CELL BIOLOGY OF ENDOMETRIAL RECEPTIVITY AND OF TROPHOBLAST-ENDOMETRIAL INTERACTIONS

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SUMMARY

Implantation initiation is commonly thought to require that 1) the trophoblast or subpopulations of it have reached a state of "invasiveness" and, synchronously, 2) the endometrium a state of "receptivity" ("implantation window"). Many questions remain open, in particular for the situation in the human. The cell biological basis of "receptivity" as well as of "invasiveness" is still largely unknown, but recently it appears that the application of modern concepts of cell and developmental biology opens promising new views of it, concentrating on cell adhesion and cell polarity phenomena.

Implantation initiation involves that the trophoblast attaches with its apical plasma membrane to the apical plasma membrane of the uterine epithelium. Since apical plasma membranes of epithelia are normally non-adhesive, this has been called a cell biological paradox. In development, cells can attain two major phenotypes and can switch between these: 1) the mesenchymal/fibroblastoïd phenotype that is compatible with cells moving individually; 2) the epitheloid phenotype which is characterized by cells expressing apico-basal polarity and strong association with neighbouring cells via various junctions, so that they can migrate as sheets but not as individual cells. Application of this concept to embryo implantation allows to reconcile many perplexing observations about the receptive endometrium as well as the invasive trophoblast. Indeed it has been found that the uterine epithelium down-regulates a number of parameters of epithelial cell polarity in this phase. This applies in a somewhat similar way to the trophoblast of blastocysts which has to give up part of its typical epithelial organization when becoming invasive: It must express cell-cell adhesion molecules or matrix receptors non-typically at its apical plasma membrane and must change its motility apparatus. Interestingly, recent data show that, in both systems, a great number of differentiation parameters of cells change in addition. It appears that part of the epithelial differentiation program is down-regulated at this phase. This new concept appears to offer interesting aspects of the basis of steroid hormone action at the endometrium, as well as of trophoblast invasiveness, postulating that switches occur in the activity of regulatory "master" genes as also involved in decision making during development.
INTRODUCTION

During the initial phase of embryo implantation, the trophoblast of the blastocyst has to attach to the endometrium, and, in invasive types of implantation, it subsequently penetrates through the uterine epithelium into the endometrial stroma. As suggested by a number of experimental data, this process includes adhesive and invasive interactions between trophoblast and uterine epithelium which can be initiated only if both partners have entered a specific physiological state: the "invasive state" in case of the trophoblast, and the "receptive (permissive) state" in case of the endometrium. It is widely believed that implantation can indeed be initiated only when both partners enter these states in synchrony. Receptivity is maintained for only a limited period of time, which defines an "implantation window" (Psychoyos, 1973, 1986, 1988; Psychoyos and Casimiri, 1980). While receptivity of the endometrium is regulated by ovarian steroid hormones (notably by progesterone and changes in the estrogen/progesterone ratio), invasiveness of the trophoblast is attained when it has reached a certain state of differentiation, the regulation of which is unclear (see also below).

These concepts and the mentioned general terms describing them have been derived in the first place from experiments on asynchronous embryo transfer performed in laboratory rodents and the rabbit, and from investigations on the endocrine regulation of early pregnancy and implantation in these species. They have proven useful in interpreting the results obtained in such experiments, and recently it has been proposed that they are likewise applicable for the human in particular with respect to problems encountered with embryo transfer after in-vitro fertilization (Psychoyos, 1986, 1988; Martel et al., 1987; Psychoyos and Martel, 1990). On the other hand, these concepts do not directly help with defining the molecular processes going on in trophoblast and endometrial cells. However, recently new information became available from a number of experimental studies based on modern cell biological concepts on epithelial cell polarity, epithelial differentiation and epithelial-mesenchymal (E-M) transition in development, and on cell adhesion phenomena related to those processes. This review will concentrate on these new concepts.

IMPLANTATION INITIATION: A CELL BIOLOGICAL PARADOX

The morphology and general physiology of trophoblast-endometrial interactions at implantation have been reviewed before (Denker, 1990, 1993). For the first phase of this process, i. e., the interaction with the uterine epithelium, morphology has revealed three different modes realized in different species: the "displacement type" (rat and mouse), the "fusion type" (rabbit, binucleate cells in ruminants, perhaps the human) and the "intrusion type" (carnivores) (Schlafke and Enders, 1975; for additional literature see Denker, 1990, 1993).

