The embryos' geneology-sorting fact from fancy

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Without dispute, most reproductive medicine and biology afficiandos would regard the transformation of the single cell oocyte into the multicellular embryo one of the more laudable wonders of the biological world. Let's face it, this happens to be the matter of choice for the propagation of organisms plant and animal alike. And somehow, this single cell must sort out its cargo of subcellular stuffs and propagate two separate lineages of cells on the pathway to implantation and beyond- a challenge of immense proportions for students of geneology!

No less of a challenge for the biomedical community that has been vested in the secrets of the zygote since it was revealed by the famous "egg hunts" of Hertig and Rock in the 1940s. Seems as though some of the secrets of early human development remain intractable-at least until earlier this year. A landmark paper has appeared in the Proceedings of the National Academy of Science that carries the debate and discourse over how the initial lineages of the mammalian embryo emerge to new heights (Home et al. Altered subcellular localization of transcription factor TEAD4 regulates first mammalian cell lineage commitment, www.pnas.org/cgi/doi/10.1073/pnas.1201595109). The significance of this work is not yet fully appreciated and it follows many years of sometimes contentious claims to have solved the sorting problem. What distinguishes the work of Home and colleagues from the earlier studies, which were performed in the mouse embryo, is

the attempt to be more inclusive and cast a wider net to several mammalian species including our own *Homo sapiens*.

To appreciate this, let's consider the phylogeny ontogeny question as it relates to patterns of early development. What lies beneath the problem is how the stage is set for achieving a balance between what the embryo does when it runs out of gas and must establish a new source of nourishment to complete gestation. For eutherians mammals like ourselves, it is a matter of getting the placenta onboard in enough time to take over feeding the fetus. Of course, most animals bypass this requirement by endowing the egg with robust stores of yolk (sic gas) that will fuel the engine of development so far as getting hatched or swimming on your own to feed (unless you are a marsupial where then name of the game is getting to mothers teat). Also a matter of choice has been the issue of building the blueprints into the structural matter of the egg for designating the major body axes. That mammals have left this basic principle-the equivalent of a female homunculus-behind in the wake of "progressive" evolution strikes many to be fanciful in owing to experimentalists reliance on the mouse model to resolve such debates. So, not surprisingly, the developmental biologists adhering to the preformist or random allocation camps engaged in an "embryonic" civil war just a few years ago with the randomizers leaving the battle field with victory flags raised.

Along comes the paper by Home et al. and the fact that looking beyond the mouse has an instructive and insightful purpose to the fields of human development and stem cell research. While the essence of this work has to do with the trafficking of transcription factors that long have been recognized as players in the process of cell lineage specification, it also sends a message to those working on the derivation and establishment of human embryonic stem cells. Three papers in this issue of JARG bear directly on this issue and exemplify why the work gracing our cover

Capsule A recent paper implicates cytoplasmic localization as a means for establishing the embryonic and placental lineages in the preimplantation mammalian embryo, including the human.

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this month will assume relevance in the field of reproductive medicine.

At the top of the list is the paper by Chen and colleagues (Triploid and diploid embryonic stem cell lines derived from tri pronuclear human zygotes) in which 130 triploid zygotes were used to establish four embryonic stem cell lines. Of these, one is triploid after selection and passaging and the remaining three were diploid. Over and above identifying a new source of embryos for derivation of new lines, this work also reinforces the more troubling dimension of human embryonic cells carrying with, in this case from the very beginning, an abnormal genetic constitution (more on this topic in an upcoming issue of JARG). Our readership

will find contributions on other aspects of stem cell biology this month. As Rho and coworkers show, prompting human ES cells to pursue a course of differentiation consistent with retinal epithelial cells requires attention to the properties of the local environment or niche. And in the porcine model system, coaxing stem cells to express and retain lineage markers as described above has proved to be challenging in this species.

As stem cell biology continues to draw upon the magic of the embryo that brings about the trophectoderm and inner cell mass lineages, we hope our readership will benefit from, and contribute to, the growth and application of this technology that touches the core challenges in reproductive medicine that impact the treatment of infertility.