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Comparative Placentation and Animal Models: Patterns of Trophoblast Invasion – A Workshop Report

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INTRODUCTION

The degree of trophoblast invasion is very variable between species [1]. However, the factors influencing it, and benefits deriving from it, are little understood. In the epitheliochorial placentation of pig, camel, and horse, trophoblast microvilli interdigitate with those of the maternal uterine epithelium, and there is no trophoblast invasion as such. One modification of this is synepitheliochorial placentation where some specialised trophoblast cells detach and migrate through to the maternal epithelium and fuse with it, as is seen in ovine and bovine placentae. Another is the trophoblast girdle cell invasion into the endometrium to form the cups in the early horse placenta. In endotheliochorial placentation there is some invasion into the maternal stroma, stopping short at maternal blood vessels, while the most invasive form is haemochorial, found in human, rodent, bat and other species, where the maternal endothelium is stripped away so that the trophoblast is in direct contact with maternal blood. There is at present some controversy about which form is the most primitive and what evolutionary pressures influenced the development of the different placental types [2,3].

In order to understand these systems and their relevance to human pregnancy, it is important to examine the modes of placentation of various other species. The contributors to this workshop covered many different facets of this subject as well as a wide range of animals, from the elephant to the mouse.

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CONTRASTING PATTERNS OF TROPHOBLAST INVASION IN THE RAT AND MOUSE

R. Pijnenborg discussed work done with L. Vercruysse, and showed how, as in the human, both rat and mouse have two pathways of trophoblast invasion, a vascular and an interstitial pathway. Vascular invasion in the mouse is limited to the decidua, and follows a perivascular route, showing gradual replacement of the endothelium from the outside. Vascular smooth muscle is absent in decidua, and much thinned in the noninvaded mesometrial triangle. The remodelling is therefore independent of trophoblast. Areas of intense vascular remodelling are associated with high numbers of uterine natural killer (uNK) cells which, when underdeveloped, allow perivascular trophoblast invasion into the distal decidua [4], suggesting a possible reciprocal relationship between trophoblast invasion and uNK cell distribution. In contrast, vascular invasion in the rat extends into the mesometrial triangle, is endovascular, and is followed by endothelial replacement from the inside, while the thinned vascular smooth muscle layer shows severe fragmentation [5]. In the mesometrial triangle of deciduomata (without trophoblast) vascular smooth muscle shows similar thinning as in mice. Further muscle breakdown in placental sites of the rat is clearly associated with trophoblast. In the rat, uNK distribution is more associated with the spiral arteries than in the mouse, but might have a similar function in initial vascular remodelling. Rat spiral artery changes include fibrinoid deposition between trophoblast and vessel wall and, as in the human, re-endothelialization after mural incorporation of invaded trophoblast. Interstitial invasion follows vascular invasion and arises from trophospongial glycogen cells in both species. However, deep interstitial invasion beyond the decidua occurs only in the rat, extending into the mesometrial triangle from day 16 and filling most of it from day 18 onwards [6].

It was concluded that it is difficult to ascribe any significant role to these interspecies differences, especially since there is no evidence for more efficient maternal placental blood flow in the rat. Additional points raised in the discussion included the importance of the yolk sac placenta, especially in early pregnancy before the chorioallantoic placenta is established, as well as the variation in the degree of lymphocyte invasion in the two species. Although it seemed that the rat was more like the human with respect to invasion, further comparative studies will be needed to understand the significance of restricted trophoblast invasion in complicated human pregnancies.

THE SUBPLACENTA AS A SOURCE OF INVASIVE TROPHOBLAST IN THE GUINEA PIG AND DEGU

A. Mess presented a phylogenetic analysis indicating that the highly invasive form of placentation in mammals, i.e. haemochorial placentation, is a derived condition [7]. In the search for animal models with trophoblast invasion similar to humans, caviomorph or hystricognath rodents are a promising group. Some of these, such as *Cavia porcellus* (guinea pig), have a highly lobulated placenta. However, *Octodon degus* (degu) is more primitive in that it lacks placental lobulation. A defining characteristic of caviomorphs is the subplacenta, a distinct area of the chorioallantoic placenta not especially involved in feto-maternal exchange. In contrast to the main placenta, the subplacenta possesses cellular trophoblast throughout pregnancy, arranged in folded layers and encircled by syncytial trophoblast. Recent work has revealed trophoblast cells and syncytial streamers to be situated along routes between the subplacenta and the maternal arterial channels [8].