All three modes have in common that the process always starts with attachment of the apical plasma membranes of trophoblast and uterine epithelial cells to each other. This attachment is characterized morphologically by membranes running parallel over longer stretches at a distance of about 200 Å, and by the development of a specialized submembranous filament network. Stability of attachment
can be demonstrated experimentally because now blastocysts cannot be torn apart anymore from the uterine epithelium without breaking cells. It is thus necessary to define adhesion molecules involved in this attachment phenomenon, and to explain on a cell biological basis what mechanisms may cause the expression of these adhesive properties.

From a cell biological point of view, implantation must be regarded as an astonishing phenomenon and has been termed a cell biological paradox (Denker, 1986, 1988, 1990, 1993): The fact that, when implantation is initiated, the trophoblast of the blastocyst attaches with its apical plasma membrane to the apical plasma membrane of the uterine epithelium, is far from being trivial. A fundamental property of simple epithelia is to possess a polarized organization and, as one aspect of this, two distinct membrane domains: the apical and the basolateral plasma membrane domain (Hay, 1985a, b; Rodriguez-Boulan and Nelson, 1989; Simons and Fuller, 1985). In contrast to basolateral membranes which are rich in adhesion molecules so that they can mediate cell-to-cell and cell-to-matrix adhesion, apical plasma membranes normally lack most of these molecules and lack adhesive properties. In addition, they may contain bulky molecules that sterically hinder the interaction of potentially adhesive molecules. However, at implantation initiation we are confronted with the fact that trophoblast and uterine epithelium make their first contact exactly via their apical cell membranes, and this is what needs to be explained at a cellular and molecular level.

**ENDOMETRIAL RECEPTIVITY**

The luminal epithelium of the uterus appears to play a central role in mediating the properties of "receptivity" or "non-receptivity" of the endometrium, and it seems to be a unique property of this epithelium in contrast to other epithelia to be able to enter a state of "receptivity" under steroid hormone control. If the uterine epithelium is removed experimentally, blastocysts can "implant" completely independent of any hormonal control (Cowell, 1969). When the trophoblast is allowed to interact with various types of tissues without having to overcome an intervening epithelium, it can invade deeply regardless of the hormonal status of the host, even in males, e.g., when blastocysts are transplanted to ectopic sites (Kirby, 1965, 1967; Porter, 1967). Even the pig trophoblast, which never becomes invasive in the normal in-vivo situation, was reported to show adhesive and invasive interactions after ectopic transplantation or in in-vitro experiments (for literature, see Denker, 1993). The uniqueness of the changes in behaviour of the uterine epithelium as seen at "receptivity" is demonstrated by the fact that other epithelia (with the exception of mesothelia and endothelia) do not seem to allow the trophoblast to attach; these obviously include the tubal epithelium which the tropoblast cannot penetrate in any hormonal state, at least not in animals (Tutton and Carr, 1984; Pauerstein et al., 1990).

It is well possible that changes seen in the physiology of the uterine epithelium at "receptivity" are secondary to changes which occur in the endometrial stroma (e.g., after a blastocyst-derived signal has before been transduced via the uterine epithelium, Denker, 1990). However, the exact sequence of events, be it as just described or any other possible variant, is of no major bearing for our arguments.
concerning the nature of the cell biological changes finally defining the "receptive state" of the uterine epithelium. The nature of that state will now be discussed on a molecular level.

In a number of investigations it has been tried to define molecular changes in the composition of the attaching apical plasma membranes, that of the uterine epithelium and the corresponding membrane of the trophoblast. Very consistently, a reduction in the thickness of the glycocalyx of uterine epithelial cells and in cell surface charge has been observed in various species (Anderson et al., 1986, 1990; Enders and Schlaeke, 1977; Morris and Potter, 1984, 1990; Morris et al., 1988; Potter and Morris, 1990). On the other hand, the expression of new cell surface proteins has also been observed (Lampelo et al., 1985; Anderson et al., 1988; Hoffman et al., 1990). Knowledge about the identity of molecules involved, however, is still very limited. The most specific conclusions concerning the nature of the involved molecules have been drawn by Carson et al. (1990, 1993) who proposed that heparan sulfate proteoglycan (HSPG) receptors are expressed at the apical plasma membrane of the uterine epithelium specifically during the "receptive phase", and that the trophoblast attaches via its cell surface-bound HSPG molecules (perlecan, not syndecan being the core protein), in the mouse. (Somewhat conflicting observations concerning syndecan have been presented by Potter and Morris, 1992, so that many questions still appear to be open). On the other hand, there is indeed evidence for other carbohydrate recognition processes (Lindenberg et al., 1988) possibly including a galactosyltransferase-galactose mechanism (Chavez, 1990).

