Mechanisms of stem cell development during human embryogenesis

Background

Six days after fertilization the human embryo contains two main types of stem cells, those that will generate the future foetus, and those that will form the organs that support pregnancy, such as the placenta and the yolk sac. As soon as the embryo implants in the womb, these stem cells start to divide, become reorganized and initiate a process of specialization, to generate cells with different identities and functions. All these events need to be carefully coordinated, as failure to do so would lead to pregnancy loss. It is estimated that approximately 30% of human embryos fail to develop shortly after implantation, but the mechanisms behind remain unknown. To understand the causes of failure, we need to study the genes, chromosomes and proteins that are important in regulating the development of the embryo and its cells.

What is the purpose of this study?

Our goal is to understand the basic mechanisms of human embryo development to shed light on the reasons behind early pregnancy loss. We hope that the results of these studies will benefit medical knowledge in a number of important ways, including:

- Understanding how cells in the human embryo become specialized. During the first two weeks of human development cells acquire different fates, and therefore different functions. A small subset of cells is set aside to form the future foetus and the amnion, the membrane that protects the developing foetus from damage. A second population of cells gives rise to the future placenta, which supports the development of the foetus throughout pregnancy. The third cell population forms the yolk sac, a sac that provides nutrients to the foetus. Understanding the molecular characteristics of these different cell types could provide insight into the mechanisms of stem cell formation and the causes of early pregnancy loss.
- Understanding how embryos acquire their shape as they develop beyond implantation. As embryos implant in the maternal uterus, they grow and their cells reorganize to form different structures, such as the amniotic cavity, which protects the future foetus throughout the pregnancy. We would like to understand how these changes in embryo shape take place and which genes are involved in this process. These findings could explain why so many human pregnancies fail shortly after implantation.
- Establishing the consequences of chromosomal alterations for early human embryo development. Alterations in the normal number of chromosomes typically lead to pregnancy loss, but the reasons behind this remain unknown. We wish to study how an abnormal number of chromosomes affects embryo development, specifically the specialization of cells into different cell types, and the changes in embryo shape that take place after implantation.
- Developing stem cell lines that can be taken out of the embryo and multiplied in the laboratory for many years can help us study and understand devastating human diseases more fully at the cellular level in the laboratory and potentially develop new drug treatments.

How is the work carried out?

To achieve our goal, we carry out the following laboratory procedures:

- Growing human embryos in a new culture system that permits correct development beyond implantation and up to day 13 of development[1]. This allows us to study how embryos grow and change their shape.
- Performing biochemical studies to understand the biological properties of the embryos. This involves labeling specific types of cells and structures using chemical compounds, and/or isolating cells to characterize the types of genes and proteins that they express.
- Modifying the conditions of culture to assess how embryos respond to the presence of specific compounds.
- Recording the development of the embryos using highly specialized time-lapse microscopy.
- Deriving stem cell lines from the embryos. If an embryo is used for the purpose of producing stem cells, it is separated into individual cells or groups of cells, so that it is no longer intact. These separated cells may die naturally, or they may survive and multiply indefinitely as stem cells. These stem cells can be used to further study many types of diseases, which can be replicated in the laboratory to look at their cause and progression as well as search for treatments.
- Altering the cellular composition of a human embryo by introducing human stem cells. The resulting embryo, a chimera, is composed of human cells with different genetic information, originally coming from different zygotes. This technology allows us to alter the genetic information of the stem cells without modifying the genetic information of the embryo.

At the end of the research all embryos are allowed to perish.

What are the benefits for the donors?

The research we do does not help donors specifically, and we are unable to provide any information on any particular embryo. However, the information we get from these studies may help us to improve fertility treatments, to develop cures for serious disorders such as miscarriage, and to generate new research tools. The collective information is studied scientifically and the information gained will be published in the appropriate medical and scientific journals. Donors are not identified personally in any way in any publication or scientific presentation.

It is possible that discoveries resulting from research on donated embryos, or stem cells that may be generated from them, could result in patents or licenses being awarded to the researchers or to commercial organisations. Donors do not receive any financial benefit from research discoveries arising from the embryos they donate or from stem cells generated from them.

Where is this work performed and how is it funded?

These studies are done at the MRC Laboratory of Molecular Biology (LMB) in Cambridge, under a research licence issued by the Human Fertilisation and Embryology Authority (HFEA) and approval of the East of England – Cambridgeshire and Hertfordshire Research Ethics Committee. The funding for this research is covered by the Medical Research Council (MRC), which supports the research in the group of Dr. Marta Shahbazi. The work is done in collaboration with the CARE Fertility group and Bourn Hall clinic.