In order to test whether the subplacenta of caviomorph rodents is the source of invasive trophoblast, a joint project is currently underway and several markers (BrdU, Mib-1, anti-vimentin, anti-cytokeratin) are being applied [9]. Results indicate that both guinea pig and degu show strong proliferation within the subplacenta, but not in the trophoblast along the routes to maternal channels. Initial findings showed incorporation of BrdU into cells of the subplacenta. Cells derived from subplacental trophoblast could be followed towards maternal blood channels, proving that proliferation of invasive trophoblast takes place in the caviomorph subplacenta.

Although the significance of the subplacenta remains a mystery, functional aspects brought out in the discussion included the presence of a secretory apparatus and the possibility that the subplacenta secretes hormones to the fetal circulation. It was also suggested that the subplacenta might be providing cells for building tissue rather than for invasion. However, in early to mid-term pregnancy, maternal arteries are found close to the subplacenta. Its trophoblast derivatives serve as a source of interstitial invasion that can extend into the peritoneum, and invasion into the arterial walls does seem likely to occur.

TROPHOBLAST INVASION IN NON-HUMAN PRIMATES

The participation of different types of trophoblast in different stages and places of endometrial invasion in the non-human primate was illustrated by A. Enders. He showed how the amounts of each type also vary proportionally at different stages. In the macaque and marmoset, masses of syncytial trophoblast provide initial infiltration into the uterine luminal epithelium [10,11]. As the macaque implantation site spreads laterally, cytotrophoblast expands along the residual uterine luminal epithelial basal lamina, increasing the proportion of cytotrophoblast in the site. Syncytial trophoblast masses subsequently infiltrate the endothelial lining of maternal capillaries, forming a confluent wall. Unilaminar (noninvasive) syncytial trophoblast develops clefts and lacunae, and the proportion of syncytial to cellular trophoblast increases. Cytotrophoblast then invades the lumen of arteries and joins the walls of maternal venules. Cytotrophoblast increases within the septae between lacunae; it then extends into the endometrial stroma, bypassing clusters of epithelial plaque cells. When cytotrophoblast forms a complete trophoblastic shell, invasion into the endometrium slows, cytotrophoblast undergoes a proximal-to-distal differentiation within the shell, and intercellular matrix is secreted abundantly by cytotrophoblast.

It appears that the nature and extent of the invasion of the endometrium is controlled largely by timely fluctuations in the amount and differentiation of different trophoblast types. Some of these differentiations, such as initial formation of syncytial trophoblast masses, appear to occur independently of external signals. Other differentiations, many of which occur in restricted positions, probably result as responses to localised factors.

The importance of syncytial trophoblast was stressed in the discussion, in that it provides a wide front for invasion with processes being inserted between cells and cytoplasm flowing behind. Once villi have formed, the cytotrophoblast can form cellular anchoring columns with swathes of cytokeratin filaments forming a mechanical support.

A COMPARISON OF PLACENTATION IN ELEPHANTS AND SEA COWS

Comparisons between placentation in the Sirenia (manatees and dugong) and Proboscidea (elephants) were made by H. Soma. These large mammals originally evolved from a common ancestor although extant forms inhabit very different environments. They do, however, share a herbivorous diet and a long gestation period.

Two manatee placentae and a stillborn dugong placenta were obtained from the Okinawa Churaumi Aquarium. A stillborn manatee placenta weighed 460 g and one born at 16 months gestation weighed 4.43 kg; the stillborn dugong placenta weighed 1.5 kg. These placentae were of the incomplete zonary type. Allantoic verrucoids were seen on the surface of the chorionic plate. Histologically, the labyrinth was