Of particular interest is that the changes seen in the uterine epithelium when entering the receptive phase are indeed surprisingly complex: they comprise many more characteristics than one would expect when focussing on changes specifically needed for allowing the trophoblast to attach to this apical plasma membrane. It was proposed, therefore, that an aspect critically involved in "receptivity" or "non-receptivity" of the uterine epithelium is the degree of expression of its polar organization (Denker, 1986, 1988, 1990, 1993; Glasser et al., 1990, 1991). Detailed investigations of the in-vivo situation have impressively shown that parameters related to the expression of general epithelial cell polarity change not only in the apical but also in the lateral and basal aspects of uterine epithelial cells at this phase. This has led to the proposition that receptivity involves a change in the expression of the general epithelial phenotype (Denker, 1986, 1988, 1990, 1993). As already mentioned, this phenotype is characterized by possessing, in simple epithelia, membrane domains (apical and basolateral) with strikingly differing composition, typical sets of adhesion molecules (like uvomorulin and certain integrins), a basal lamina at one pole, and cytokeratins.

The major relevant changes seen in the uterine luminal epithelium at receptivity can be listed as follows:

**Plasma Membrane Domains**

*Apical Plasma Membrane*

- Loss of marker enzymes of the brush border type (Classen-Linke et al., 1987).
- Reduced lectin binding properties.

Literature is somewhat confusing insofar as it was proposed that the expression of glycoconjugates with terminal galactose is positively correlated with receptivity (Chávez and Anderson, 1985; Anderson et al., 1986; Anderson et al., 1990). However, in the implantation chamber there is an overall trend towards reduction of lectin binding including lectins that recognize galactose (Nalbach, 1985; Bülkers et al., 1990). This is consistent with findings on reduction of the thickness of the glycocalyx and of cell surface charge at receptivity in various species as cited above.

- Increased density of intramembranous protein particles as seen in freeze fracture morphology, so that the resulting density of particles corresponds to that typical for basolateral membranes (Murphy et al., 1982a; Winterhager, 1985; Winterhager et al., 1990). Unfortunately, so far little is known about the interesting question to what extent these particles may represent adhesion-related molecules, e.g., cell-cell adhesion molecules, matrix receptors, glycosyl transferases, lectins and others. A re-distribution of HSPG "receptors" to the apical plasma membrane of mouse uterine epithelium in the receptive phase was proposed by Carson et al. (1990) (see also above). Alternatively, receptors may not be relocated but simply be made available for binding by release of previously bound HSPG (Morris and Potter, 1990; Morris et al., 1988; Potter and Morris, 1990).

- Formation of "reflexive" gap junctions (Murphy et al., 1982 d) and (under certain experimental conditions) hemidesmosome-like junctions (Denker, 1977). These observations demonstrate that, in addition to the HSPG receptors mentioned above, other types of adhesion molecules (such as those involved in formation of these junctions) obviously become expressed in the apical plasma membrane.

**Lateral Plasma Membrane**

- Translocation of the subapical band of intercellular junctions (an indicator of changes in functional polarity of epithelia, Chevalier at al., 1985; Kitajima et al., 1985).

Tight junctions: strands proliferate towards the basal cell pole (Murphy et al., 1982 b; Murphy et al., 1982 c; Winterhager and Kühnel, 1982).

