Metabolic Enhancement of Mammalian Developmental Pausing

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Mammalian developmental timing is adjustable in vivo by preserving pre-implantation embryos in a dormant state called diapause. Over 130 mammalian species use this reproductive strategy to ensure that their offspring is born under most favorable conditions, thereby safeguarding survival. Inhibition of the growth regulator mTOR (mTORi) pauses mouse development in vitro. However, how embryonic dormancy is maintained is not known. Proteomics analyses of mTORi paused embryonic and trophoblast stem cells revealed that embryonic, but not trophoblast stem cells switch to fatty acid degradation as primary energy source. Moreover, diapausing embryos accumulate fatty acids into large lipid droplets in the trophectoderm, but not in the epiblast. The transfer of fatty acids from the cytosol into mitochondria requires their conjugation to carnitine by carnitine palmitoyltransferase 1a (CPT1a). We reasoned that supplementing the embryos with free L-carnitine may enhance fatty acid degradation in the epiblast and promote it in the trophectoderm, thus alleviating the current constraints and maintaining the paused embryos longer in culture. Notably, L-carnitine balances lipid consumption, puts the embryos in deeper dormancy and boosts embryo survival from 15 to 34 days. Our results lift a constraint on in vitro embryo survival and suggest that lipid metabolism may be a critical metabolic transition relevant for longevity and stem cell function across tissues.