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The Role of Calcium Influx on Apical Adhesiveness of Human Uterine Epithelial RL95-2 Cells for Trophoblast-like JAR Cells

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Implantation of mammalian embryos in the uterus is a regulated event that depends on acquisition of adhesive properties of apical plasma membranes in two epithelia, uterine epithelium and trophoblast. A recent hypothesis postulates that uterine epithelial cells (UECs) can enter a state of receptivity by partially down-regulating their polarized phenotype, thus preparing their free surface for cell-cell interaction with the trophoblast. The aim of experiments presented here was to obtain insight into the signaling mechanisms leading to the formation of stable cell-cell bonds between receptive (adhesive) UECs and trophoblast. Using human uterine epithelial RL95-2 cells (RL) which show adhesiveness 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 transient increase in $[Ca^{2+}]_i$ in RL while JAR spheroids simply resting on RL did not. Prolonged rest of JAR spheroids on RL, however, enabled formation of cell-cell bonds. Disruption of these bonds again produced increase in $[Ca^{2+}]_i$ in RL. In each case, the increase of $[Ca^{2+}]_i$ in RL was due to Ca^{2+} influx as it could be blocked not only by removing extracellular Ca^{2+} but also by the Ca^{2+} channel inhibitor Ni^{2+}. Correspondingly, cell-cell binding of JAR spheroids to RL was blocked by removal of extracellular Ca^{2+} from the culture medium as well as by pretreatment of RL with Ni^{2+}. Collectively, these findings demonstrate that Ca^{2+} influx in uterine RL95-2 cells is required for trophoblast-like JAR cell binding. These data suggest that during embryo implantation signaling of the blastocyst to the uterine epithelium involves Ca^{2+} influx into UECs and that this, in turn, initiates a cascade leading to the formation of stable cell-cell bonds with the trophoblast.