Adhaerens junctions: Uvomorulin (E-Cadherin, cell-CAM 120/80) an integral membrane protein typically associated with the zonula adhaerens, is maximally concentrated in the subapical region of the lateral plasma membrane during pre-receptive phases; in those parts of the uterine epithelium that immediately surround a blastocyst in rabbit implantation chambers this adhesion protein is seen to lose its subapical maximum and to become more evenly distributed over the lateral plasma membrane, most obviously at the endometrial "placental folds" on days 8 and 9 post coitum immediately before the trophoblast attaches and fuses with this epithelium. In this part of the epithelium, relocation of uvomorulin locally reaches very impressive degrees so that it becomes maximally concentrated in parts of the basal plasma membrane where it cannot be shown (or only in traces) with the same methodology in pre-receptive phases. It is here located at small cytoplasmic processes of uterine epithelial cells that penetrate the basal lamina (see below) (Donner et al., 1991, 1992; Donner and Denker, unpublished; Denker, 1993).
The desmosome-associated protein desmoplakin equally shows a loss of maximal concentration in the subapical region like uvomorulin, although in this case a re-distribution to the basal plasma membrane was not seen (Classen-Linke and Denker, 1990; Donner et al., 1991).

**Basal Plasma Membrane**

- Reduced adhesion to the basal lamina in rodents (Bitton-Casimiri et al., 1977; Schlaflke and Enders, 1975; Tachi et al., 1970).

- Formation of cytoplasmic processes of the uterine epithelium that penetrate through the basal lamina into the underlying stroma (Roberts et al., 1988; Marx et al., 1990).

**Intracellular/Transcellular Transport Activities**

- Stage-dependent changes in vectorial transport activities through the uterine epithelium are traditionally thought to serve the specific changes in secretory activity that provide a stage-specifically optimized milieu for blastocyst development (Beier, 1974; Parr, 1980, 1982, 1983; Parr and Parr, 1977, 1978; Marengo et al., 1986). However, in the context that we are discussing here they must be regarded as also potentially serving as a mechanism contributing to sorting and re-distribution of membrane precursors and differential transport of degradation products thus regulating differential composition of apical vs. basolateral plasma membranes. Problems of mimicking this in in-vitro systems have been addressed by Glasser et al. (1991).

**Cytoskeleton**

- Upregulation of vimentin and a re-distribution along the apico-basal axis of polarity in the implantation chamber in the rabbit (Hochfield et al., 1990).

It was proposed that the changes seen in this large number of parameters can be interpreted as follows: All mentioned parameters are characteristics of the apico-basal polarity of epithelia. During the pre-receptive phases, these parameters are organized in a polarized fashion along the apico-basal axis, but during acquisition of "receptivity", there is an overall trend towards loss of this polar organization with many of these parameters, and with some of them polarity even appears to become inverted (e.g., uvomorulin and vimentin). It was proposed, therefore, that steroid hormone action may (directly or indirectly via the endometrial stroma) change the expressed genetic program of the uterine epithelium in such a way that **part of the epithelial type differentiation program is being down-regulated at receptivity** (Denker, 1986, 1988, 1990, 1993). As a consequence, the receptive uterine epithelium shows changes in cell behaviour (cells detaching from their basal lamina in rodents, and behaving in a semi-invasive manner by sending projections through their basal lamina in the human and the rabbit), thus facilitating trophoblast invasion.

There is much evidence that locally acting signals derived from the blastocyst are contributing considerably to modifying the properties of the uterine epithelium. So, the behaviour of this epithelium would be determined in the first place by preconditioning through systemically acting maternal steroid hormones and would then be
modulated in addition locally in the vicinity of the implanting blastocyst. Changes in polarity parameters are indeed particularly obvious in the implantation chamber in contrast to interblastocyst segments of the uterus. It appears that local signals provided by the blastocyst drive the switches even further than the maternal steroids (for literature, see the listing of changes, above). The nature of such local signals is at present a matter of discussion: They may include interferon-type molecules like oTP-1 and bTP-1 in ruminants (Roberts, 1989), or other cytokines, growth factors, steroids, prostaglandins, and others. As discussed previously (Denker, 1990), matrix-type molecules (including fragments retaining ligand properties) could also act as such short-range signals since it was shown in other cellular systems that they can very well promote changes in polar organization (Garbi et al., 1986; Greenburg and Hay, 1982, 1986, 1988; Hay, 1985a, b; Mauchamp et al., 1987).

TROPHOBLAST INVASIVENESS

Recent data on the regulation of trophoblast differentiation (e.g., on the actions of cytokines and growth factors as well as matrix molecules) have been reviewed by Aplin (1991), Graham and Lala (1991), Lala and Graham (1990), and Hohn et al. (1992). On the other hand, with respect to trophoblast invasiveness nearly as little is known as it is about the cellular basis of tumor cell invasion. However, recent progress in two fields appears promising: adhesion molecules and motility properties. It appears that in both systems regulation of the expression of adhesion molecules, matrix degrading hydrolases and motility factors as well as of their receptors seems to be of central importance (for reviews, see Mareel et al., 1990; Behrens et al., 1991; Birchmeier et al., 1991).

