HORIZON 2020

Four-dimensional physical modeling and numerical simulation of the early mouse embryo morphogenesis.

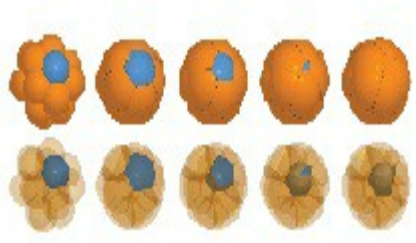
Results in Brief

Quantitative simulation of the developing embryo

Understanding early development in mammalian embryos is essential to advance reproductive medicine. A European research team created the necessary theoretical framework to realise this.

FUNDAMENTAL RESEARCH

HEALTH



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Early steps of embryogenesis involve a self-organised succession of cell divisions, deformations and rearrangements, leading to the formation of two distinct cell lineages segregated into inside and outside layers. A precise 4-dimensional imaging of the early embryos could reveal intense surface dynamics.

The main goal of the MecaMorphEME project was to build a realistic physical model of the preimplantation mouse embryo taking into account the interplay between surface contractility and cell-cell adhesion. Dr. Turlier, the award recipient, points out “More generally, the project was intended to build a numerical framework that could be useful to quantitatively study the morphogenesis of a small group of cells.”

Critical steps in early embryo development

At the 8-cell stage, mouse embryo undergoes compaction when cell-cell contacts increase their size and the embryo rounds up. During the next 8-to-16 cell stage transition, the blastomere cells segregate into two layers: the inner-cell mass (ICM) and surrounding epithelial layer, the trophectoderm (TE). Based on spatial allocation, blastomeres acquire different cell fates, which determine their future outcome. TE cells only form extra-embryonic structures such as the placenta. The ICM cells give rise to the embryo proper and the other extra-embryonic structures.

The physical model of early embryo morphogenesis

Researchers developed an initial minimal physical model based on surface tensions, which describes the configuration of cell doublets. This would aid in understanding the process of compaction.

To study the formation of the ICM at the 8-to-16 cell stage transition, researchers generalised this approach to asymmetric cell doublets. This doublet is the result of an asymmetric cell division segregating an apical domain formed at the 8-cell stage to only one of the daughter cells.

The experimental data show that the apical domain has a reduced contractile tension. As a result, the doublet is asymmetric in shape and this asymmetry leads to the full internalisation of the non-apical cell into its sibling, which inherits an apical domain.

The framework demonstrates that asymmetric segregation of the apical domain generates blastomeres with different contractility, triggering their sorting into inner and outer positions. Three-dimensional modelling of embryo morphogenesis predicts that cells internalise when differences in surface contractility exceed a certain threshold and that the shape of blastomeres in the embryo is determined by the tension at their interface. Importantly, this prediction could be validated experimentally and applied for redirection of cell sorting within the developing blastocyst in the mouse embryo.

Valuable application of the model

MecaMorphEME project presented a simple theoretical framework for analysis of the mechanics of cell internalisation leading to the formation of the ICM in the 16-cell embryo. This is one of the critical steps in the development of mammalian embryos and the model reveals that contractility couples the positioning and fate specification of blastomeres.

In assisted reproduction medicine, the embryos to be implanted are selected in vitro by visual inspection. Authors of the project believe, “mathematical models can help in reaching more accurate decisions, by considering the shape of the cells within the

embryo.”

Future directions and development

Project members have made exciting advances in numerical modelling of embryo morphogenesis. Besides improving the outcome of assisted reproductive medicine, Prof. Nedelec and Dr Turlier envision, “There are several extensions that will be exciting to pursue. One is to couple the mechanical model with a model of how cells respond or signal to their neighbouring cells. This is essential to unravel the complex dynamics within the early mammalian embryos that imply in particular genetic or epigenetic changes.”

Keywords

MecaMorphEME | contractility | ICM | compaction | physical model | embryogenesis

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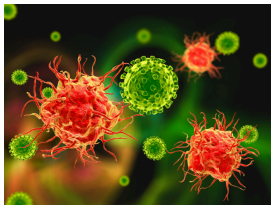

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MecaMorphEME

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