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Implantation: Cell biology of embryo penetration route revisited.
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Summary

This article comments on a paper by Uchida et al. (How to Create an Embryo Penetration Route. *Am J Reprod Immunol* 75(3): 326–332; 2016; doi: 10.1111/aji.12476). In that publication, the authors discussed cell biological views of embryo implantation based on recent experimental data they had obtained with an in vitro model employing human endometrial and trophoblast cell lines. The authors concluded that they can define a precondition which must be met by uterine epithelial cells in order to allow trophoblast attachment to occur at their apical cell pole, i.e. that the cells must undergo certain changes in specific epithelial properties combined with a change in cell behaviour. A major point that Uchida et al. were making is that they interpreted their observations as being indicative of (partial) epithelial–mesenchymal transition (EMT) of the uterine epithelium occurring at endometrial receptivity. In fact they presented this hypothesis as a new theory of endometrial receptivity and implantation initiation.

In the present commentary I point out that Uchida et al. deserve to be congratulated for their careful investigation and their findings. In addition, it is also a merit of their article to draw attention to the EMT concept as applied to embryo implantation. However, it must be made clear that this theory is not new, in contrast to the impression to the contrary that these authors have given. This hypothesis had originally been developed many years before, on the basis of a comparison with certain processes in embryology, i.e. the so-called embryonic fusion processes. Its validity was subsequently explored experimentally in our lab, in a large series of investigations.

For heuristic reasons, we had proposed to view embryo implantation as a cell biological paradox, and to take advantage of a comparison with studies on other EMT processes (e.g. fusion of palatal shelves during development, or tumor cell invasion) in order to derive detailed concepts for investigating involved mechanisms. This concept of comparability of embryo implantation with other EMT-like processes indeed still appears to be the only existing cell biological theory on embryo implantation that focuses on global aspects of cytoplasmic organization and of cell behaviour of trophoblast and uterine epithelium. It specifically postulates that parts of an EMT program are used as the machinery to set hormone signalling into action at the level of cell behavior, without, however, involving a complete switch from the epithelial into the mesenchymal cell program, in the case of uterine epithelium. In the trophoblast, EMT-like changes are more extensive and obvious.

To apply the EMT concept to embryo implantation research has proven very useful as a heuristic approach, allowing our laboratory to plan and perform over the years a large series of experimental investigations into cell biological details behind the changes in epithelial cell behavior at receptivity. These studies have originally used ex-vivo material from laboratory animals and human endometria.

Later on, we developed an in vitro system employing human choriocarcinoma cell spheroids attaching to uterine epithelial monolayers, i.e. the system Uchida et al. have now also been using. Other groups have not focused on complex changes in the epithelial program and cell behavior (as in EMT) but on partial aspects such as apico-basal polarity, or properties of the apical plasma membrane and junctions.

Previous data from our group that may be of interest but have not been mentioned by Uchida et al. include:

- Reorganization of the actin cytoskeleton indicating changes in the motility apparatus, incl. Rho regulation.
- Monitoring of adhesive forces during attachment of trophoblast to uterine epithelium, and of the time course of this attachment.
- Calcium signalling as a typical response.
- Role of junctional complex reorganization; redistribution of integrins, E-cadherin, marker proteins of apical vs. basolateral membrane domains, and glycocalyx glycoconjugates.
- Vimentin upregulation.
- Changes in cell membrane lipid organization.
- Penetration of basal processes of uterine epithelial cells through their own basement membrane.
- The role of aspects of trophoblast differentiation status has been studied in detail, and we have taken a side view (as also Uchida et al. have been doing now) to leukocyte transmigration through the vascular endothelium at inflammation, in order to compare partial processes.

The data have led to a change of traditional views about the role of the host tissue in embryo implantation: The uterine epithelium appears not to be passive but to participate actively in trophoblast adhesion and penetration and may thus control it in a subtle way from the start.

In the present commentary, this series of previous publications of our group on this subject is listed, with regard to the various individual topics. An account of that research can also be found on my website at https://www.uni-due.de/denker/en/publ_impl_endo.htm.