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The placenta may predict the baby

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At the basis of the structure of biological systems are genes that regulate the development of the cells that make up the tissues and organs. We humans start off as a symmetrical ball of cells. Even as our first 50 cells begin to separate themselves into an inner cell mass (which will become the embryo, fetus and, eventually, baby) and the trophoblasts (which will become the placenta), genes are regulating the creation of the developmental axes that will form the basis of the entire organism. Defects in the genes that regulate these processes lead to a wide range of embryonic, fetal and neonatal defects, from minor cosmetic abnormalities, to disasters that terminate pregnancy within a few days to weeks after fertilization. Here we describe a particular placental abnormality, propose a mechanical basis for the formation of this defect, and suggest that its presence may be a general marker of developmental abnormalities.

By 21 days after fertilization the trophoblasts have begun to sort themselves out into what will become the tree-like structures that make up the placenta: the chorionic trees, branches and villi. The terminal villi (from the Latin for shaggy hair) are finger-like structures that contain the fetal circulation, and like our fingers, are covered with an epithelial layer (in the case of the villi, two layers). The trophoblast bilayer has an inner cytotrophoblast layer made of single nucleated cells and an outer syncytiotrophoblast layer made of giant multinucleated sheets (Fig. 1). Starting with purified cytotrophoblasts, we demonstrated using in vitro time lapse cinamatography that cytotrophoblasts fuse to form syncytiotrophoblasts (Kliman et al., 1986), an observation that has now been confirmed in situ (Huppertz et al., 2001). The critical conclusion from these studies is that only the cytotrophoblasts proliferate, making the growth of the syncytiotrophoblast layer completely dependent on the absorption of fusing cytotrophoblasts.

Abnormalities in the regulation of trophoblast growth may result in the formation of trophoblast inclusions (Fig. 2). These inclusions are the result of abnormal invaginations of the trophoblast bilayer (Fig. 3), which, when cut appropriately, appear to be free-floating, inverted islands of trophoblasts (Fig. 4). It is well known that the presence of trophoblast inclusions in placentas are associated with a long list of genetically abnormal gestations, including triploidy (an extra complete set of chromosomes), trisomies (an extra individual chromosome, such as trisomy 21—Down's syndrome, trisomy 18 and 13), Turner's syndrome (female with one X chromosome missing) and even genetic diseases without obvious chromosome abnormalities (Honore et al., 1976; Szulman, 1984). But what is the relationship between trophoblast inclusions and these genetic defects? We present here a simple mechanical model that can explain why quantitative changes in the frequency of cytotrophoblast absorption can give rise to inclusions. Since cytotrophoblast absorption is doubtless regulated by many genes, this model explains the multi-gene nature of the phenomenon and focuses efforts for pin-pointing the effects of particular genetic defects.

We start with the fact, as stated above, that the cytotrophoblasts are the proliferative cells of the placenta and that the syncytiotrophoblasts expand only by fusion of cytotrophoblasts into the syncytium. If we call the rate of cytotrophoblast proliferation P and the rate of fusion F, we can see that there are three possible scenarios (Fig. 5). When $P = 2F$ (middle pathway of Fig. 5), half the proliferating cells fuse into the syncytiotrophoblast and half remain in the cytotrophoblast layer, and the planar bilayer remains stable, a normal pattern of growth which increases villous length and placental mass. When $P < 2F$ (right pathway of Fig. 5), the mass of the syncytiotrophoblast increases

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relative to the cytotrophoblast, and due to elastic and compressive forces the bilayer is forced to buckle outward (evagination). This becomes the starting point of a new branch, which leads to an increase in surface area of the normal placenta. If, on the other hand, $P > 2F$, the mass of the cytotrophoblast increases relative to the syncytiotrophoblast and the bilayer is forced inward (invagination). This abnormality in the developmental program leads to trophoblast inclusions. This single model can explain the two normal and one abnormal growth patterns seen in the placenta.