In the context of the concepts discussed in the present paper the following findings are of particular interest: As recent analysis (Aplin, 1991; Damsky et al., 1992; Korhonen et al., 1991) of trophoblast emigration out of the so-called cytotrophoblastic cell columns of anchoring villi suggests, acquisition of invasiveness of trophoblast cells is accompanied by:

- loss of polar organization with respect to integrin (α6β4, α3β1) distribution in relation to the basement membrane on which these cells sit originally,
- subsequent loss of certain integrins (α6β4),
- acquisition of new types of integrins (α5β1) that enable the emanating invasive cells to interact with interstitial matrix materials (such as fibronectin, type I collagen and fibrinogen/fibrin). Fibronectin was found to be the best substrate for adhesion of isolated normal (placental) and malignant trophoblast in vitro (Aplin and Charlton, 1990; Foidart et al., 1990).

Remarkably, therefore, a loss of polar organization of cells in addition to the expression of new types of adhesion molecules is found in invasive trophoblast as it is in receptive uterine epithelium. This will be discussed below with respect to genetic re-programming.
A UNIFYING CELL BIOLOGICAL VIEW OF ENDOMETRIAL
RECEPTIVITY AND TROPHOBLAST INVASIVENESS

The described features of trophoblast invasiveness and of endo-
metrial receptivity show certain fascinating similarities. The com-
mon denominator appears to be a decrease in expression of apico-
basal polarity (Fig. 1). This is of particular interest when comparing it
with a process in embryology that recently attracts much attention:
epithelial-mesenchymal (E-M) transformation. During development,
cells can switch (even various times subsequently) between two ma-
jor phenotypes, the epitheloid and the mesenchymal or fibroblastoid
phenotype (Hay, 1985a, b; Greenburg and Hay, 1986; Rodriguez-
Boulan and Nelson, 1989; Ekblom, 1989). Characteristics of these
two phenotypes include:

- epithelial phenotype: apico-basal polarity, cytokeratins, laminin,
collagen type IV, the integrin α6 β1, uromorulin (E-cadherin).

- mesenchymal/fibroblastoid phenotype: front-rear polarity,
vimentin, fibronectin, collagen type I, the integrin α5 β1.

Switches between these two major phenotypes involve, in various
experimental systems, many or all of the mentioned parameters. It is
postulated, therefore, that certain master genes regulate these pro-
grams and switches. Recently there is great interest in these types of
master regulatory genes, and attempts are being made to apply these
views to the changes in cell behaviour seen in invasive tumors
(Birchmeier et al., 1991; Mareel et al., 1990, 1991).

In the context of trophoblast-endometrial interactions it is of
much interest to ask whether similar genes may be involved. As
pointed out earlier (Denker, 1986), what appears as a paradox in
implantation initiation, i.e., contact formation between two epithelia
via their apical cell poles, is indeed found in many examples in em-
bryology. Of greatest interest is that recent investigations increas-
ingly show that those processes are typically combined with E-M trans-
formations, and not primarily with cell death as thought traditionally.
Examples include the following embryonic "fusion" processes:

Figure 1. (see opposite page)
Schematic sketch of changes in polar organization of trophoblast when acquiring
attachment capability/invasiveness, and uterine epithelium when entering
"receptivity", at implantation initiation. This scheme concentrates on distribution of
adhesion molecules represented by the symbols. It is still highly speculative since
only very limited data are available so far; it does not intend to be correct in detail but
is meant to be thought-provocative, illustrating the principle behind the concept on
partial loss of epithelial-type characteristics as discussed in the text. Whereas in the
pre-invasive/pre-receptive state, apical plasma membranes of trophoblast (Tm) and of
uterine epithelium (U) are non-adhesive (A), they express adhesion molecules when
acquiring attachment competence (invasiveness)/receptivity (B, C) and (D) show
attachment, fusion and beginning penetration into the endometrial stroma for the
fusion type (rabbit), (E) and (F) for the intrusion type of epithelial penetration
(carnivores). T: apical type integral membrane proteins (ectodomain non-adhesive);
filled circles: homotypically binding cell-cell adhesion molecules; Y: heterotypically
binding receptors (e.g., HSPG receptor); triangles: various ligands for Y receptors;
stars: matrix receptors, e.g., mesenchymal type integrins. (Modified after Denker,
1990).
- various epithelia:
  formation of the neural tube (combined with differentiation and
  emigration of neural crest cells), of the ear vesicle, the semicircular
  canals, the lens vesicle, the secondary palate and the naso-
  lacrimal duct as well as the fusion of nasal swellings;
- mesothelium:
  closure of the pleuroperitoneal canal at formation of the dia-
  phragm;
- endothelium:
  fusion of endocardial cushions at septation of the heart (see Den-
  ker, 1986, for literature).

