MedicalXpress

Stem cell research paves way for progress on dealing with Fragile X retardation

May 22 2012

Researchers at the Hebrew University of Jerusalem have achieved, for the first time, the generation of neuronal cells from stem cells of Fragile X patients. The discovery paves the way for research that will examine restoration of normal gene expression in Fragile X patients.

Fragile X syndrome is the most common cause of inherited mental retardation, affecting hundreds of thousands of patients worldwide. The syndrome is caused by lack of normal expression (functioning) of the FMR1 gene that is critical for normal cognitive function in brain neuronal cells.

Absence of expression of the FMR1 gene is caused by a mutation in the regulatory elements that govern its expression. The abnormal addition of chemical methyl groups to the regulatory elements causes gene silencing in patients, culminating in severe mental retardation.

A potential way to help patients is to find compounds that will clear the abnormal methyl groups from the regulatory elements and reactivate normal gene expression. In their work, the Hebrew University researchers have identified a chemical compound that restored normal gene expression specifically in neuronal cells, the cell type most affected in patients.

The research was conducted in the laboratory of Nissim Benvenisty, the Herbert Cohn Professor of Cancer Research at the Hebrew University, by PhD student Ori Bar-Nur and undergraduate student Inbal Caspi.

They demonstrated, for the first time, the generation of brain neuronal cells from patients of Fragile X syndrome in a dish culture. In doing so, they were able to find a substance that restored normal gene expression in patients' cells.

In a previous study conducted in the Benvenisty laboratory, a novel technology was used to induce pluripotent stem cells from skin cells of Fragile X patients. Pluripotent stem cells have the amazing ability to differentiate into any human cell type in a dish culture.

In their latest study (published in the *Journal of* Molecular Cell Biology), the researchers harnessed this ability to turn the stem cells into neuronal brain cells. After generating the cells, they screened several chemical substances with the aim of finding one that would restore FMR1 normal gene expression. They showed that the substance 5-azaC was able to clear the methyl groups from the regulatory elements of the gene, allowing for the efficient restoration of FMR1 expression in both stem and neuronal brain cells.

The substance 5-azaC has been known for many years to clear methyl groups from regulatory elements of genes, and is also an already established drug for other diseases. However, this is the first time that it has been shown to successfully clear the methylation in neurons or stem cells of Fragile X patients.

In addition, the researchers were able to show that gene expression is maintained even after 5-azaC withdrawal, so there is no need to administer it continuously. This raises hopes for the use of the compound as a potential drug for the benefit of Fragile X patients.

According to Bar-Nur, "There is still a substantial gap between the restoration of gene expression in cultured patients' cells and restoring it in patients; however, the finding that it is possible to restore gene

expression in neuronal cells paves the way for further study of its restoration in patients." He concludes: "New technologies developed in recent years in the stem cell field allow us to conduct research that was not possible until recently".

Provided by Hebrew University of Jerusalem