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Exogenous Amino Acids Regulate Trophectoderm Differentiation in the Mouse Blastocyst through an mTOR-Dependent Pathway

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Abstract

At the late blastocyst stage, the epithelial trophectoderm cells of the mammalian embryo undergo a phenotypic change that allows them to invade into the uterine stroma and make contact with the maternal circulation. This step can be regulated *in vitro* by the availability of amino acids. Embryos cultured in defined medium lacking amino acids cannot form trophoblast cell outgrowths on fibronectin, an *in vitro* model of implantation, but remain viable for up to 3 days in culture and will form outgrowths when transferred into complete medium. The amino acid requirement is a developmentally regulated permissive event that occurs during a 4- to 8-h period at the early blastocyst stage. Amino acids affect spreading competence specifically by regulating the onset of protrusive activity and not the onset of integrin activation. Rapamycin, a specific inhibitor of the kinase mTOR/FRAP/RAFT1, blocks amino acid stimulation of embryo outgrowth, demonstrating that mTOR is required for the initiation of trophectoderm protrusive activity. Inhibition of global protein translation with cycloheximide also inhibits amino acid-dependent signals, suggesting that mTOR regulates the translation of proteins required for trophoblast differentiation. Our data suggest that mTOR activity has a developmental regulatory function in trophectoderm differentiation that may serve to coordinate embryo and uterus at the time of implantation.

Keywords

mouse; trophectoderm; trophoblast; amino acids; mTOR; rapamycin; differentiation; p70S6 kinase

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