Systematic studies of the cell biological changes that take place
during these processes in embryonic development are still largely
lacking. In particular, we do in most cases not yet have sufficient data
on the parameters listed above that would allow to monitor E-M
transformations, with the exception of neural crest formation and
formation of the secondary palate, the most widely studied examples.
In particular, the action of the postulated master regulatory genes
during embryonic development and their supposed de-regulation in
tumors are still little understood. If we are right with our supposition
that lines can be drawn between these processes and endometrial
receptivity, the endometrium could be a particularly valuable system
for continuing studies along these lines, since in this tissue the
"master" genes are obviously regulated by steroid hormones. This
may open excellent new experimental approaches to study their
identity and their regulation.

However, it must be pointed out that application of this concept
to endometrial receptivity and trophoblast invasiveness is still very
hypothetical. Loss of polar organization along the apico-basal axis is
certainly a common theme for all systems. Changes in molecular pa-
rameters appear to be far less consistent as far as data are available.
So the changes seen in the trophoblast at acquisition of invasiveness
and in uterine epithelium at receptivity do not seem to comprise the
complete set of parameters just mentioned for E-M transformation.
For example, loss of $\alpha_6\beta_4$ integrin and acquisition of $\alpha_5\beta_3$ integrin is
found in E-M transformation as well as in acquisition of the invasive
phenotype by the trophoblast (literature, see above), but has not been
described for the uterine epithelium. However, the latter does show
changes in expression of other integrin subunits (notably appearance
of the $\alpha_5$, $\alpha_6$, and $\beta_3$ subunits in the secretory phase) and changes in the
polar distribution that may be indicative of such switches (Lessey et
al., 1992; Albers, Thie and Denker, unpublished data).

Uregulation of vimentin is found in E-M transformation and
receptive uterine epithelium but not in trophoblast. Uvomorulin (E-
cadherin) was reported to be down-regulated in E-M transformation
as well as in invasive tumor cells (Gumbiner et al., 1988; Mareel et
al., 1991; Behrens et al., 1991; Birchmeier et al., 1991). In the in-
vasive trophoblast, this was reported for the mouse (Damjanov et al.,
1986) but may (Castellucci, personal communication) or may not
(Fisher et al., 1989) be seen in the human; in the latter, it was rather
described to occur in connection with fusion of cytotrophoblast to
syncytiotrophoblast (Coutifaris et al., 1991). Such down-regulation of
uvomorulin is also not seen in the uterine epithelium at receptivity
(Donner and Denker, unpublished). Data on other relevant parame-
ters (laminin vs. fibronectin, type IV vs. type I collagen) are still very incomplete for trophoblast and uterine epithelium, or as in case of syndecan and perlecang, partially contradictory (Carson et al., 1993; Potter and Morris, 1992).

Therefore, many questions remain open when we try to compare trophoblast invasiveness and endometrial receptivity with E-M transformation: this is in particular true with respect to the question what master gene-regulated switches in the general genetic programs transcribed may be involved. So far one can only say that there are reports on steroid-dependent changes in activity of regulatory genes coding for transcription factors in endometrium and that these findings are basically consistent with such a view (Webb et al., 1990; Jouvenot et al., 1990; Baker et al., 1992). Clearly data on genes that control major switches in differentiation pathways are urgently needed, for both the uterine epithelium and stroma cells at receptivity and for the trophoblast at acquisition of invasiveness. It can be expected that such data will become available during the next few years and they will clarify to what extent the hypothetical views presented in this paper will hold.

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