BİLKENT UNIVERSITY

MOLECULAR BIOLOGY AND GENETICS

DEPARTMENTAL SEMINAR

"Inhibition of mTor induces a paused pluripotent state"

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Cultured pluripotent stem cells are a cornerstone of regenerative medicine due to their ability to give rise to all cell types of the body. Although pluripotent stem cells can be propagated indefinitely in vitro, pluripotency is paradoxically a transient state in vivo, lasting 2-3 days around the time of blastocyst implantation. The exception to this rule is embryonic diapause, a reversible state of suspended development triggered by unfavorable conditions. Diapause is a physiological reproductive strategy widely employed across the animal kingdom, including in mammals, but its regulation remains poorly understood. I will discuss our finding that partial inhibition of mechanistic target of rapamycin (mTor), a major nutrient sensor and promoter of growth, induces reversible pausing of Mouse blastocyst development and allows their prolonged culture ex vivo. Paused blastocysts remain pluripotent and competent to give rise to embryonic stem (ES) cells and mice. We show that both naturally diapaused blastocysts in vivo and paused blastocysts ex vivo display pronounced reductions in mTor activity, translation, histone acetylation and transcription. Pausing can be induced directly in cultured ES cells and sustained for weeks without appreciable cell death or deviations from cell cycle distributions. We show that paused ES cells display a remarkable global suppression of transcription and maintain a gene expression signature of diapaused blastocysts. These results uncover a new pluripotent stem cell state corresponding to the epiblast of the diapaused blastocyst and indicate that mTor regulates developmental timing at peri-implantation. Our findings have important implications in the fields of assisted reproduction, regenerative medicine, cancer, metabolic disorders and aging.

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