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Calcium influx in human uterine epithelial RL95-2 cells is required for trophoblast-like JAR cell binding - signaling mechanisms in an embryo implantation model

M. Thie, H. Tinel*, and H.-W. Denker

Institut für Anatomie, Universitätsklinikum, Hufelandstraße 55, D-45122 Essen, and *Max-Planck-Institut für molekulare Physiologie, D-44227 Dortmund

At the initial phase of embryo implantation, the trophoblast of the blastocyst has to establish contact to the free surface of the uterine epithelial cells (UECs) and to adhere there. Adhesion to an apical plasma membrane is a very unusual phenomenon, and mechanisms involved are poorly understood. Determination of binding forces using atomic force spectroscopy demonstrated that formation of strong cell-to-cell bonds between UECs and trophoblast might be a relatively slow process, possibly including sequential steps of bond formation. It may be expected, therefore, that a complex cascade of events is initiated at the free pole of UECs starting with signaling and culminating in binding of trophoblast. The aim of experiments presented here was to obtain insight into the signaling mechanisms leading to the formation of stable bonds between UECs and trophoblast. Using human uterine epithelial RL95-2 cells (RL) which show adhesion competence for human trophoblast-like JAR cells (JAR) we investigated whether the contact of JAR spheroids to RL monolayers elicits changes of intracellular free calcium ($[Ca^{2+}]_i$) in RL. $[Ca^{2+}]_i$ was determined by ratio imaging in RL loaded with fluorescent indicators (Oregon Green 488 BABTA-1; Fura Red). Impact of JAR spheroids upon, and movement of spheroids across RL produced a transient increase in $[Ca^{2+}]_i$ in RL while spheroids resting on RL did not. Prolonged rest of JAR on RL, however, enabled formation of cell-to-cell bonds. Separation of established bonds did produce an increase in $[Ca^{2+}]_i$. In all experiments, the increase in $[Ca^{2+}]_i$ was due to influx from the external medium as it could be blocked both by removing extracellular Ca^{2+} and by the Ca^{2+} channel inhibitor nickel. Correspondingly, JAR binding to RL was reduced by removal of extracellular Ca^{2+} and by nickel. These data show that Ca^{2+} signaling is elicited in RL upon contact with JAR and that this plays a role in subsequent binding; these data suggest that Ca^{2+} signaling might be an important element in the embryo-endometrium interaction.

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