decades before (Waddington, 1932). Less frequently studied are the interactions between embryonic and extraembryonic tissues that regulate left-right asymmetry, which were described by Richard Gardner and Elizabeth Lacy concerning embryonic turning in the mouse, and by Karen Hansen for the wallaby. We also heard about how such interactions are involved in the development of germ cells in talks from Susana Chuva de Sousa Lopes, Terry Magnuson and Ali Rahjouei, and how they play a role in haematopoiesis, as presented by Naiche Adler (National Cancer Institute, Frederick, USA). Here it would have been interesting to hear more about the role of extraembryonic tissues during the migration of germ cells, including the extent to which these functions differ among amniote species. What evolutionary pressures might have caused the majority of blood cell formation to be taken out of the embryo, and for extraembryonic tissues to acquire a role in moving the germ line around?

Shankar Srinivas and Diana Suarez-Boomgaard (Free University of Brussels, Belgium) discussed the mechanisms that drive movements of the visceral endoderm. These studies take advantage of increasingly sophisticated live imaging techniques that are allowing the early mouse embryo to start giving up its secrets. However, it seems that the intensity of work that went on in this area a few years ago is starting to subside.

A huge body of work done by Janet Rossant (University of Toronto, Canada) over a long time to understand some of the mechanisms that establish differences between embryonic and extraembryonic identity in the very early mouse embryo was reviewed in her opening lecture. *Cdx2* is a crucial gene in extraembryonic fate specification and it has many roles in embryonic development, as touched upon by at least four speakers – Janet Rossant, Jacqueline Deschamps, Ken Cho (University of California, Irvine, USA) and Sergio Menchero (from the group of Miguel Manzanares, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain). The latter speaker also revealed a novel role for Notch in cell sorting during this process.

Last but not least, the meeting included several very interesting and diverse talks touching more directly on clinical aspects, including FOAD (here referring to 'fetal origin of adult onset disease'). Peter Nichol shared his experience as a surgeon and explained how different types of congenital abnormalities of the umbilicus and gut can illuminate our understanding of normal human development. In addition, Brian Cox applied transcriptomics and unbiased clustering analysis of the results to reveal that different placental pathologies can be classified by their gene expression profiles, while John Opitz, who has given his name and most of his life to the study of many congenital anomalies, surveyed many aspects of the biology of ADAM (Amniotic Disruptions-Adhesions-Mutilation), a condition that causes pinching off of a portion of the amnion. Interesting insights emerged from comparing his talk with those of An Zwijsen and Elizabeth Lacy who explored the role of BMP signalling in tissue interactions involving the amnion, including studies on an interesting mouse mutant called amnionless.

In addition to giving a taste of the huge range of topics, the richness of the model systems, the vast array of techniques now being used to study them (ranging from comparative morphology, palaeontology and classical genetics and embryological manipulation but then venturing out into human clinical experience, epidemiology, bioinformatics, epigenetics and live cell imaging), the organisers made an effort to put together the experience and wisdom of pioneers with the next generation of researchers exploring this area. Participants were particularly appreciative of the extent to which many speakers had integrated knowledge from across a variety of model systems not only to study evolution, but also to uncover important general principles. The gathering was small, and there was much opportunity to exchange views, as well as to explore some of the history of embryological enquiry from more than 100 years ago at the Anatomy Department (including the famous Blechschmidt Human Embryo Collection, with its series of giant three-dimensional reconstructions at different stages during the first 8 weeks) at Göttingen University. Thank you to the organisers and to EMBO and the Deutsche Forschungsgemeinschaft, the funders, for their insight in realising just how diverse and fertile an area this really is.

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Competing interests

The author declares no competing or financial interests.

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