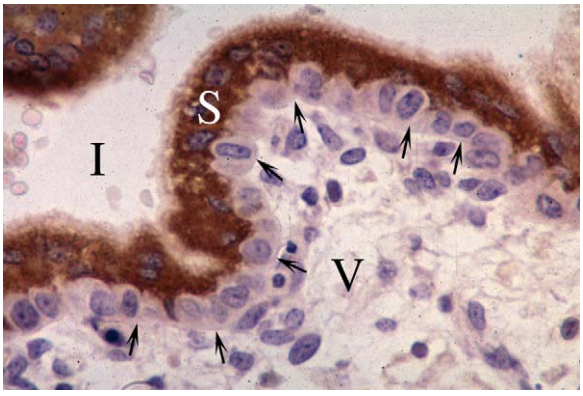

Fig. 1. Trophoblast bilayer in a first trimester chorionic villous. The villous core (V) is covered by two layers of trophoblasts. The intensely stained syncytiotrophoblast layer (S), which here is immunohistochemically reactive for human chorionic gonadotropin, is in direct contact with the intervillous space (I) which contains the maternal blood. Underlying the syncytiotrophoblast layer is a continuous layer of cytotrophoblasts (arrows), the proliferative cell type of the placenta.

Abnormalities that affect the regulation of such basic cell processes as proliferation, cell movement and fusion are likely reflected in abnormal placental growth patterns—such as changes of the P/F ratio, which can give rise to trophoblast inclusions. Since the fetus and placenta share the same genome (except in rare cases of confined placental mosaicism), the presence of trophoblast inclusions may serve as a marker for fetal genetic abnormalities. While the presence of trophoblast inclusions has no obvious effect on placental function (Rockelein et al., 1990), the same genetic abnormalities that cause these trophoblast inclusions may have profound effects elsewhere, particularly in systems and organs that require exquisite organization, such as the head (including the brain, eyes, ears and face), urogenital system (the kidney in particular), heart and extremities.

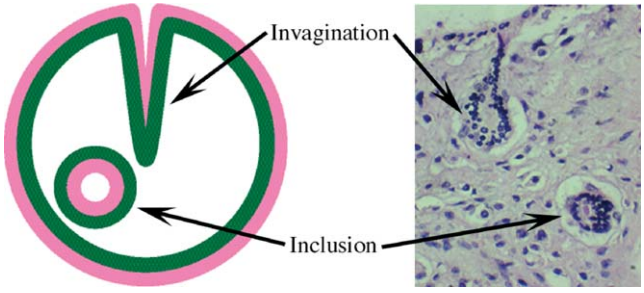

Fig. 2. Trophoblast invagination and inclusion. Diagram of an invagination and inclusion on the left with a corresponding photomicrograph on the right. The syncytial trophoblast layer (pink) and cytotrophoblast layer (green) appear reversed when an invagination is cut in cross section, resulting in an inclusion.

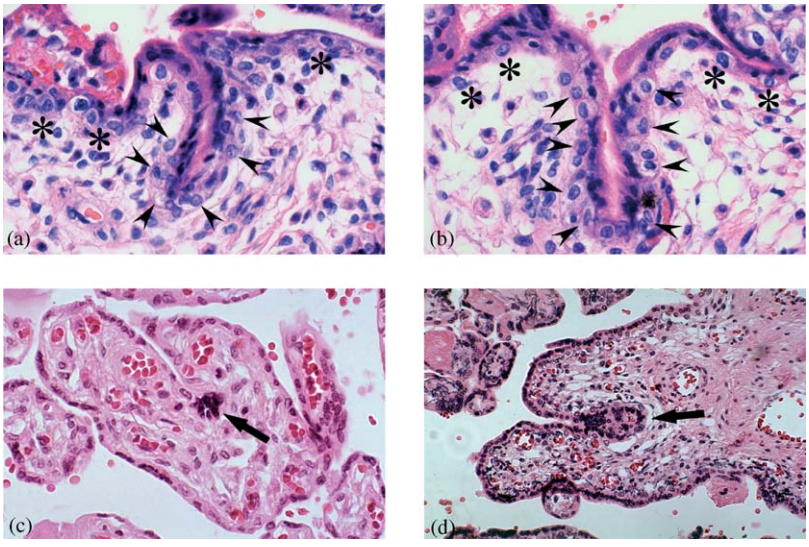

Fig. 3. Trophoblast invaginations. (a, b) Trophoblast invaginations forming cleft-like structures. Note the many cytotrophoblasts lining the invaginations (arrowheads) and the fewer cytotrophoblasts underlying the normal bilayers (*). (c) Invagination ending in an area of increased syncytiotrophoblasts (arrow). Even though the bilayer is invaginated, syncytiotrophoblasts still form. (d) Bulb-like prominence of syncytiotrophoblasts at base of an invagination (arrow).

