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Human Embryonic Stem Cells Derived From Preimplantation Genetically Diagnosed Embryos

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ScienceDaily (Nov. 15, 2007) — A human stem cell line derived from embryos that were identified by preimplantation genetic diagnosis (PGD) to carry the mutation for fragile X syndrome has provided an unprecedented view of early events associated with this disease. In addition to giving scientists fresh insight into fragile X, results from this unique model system have emphasized the value of this new source of embryonic stem cells and may have a significant impact on the way that genetic diseases are studied in the future.

Fragile X syndrome, the most common cause of inherited mental impairment and of autism, is caused by the absence of the fragile X mental retardation protein (FMRP). Most individuals with fragile X exhibit a specific mutation in the fragile X mental retardation 1 (FMR1) gene that usually coincides with epigenetic DNA modifications. However, the developmental timing and mechanisms associated with acquisition of these characteristics are not clear due to the absence of appropriate cellular and animal models.

To examine developmentally regulated events involved in fragile X pathogenesis, Dr. Nissim Benvenisty and Dr. Rachel Eiges from the Hebrew University Department of Genetics in Jerusalem, Israel, together with Dr. Dalit Ben-Yosef from the IVF unit at the Tel-Aviv Sourasky Medical Center, established a human embryonic stem cell (HESC) line from a preimplantation fragile X-affected embryo identified by PGD. The fragile X cell line, called HEFX, displayed all characteristics typical of an HESC line and possessed the full genetic mutation observed in fragile X patients.

The researchers found that undifferentiated HEFX cells transcribed FMR1 and expressed FMRP, suggesting that the fragile X mutation by itself is not sufficient to cause FMR1 inactivation. The research team went on to show that differentiated derivatives of HEFX cells exhibited a decrease in FMRI transcription and FMRP expression along with an increase in epigenetic modifications associated with fragile X syndrome. "The fact that FMR1 inactivation and other modifications take place after differentiation suggests that it might be possible to prevent some of these events as an attempt to rescue the abnormal phenotype in cells with the full fragile X mutation," suggests Dr. Benvenisty.

HEFX cells represent an excellent model for examination of early embryogenesis and will contribute to a clearer understanding of the molecular mechanisms underlying fragile X pathogenesis. This research is also compelling on a more general level in that it validates the usefulness of HESCs derived

from embryos that have been screened for specific mutations with PGD. ESC lines derived in this manner represent a potent tool for the study of a variety of human diseases and the development of new therapeutic strategies.

The research is published in the November issue of the journal Cell Stem Cell, published by Cell Press.

The researchers include Rachel Eiges, Achia Urbach, Amir Eden, Ofra Yanuka, andNissim Benvenisty, of the Silberman Institute of Life Science, The Hebrew University, Jerusalem, Israel; Mira Malcov, Tsvia Frumkin, Tamar Schwartz, Dalit Ben-Yosef, Ami Amit, and Yuval Yaron, of the Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel.