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IMPLANTATION: RECENT APPROACHES TO UNDERSTAND A CELL BIOLOGICAL PARADOX

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Concepts of implantation physiology developed on the basis of previous work postulate that embryo implantation is initiated when trophoblast invasiveness coincides with a state of 'receptivity' of the endometrium, the latter being controlled by steroid hormones. However, neither trophoblast invasiveness nor endometrial receptivity are well understood in terms of their cell biological basis: a role of trophoblast-dependent proteinases in implantation has been well documented, but it remains unclear whether they are directly involved in invasion in the strict sense (4). The concept of endometrial 'receptivity' (15,16) has been developed on the one hand on the basis of heterochronous embryo transfer experiments, although these could not equivocally discriminate between generally hostile (embryo-toxic) effects of the uterine milieu and specific inaccessibility of the endometrium for trophoblast attachment and invasion. On the other hand, work on the hormonal control has largely concentrated on decidualization, a process whose significance for trophoblast invasion is far from clear (9,15). We are discussing here new data on cell-cell interactions in embryo implantation which may shed some new light on involved mechanisms. These data have in part been derived from experiments with a novel endometrial organ culture system allowing the study of trophoblast attachment and invasion, in vitro (6,8).

The initial events in embryo implantation involve an interaction of two epithelia, trophoblast and uterine epithelium, via their apical cell poles, resulting in adhesion, followed (in invasive types of implantation) by penetration of the trophoblast through the uterine epithelium into the endometrial stroma. Acquisition of mutual adhesiveness of apical plasma membranes of trophoblast and uterine epithelium appears to be a critical step in implantation initiation. It can be regarded as a cell biological paradox since epithelia are normally non-adhesive at their apical cell pole (5). A side-view at certain other phenomena observed during embryogenesis, however, the so-called embryonic 'fusion' processes (closure of the neural tube, formation of the secondary palate, etc.), shows that in certain cases epithelia can indeed interact with each other and attach via their apical cell poles. It appears that such a side-view can teach us a lot about general mechanisms involved which may in part also apply to trophoblast-uterine epithelial interactions at embryo implantation (5).

Does the uterine epithelium, like epithelia involved in embryonic 'fusion' processes, show a behavior that is non-typical for well-polarized epithelia (like transporting epithelia)? Does it perhaps loose certain of the typical epithelial properties that would preclude trophoblast attachment, specifically in the phase when it is hormonally prepared for trophoblast attachment ('receptive phase')?

TABLE 1
ENDOMETRIAL 'RECEPTIVITY' FOR BLASTOCYST IMPLANTATION: PARTIAL LOSS/ DESTABILIZATION OF APICO-BASAL POLARITY OF THE UTERINE LUMINAL EPITHELIUM

Properties of plasma membranes	
Apical	loss of marker enzymes (3) changed lectin binding properties (1,2,14) increased density of intramembranous protein particles (= basolateral membrane) (12,18) acquisition of new proteins (10) (redistribution of proteins that were restricted to the basolateral membrane in the pre-receptive phase?)
Lateral	proliferation of tight junctional strands towards basal cell pole (13,18)
Basal	reduced adhesion to basal lamina (rat) (17) defective basal lamina (rabbit) (11)
Intracellular/transcellular transport	
	changed activity and direction of endocytosis and transepithelial transport (13)
	changed sorting of membrane precursors (inferred from membrane changes, see above)
Organization of cytoskeleton (7)	

Recent results from studies based on this concept give evidence that this may indeed be the case (see Table 1). In the 'receptive phase', the uterine epithelium of the rabbit shows dramatic changes in the composition and properties of plasma membranes not only at the apical cell pole but also in the basolateral membrane domain.

All the phenomena listed in Table 1 are characteristics of the apico-basal polarity of epithelial cells. It appears remarkable that there is a general trend towards a reduction in the expression of such characteristics, in the 'receptive phase'. As one would expect, activity and direction of endocytosis and transcellular transport must then also change during this phase. This may not only be seen in the context of requirements for a changed uterine milieu as discussed before (13), but it may, in addition, indicate that the cell physiological state of the uterine epithelium is indeed grossly altered at this stage, probably including changes in the intracellular sorting pathways for membrane precursor molecules, towards the apical or the basolateral membrane domain. Changes in the polar organization of the

uterine epithelium should be reflected in the organization of the cytoskeleton. This is at present being investigated in our laboratory (7).

In conclusion, analysis of endometrial receptivity on the basis of recent cell biological concepts reveals that there is partial loss of elements of polar organization of the epithelium. Expression of adhesion molecules at the apical cell membrane, in this phase, may be part of this general reorganization. This hypothesis offers a new explanation for the cell biological paradox of trophoblast attachment to an intact-appearing epithelium. The presented concept should open a number of new approaches for studying the molecular basis of endometrial receptivity for embryo implantation.

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