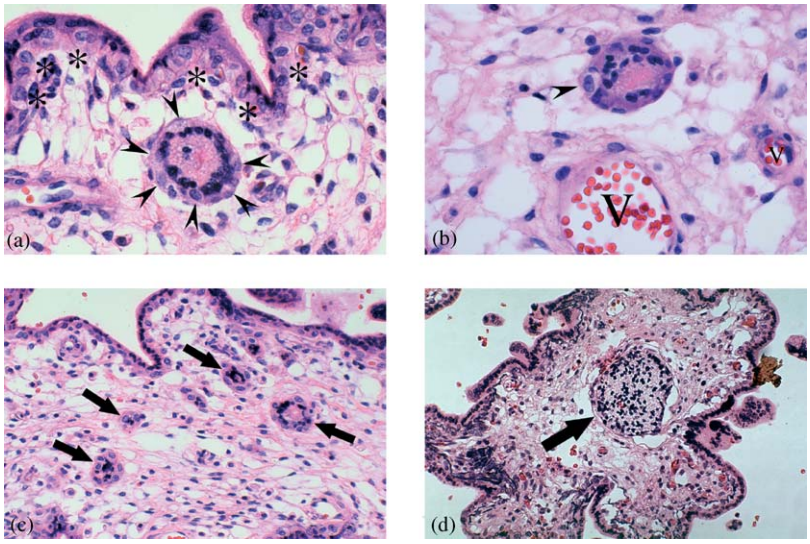

Fig. 4. Trophoblast inclusions. (a) Trophoblast inclusion within the villous core. Note how the cytotrophoblasts of the bilayer (*) and the cytotrophoblasts of the inclusion (arrowheads) both are adjacent to the villous core. (b) Trophoblast inclusion with a prominent syncytiotrophoblast layer and a lone cytotrophoblast (arrowhead). Fetal vessels (V). (c) Chorionic villous with four prominent trophoblast inclusions (arrows). (d) Trophoblast inclusion with very expanded syncytiotrophoblast component (arrow).

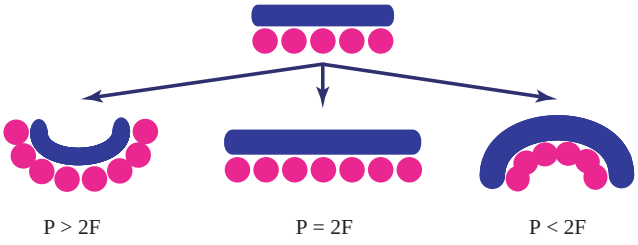

Fig. 5. Proliferation fusion model. A model illustrating the different ratios of proliferation (P) and fusion (F). Cytotrophoblasts (pink circles) proliferate and intermittently fuse into the upper syncytiotrophoblast layer (blue bars). Stability (relative flatness) of the bilayer is maintained at, or near, an ideal ratio: $P = 2F$. Normal outward budding (evagination) is observed from the ratio: $P < 2F$, while an abnormal trophoblast inclusion (invagination) results from the ratio: $P > 2F$.

Our hypothesis and model will need to be tested by comparing the frequencies of trophoblast inclusions in cases of known genetic defects to large numbers of normal gestations without evidence of genetic defects. If confirmed, this finding could be useful in cases of pregnancy loss where karyotypic analysis was not or could not be performed or even as an early marker in term placentas for subtle developmental abnormalities—such as autism, which has recently been shown to be a consequence of genetic abnormalities (Lauritsen and Ewald, 2001).

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