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Cells in focus

Uterine epithelial cells: Serving two masters

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ABSTRACT

Uterine epithelial cells are unique cells in that they are both epithelial in the typical barrier sense but in many mammalian species, they characteristically allow the blastocyst to penetrate them from the apical surface. Here we examine how these cells subserve both functions and in particular we synthesize recent evidence on focal adhesions and how these membrane structures contribute to uterine receptivity for blastocyst implantation. Focal adhesions emerge as a dynamic new player in the 'plasma membrane transformation' of early pregnancy and uterine receptivity in that they disassemble at the time of implantation in common with many other structures on the basolateral plasma membrane of these cells.

Cell facts

- Uterine epithelial cells are the first site of interaction between maternal and foetal cells during early pregnancy.
- Uterine epithelial cells in many species display both typical 'barrier' functions and unique non-epithelial invasion-allowing functions.
- Uterine epithelial cells undergo a unique 'plasma membrane transformation'.

1. Introduction: uterine epithelial cells and their unique 'plasma membrane transformation'

Modes of blastocyst implantation into the uterus vary widely across species which have placentas and range from those in which the blastocyst does not actually breach the maternal epithelium (the epitheliochorial type) to those in which the uterine epithelium is breached forming a deeply invasive hemochorial placenta (Schlafke and Enders, 1975; Murphy, 2004; Moffett and Loke, 2006). The latter is typical of humans and many rodents and involves a unique biological situation in which an epithelium is invaded from its apical side by a genetically different tissue. Regardless however of the mode of implantation, the process starts with contact between the apical surfaces of maternal (i.e., uterine) and foetal (i.e., trophoblast) epithelial cells and very similar phenomena are seen, across species, at the plasma membrane level of uterine epithelial cells. The term 'plasma membrane transformation' is used to encapsulate the concept of common membrane events occurring in the plasma membrane of uterine epithelial cells in preparation for implantation (Murphy, 2001, 2004). The plasma membrane transformation concept also encapsulates the changes which occur in all compartments of the plasma membrane of uterine epithelial cells, apical, lateral and basal, although to date, those on the apical plasma membrane have received the greatest attention probably because this is the first site of contact between maternal and foetal tissues. Such major changes in an epithelium may have similarities to an epithelial–mesenchymal transition (Kalluri and Weinberg, 2009) but in uterine epithelial cells an EMT seems unlikely since the plasma membrane transformation is quickly reversed (Png and Murphy, 1997) unlike a typical EMT. Moreover, the tight junction, usually considered a sine-qua-non of polarity, is actually considerably deepened in uterine epithelial cells during the plasma membrane transformation indicating more, rather than less, cellular polarity (Murphy, 2004).

2. Cell origin and plasticity

During development the female reproductive tract begins to form soon after gastrulation, when the invagination of the coelomic epithelium gives rise to two paramesonephric (Müllerian) ducts,

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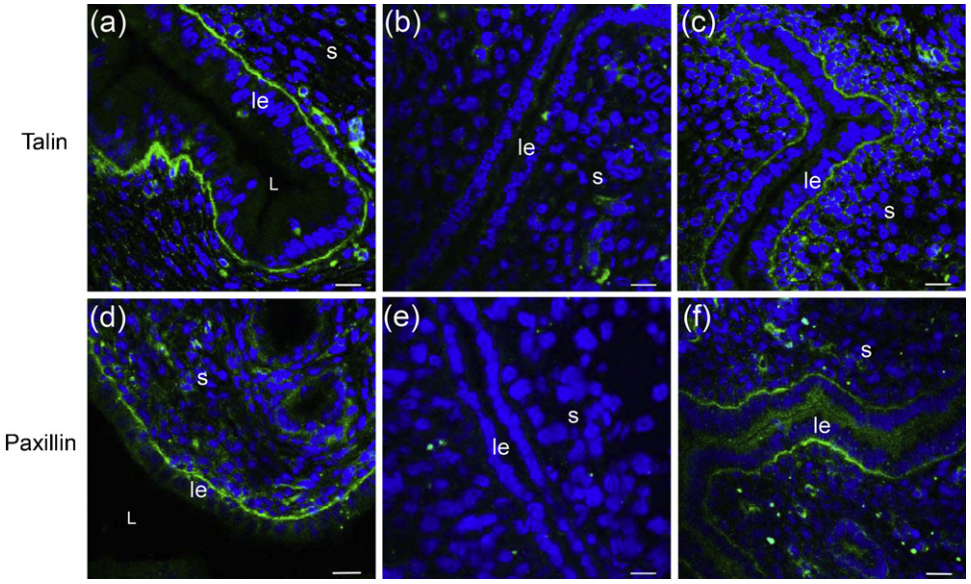

