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Cells in focus

The human cytotrophoblastic cell, a mononuclear chameleon

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Abstract

The human placenta represents an abundant; easily accessible and unlimited study material (at birth a human placenta provides about 500 g of trophoblast). Cytotrophoblastic cells (CTB) are one constituent of the human placenta and represent epithelial cells with fascinating properties: They are able to fuse to form syncytia, can behave like immotile polarized epithelial cells, can phenocopy stromal fibroblasts or endothelial cells or undergo a mesenchymal-like transformation that converts them into non proliferative and highly invasive cells. Like a chameleon, CTB are thus able to adapt to their immediate environment by phenocopying their neighbor cells.

This review describes the different routes that CTB follow during their differentiation pathways, the regulation of these at the molecular level, it gives also an overview of the *pathologies associated with faulty pathways* and describes the usual phenotypic markers used to identify the different CTB subsets. This review is intended to stimulate investigators not acquainted with the field of placental biology to use CTB as a model to study important biological functions in vitro, such as cell fusion, cell invasion and cell transformation.

Keywords: Cytotrophoblast; Syncytiotrophoblast; Placenta; Invasion; Fusion

1. Introduction

As life moved out of the oceans, new reproductive strategies developed to account for the loss of nutrients and oxygen normally provided by the water environment. Despite the fact that many examples of viviparity exist in invertebrates, fish, amphibians and reptiles, placentation is a relatively new acquisition in evolution. The establishment of an intimate trophic connection between mother and embryo is a characteristic of mammals. Placentation is thus a new strategy in reproduction, which allows the development of a small number of fetuses within the protective maternal organism. As the mammals evolved from small rodent-like creatures with short gestational periods to larger animals with prolonged gestations, the placenta had to adapt to the increasing needs of the growing fetus. The placenta became larger, increased considerably its contact surface area between the fetal and the maternal circulation and acquired an array of specialized metabolic, hormonal and immunological functions.

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The term “trophoblast” was introduced by A.A.W. Hubrecht. A Dutch scholar, at the end of the 19th century (Hubrecht, 1899, cited by Boyd & Hamilton, 1970) to designate those cells derived from the blastocyst, that do not contribute to the embryo but are essential for its nourishment. The placenta, the amniotic membranes and the decidua (transformed maternal endometrium) contain different subtypes of trophoblastic cells fulfilling different functions. All these trophoblastic subsets differentiated from the trophectodermal cells of the blastocyst (Boyd & Hamilton, 1970). Once the blastocyst is implanted in the uterus, the trophectodermal cells change their name into *cytotrophoblast*.

2. The origin of trophectodermal cells

During embryonic development, mitotic divisions of the blastomeres give rise to a morula, comprising about 16–32 fetal cells and later a blastocyst (32–64 blastomeres). Until the four- or eight-cell stage, the blastomeres are distinct and can easily be counted; the embryo has no polarity (Fig. 1). After the eight cell-stage, each blastomere interacts with its neighbors through homotypic cell-surface adhesion molecules such as E-cadherin also known as uvomorulin. This interaction is known as *compaction* (Fig. 1). This process can, to a certain extent, be mimicked in vitro. Human embryonic stem cells (H1 cells), cultured in suspension, form embryonic bodies that differentiate into trophoblastic cells (Gerami-Naini et al., 2004). It seems that the bone morphogenic protein-4 (BMP4) induces differentiation of human embryonic stem cells to trophoblast (Xu et al., 2002). How BMP4 is related to compaction remains to be established. The trophectodermal cells acquire the characteristics of epithelial cells in being flattened and joined together by tight junctional complexes. When the embryo reaches about 32 cells, the trophectodermal layer probably pumps fluid into the extra-cellular space forming thereby the blastocoelic cavity (Watari et al., 1996, Fig. 1), a characteristic of the late blastocyst. It is at this stage that the embryo, which started its cleavage in the fallopian tube, reaches the uterine cavity about 3–4 days after ovulation.

In order to understand the differentiation steps that transform the trophectodermal cells into specialized subsets of cytotrophoblastic cells (CTB) one needs to briefly review the implantation process in humans.

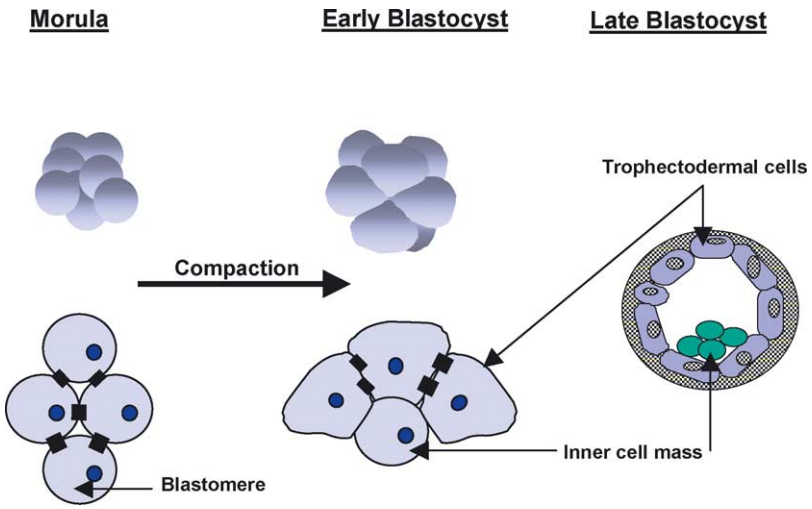

Fig. 1. The process of compaction during embryonic development. Compaction results in the acquisition of a cell polarity with an apical border covered by microvilli and a baso-lateral border characterized by the presence of gap junction and E-cadherin expression. Compaction, is the first event of morphogenic and cellular differentiation. The most significant event occurring at compaction is the emergence of two distinct cell populations: the blastomeres remaining in contact with the outside (zona pellucida) are destined to form the trophectodermal lineage (the future placenta and its membranes) while the blastomeres inside the embryo are destined to form the inner cell mass (ICM) and later the embryo proper.