

JAN
25th
2022

4PM CET
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iPSZÜRICH

A Lecture Series Focused on Induced Pluripotent Stem Cells
funded by a GRC Grant, UZH



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AMNIOGENESIS OCCURS IN TWO INDEPENDENT WAVES IN PRIMATE EMBRYOS

Human peri-implantation development remains a black box of developmental biology, as embryos at this stage are practically inaccessible for studies due to the ethical considerations. Moreover, we learn only little using conventional model organisms such as mouse, because early human development strikingly differs in terms of timing, morphology and signalling cues. One particular difference is the formation of an extra-embryonic tissue amnion. In primates including human the amnion emerges through cavitation of the epiblast during implantation, whereas in mice and many other mammals the amnion is formed by folding of the ectoderm later during or after gastrulation. Moreover, the amniogenesis by cavitation characteristic for human, occurs in other mammalian lineages including bats and hedgehogs, and hence it evolved independently multiple times in evolution, which is difficult to explain. In previous work, we established an *in vitro* differentiation system using human pluripotent stem cells (hPSCs) that closely recapitulates peri-implantation period of epiblast development. This system allows to model the distinct features of human early embryo development closely reproducing temporal, transcriptional and morphological characteristics, including formation of 3D structures. Using our hPSC-based experimental system and single cell transcriptome analysis of human and monkeys embryos, we discovered two transcriptionally distinct waves of amnion formation from the epiblast. The early wave occurs through a trophectoderm-like route and encompasses cavitation. The late wave follows an ectoderm-like pathway during gastrulation and thus resembles the amniogenesis by folding in other species. Both waves can be modelled *in vitro* including 3D morphogenesis of the amniotic cavity. The discovery of two independent waves of amniogenesis explains how amniogenesis through cavitation emerged via addition of the distinct early pathway to the conservative late route during the evolution.

