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INTERVIEW

The people behind the papers – Kelsey Brooks and Shawn Chavez

Aneuploidy can occur in embryos due to errors in chromosome segregation during the first mitotic cleavage divisions, and often results in developmental arrest. A new paper in Development characterises the molecular events that lead to abnormal chromosome numbers in the cells of bovine embryos. We caught up with first author Kelsey Brooks and corresponding author Shawn Chavez, Associate Professor at the Oregon National Primate Research Center and Oregon Health & Science University, to find out more about their research and the impact it may have on *in vitro* fertilisation procedures in the future.

Kelsey Brooks (L) and Shawn Chavez (R)

Shawn, can you give us your scientific biography and the questions your lab is trying to answer?

SC: I did my PhD at Yale University, where I studied apoptosis during normal and abnormal human placentation, and my postdoctoral work in human embryonic aneuploidy at the University of California, San Francisco and Stanford University. In 2013, I joined the faculty of Oregon Health & Science University (OHSU) to continue my research in investigating the molecular mechanisms of chromosome mis-segregation during early mammalian embryogenesis. My primary appointment is in the Division of Reproductive and Developmental Sciences at the Oregon National Primate Research Center, which is located on the West Campus of OHSU. Using a combination of live-cell imaging to assess embryo potential, single-cell sequencing for copy number variation analysis and preimplantation embryos from multiple mammalian species, my laboratory is trying to determine why there is such a high frequency of aneuploidy in certain mammals and how it may be overcome in subsequent development to improve *in vitro* fertilisation (IVF) outcomes in women and for agricultural purposes.

Kelsey, how did you come to work in Shawn's lab and what drives your research today?

KB: During my PhD, I was investigating early pregnancy loss in ruminants during conceptus elongation and implantation in a lab that was mostly focused on the uterine environment. I was drawn to Shawn's work to expand my knowledge of early pregnancy loss, focussing on the embryo. I specifically appreciated the cross-species work the Chavez lab is doing and Shawn's emphasis on translational experiments to improve IVF success rates in the clinic.

Can you give us the key results of the paper in a paragraph?

SC: The main finding of the paper is that embryonic micronuclei can sustain multiple fates, which likely contributes to the high frequency of non-reciprocal mitotic errors and karyotypic complexity observed during preimplantation development. We also provide evidence that the lack of fusion between the maternal and paternal pronuclei (syngamy), followed by a multipolar division, is potentially one way that embryos could contain uniparental cells. Last, we show that cell cycle checkpoints are indeed active during the early mitotic cleavage divisions of mammalian embryogenesis, and disruption of the key checkpoint components results in chaotic aneuploidy, developmental arrest and dysregulation of the kinase-substrate network mediating mitotic progression.

Do you know what determines the fate of the micronuclei and what the consequences are for embryo survival?

SC: At this point, we do not know what determines micronuclei fate, but I suspect it will depend on the embryonic stage at which micronuclei form, which chromosome(s) are affected and the chromosomal make-up of the remaining cells in the embryo. What is clear is that embryonic micronuclei are very fragile and more likely to undergo nuclear envelope rupture, the consequences of which are not fully understood and something we hope to uncover.

Given the high incidence of aneuploidy in both human and bovine embryos, do you think that having some aneuploid cells, or a more relaxed checkpoint during the cleavage divisions, could be an evolutionary advantage?

SC: The idea that the vast majority of embryos are chromosomally mosaic, providing a selective advantage, is a hot topic in the IVF field right now. I often think about whole chromosomal abnormalities, such as trisomy 21 (Down's syndrome) and monosomy X (Turner's syndrome) that are supposedly compatible with live birth. It's now well-known that these patients are mosaic to some extent and, perhaps, this is what enabled them to continue in development. I think it's also generally accepted that cell cycle checkpoints are relaxed during cleavage divisions, but whether that's to eliminate those embryos that don't pass the test or

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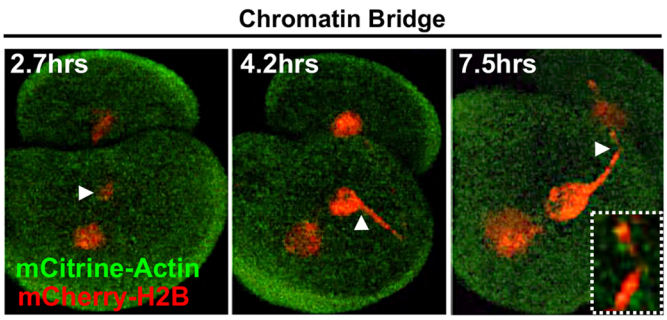

A chromatin bridge formed between blastomeres in a bovine zygote following micronuclei formation.

to give others a second chance at survival is difficult to study and remains to be determined.

What impact do you hope your work will have on screening during IVF procedures?

SC: Our ultimate goal is to identify, preferably non-invasively, the embryos with the greatest potential for implantation and live birth, whilst avoiding the production of supernumerary embryos that will likely never be transferred back to a patient. Although we might not be able to determine what is happening in each cell of an embryo without the use of intracellular markers, I still hold onto the hope that a combination of mitotic timing, division dynamics, morphological characteristics and probably other criteria may be used to reliably distinguish embryos that are destined to fail versus those that are going to result in a successful IVF outcome.

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When doing the research, did you have any particular result or eureka moment that has stuck with you?

KB: For me, the eureka moment came early in the development of this project, when we first began injecting BUB1B morpholinos into bovine embryos and analysing the time-lapse imaging. Viewing the first divisions of these embryos and seeing how dysregulated they were was really exciting and a key part of what drove the continuation of this project.

And what about the flipside: any moments of frustration or despair?

KB: Working with the small number of cells available in each cleavage stage embryo posed some unique challenges. It was frustrating to know that there were ideas that we just couldn't pursue due to the sheer number of embryos that would need to be generated to test these hypotheses.

What is next for you after this paper?

KB: This paper actually concludes my academic work and I am delighted to have it featured in Development! I am currently working as a Study Director for Altasciences, a contract research organisation.

Where will this story take your lab next?

SC: The lab is now more focused on using live-cell fluorescent imaging of additional intracellular structures to visualise the mechanism(s) of mitotic chromosome mis-segregation in real-time, assessing the subcellular distribution of aneuploidy at the blastocyst stage, and whether there are mechanistic differences in chromosome segregation, micronuclei fate and the allocation of aneuploid versus euploid cells in embryos based on maternal age. I'm excited to see where the research takes us next!

Finally, let's move outside the lab – what do you like to do in your spare time?

KB: Outside of working hours, I leave my screens behind to enjoy the beautiful Pacific Northwest, and try to keep my toddler out of trouble.

SC: I enjoy running, hiking, gardening and spending time with my family and pets (we have five!). But, living in the Portland area, it's also hard not to be a football (soccer) fan.

Reference

Brooks, K. E., Daughtry, B. L., Davis, B., Yan, M. Y., Fei, S. S., Shepherd, S., Carbone, L. and Chavez, S. L. (2022). Molecular contribution to embryonic aneuploidy and karyotypic complexity in initial cleavage divisions of mammalian development. *Development* **149**, dev198341. doi:10.1242/dev.198341