Fig. 1. Immunofluorescence micrographs of rat uterus stained for principal focal adhesion proteins. Talin on day 1 of pregnancy (a), day 6 of pregnancy (at the time of implantation; b) and day 9 of pregnancy (after implantation; c). Paxillin on day 1 of pregnancy (d), day 6 of pregnancy (e) and day 9 of pregnancy (f). Talin and paxillin formed prominent bands along the basal region of uterine luminal epithelial cells showing focal adhesions on day 1 of pregnancy. At the time of implantation on day 6, talin and paxillin are both markedly lost from the site of focal adhesions leading to the disassembly of focal adhesions but reassembly occurs soon after implantation on day 9. Nuclei are counterstained in blue. le, uterine luminal epithelial cells; L, lumen; s, stroma. Scale bar, 20 μm.
Original plate based around Kaneko et al. (2008).

comprised of two cell layers: an epithelial cell layer and the surrounding mesenchyme. A subset of the epithelial cells in these ducts differentiates into the columnar epithelial cells that line the lumen of the uterus.

2.1. Functions

In species with highly invasive-hemochorial placentation, in which uterine epithelial cells under the blastocyst are removed, it is evident that the basal plasma membrane plays a critical role. Indeed, in 1995 in an early ultrastructural study in the rat, Shion and Murphy (1995) recognised that the loss of electron-dense basal plasma membrane plaques at the time of uterine receptivity was likely involved in allowing blastocyst entry to the endometrium. These plaques were then called "immature hemidesmosomes" (Shion and Murphy, 1995) but they are now known to bear a strong ultrastructural resemblance to the focal adhesions which are routinely observed in cultured cells forming contact with the substratum (Abercrombie et al., 1971). Focal adhesions provide adhesion between the extracellular matrix and the intracellular actin fibres and play a key role in anchoring cells, especially epithelial cells, to the underlying connective tissue (Burridge et al., 1988; Lo, 2006). Thus understanding the molecular dynamics of focal adhesions during early pregnancy may provide insight into the unique aspect of uterine epithelial cells: that they are removed during early pregnancy to allow penetration of the blastocyst.

Focal adhesions were first identified as an electron dense region of the plasma membrane forming contact with the cell and the substratum in cultured cells (Abercrombie et al., 1971). They were at first thought to be an artefact of cultured cells since morphological focal adhesions were not observed in many tissues *in vivo*. However, later reports established the reality of focal adhesions *in vivo* (Burridge et al., 1988) and morphologically similar structures in uterine epithelial cells (Shion and Murphy, 1995). Focal adhesion formation is initiated by the clustering of transmembrane receptors, integrins, which bind to the extracellular matrix and subsequently initiate the activation and recruitment of the many cytoplasmic proteins to the site of the focal adhesion (Lo, 2006). The focal adhesion is also a central site for signal transduction regulating cell adhesion, cell migration, cell proliferation, apoptosis and gene expression (Lo, 2006).

The dynamics of focal adhesions are well documented in migrating cells, since migration involves remodelling of focal adhesion complexes at the front and rear of the cell (Webb et al., 2002). The leading edge of migrating cells form adhesion complexes at the base of membrane protrusions, initiated by clustering of integrins binding to ECM components. This is followed by recruitment of other focal adhesion proteins to the protrusion which grows into a more adhesive complex with extensive remodelling occurring to assemble a complete focal adhesion structure (Zaidel-Bar et al., 2003).

Focal adhesion disassembly is not simply the reverse of assembly and involves several key proteins including paxillin, talin and the integrins, β1 and β3. Paxillin is a phosphotyrosine-containing cytoskeletal protein and a molecular adaptor protein which recruits structural and signalling proteins to the focal adhesion to regulate actin (Brown and Turner, 2004; Hu et al., 2006). Talin is another principal focal adhesion protein which directly binds to the cytoplasmic domain of the integrin β cytoplasmic tail and actin fibres so providing an actin-membrane linkage (Nayal et al., 2004). Integrins are transmembrane cell surface receptors composed of α and β subunits (Hynes, 2002). The N-terminus of α and β subunits are extracellular and combine to form the ECM ligand binding region, while the cytoplasmic domains are responsible for interaction with the cytoskeletal proteins (Hynes, 2002). Specific integrins are associated to focal adhesions and in particular, integrin β1 and β3 subunits interact with talin *in vitro* at the site of focal adhesions (Tadokoro et al., 2003; Calderwood, 2004; Wegener et al., 2007) and these two particular integrins colocalise and structurally interact with talin along the basal cell surface of rat uterine luminal epithelial cells (Kaneko et al., 2011).

These focal adhesion proteins undergo dynamic distributional changes in rat uterine luminal epithelial cells during early pregnancy (Kaneko et al., 2008, 2011). On day 1 of pregnancy, the