MedicalXpress

Mutant gene's true effect revealed - giving new therapy hope

October 19 2009

(PhysOrg.com) -- Scientists have revealed how a mutant gene that causes a connective tissue disease resulting in dwarfism does so by significantly affecting the inside of cells - opening up new therapy strategies that involve drugs already under development.

In disorders such as many forms of dwarfisms or brittle bone disease, mutations in genes for extracellular matrix proteins were thought to exert their pathogenic effects because of resulting defects in extracellular matrix. But Dr Mike Briggs, Professor Ray Boot-Handford and their team in the Wellcome Trust Centre for Cell-Matrix Research at The University of Manchester have shown in a series of recent papers that they also have significant effects inside the cell.

Professor Boot-Handford, at the Faculty of Life Sciences, explains: “The mutant genes cause stress in the endoplasmic reticulum (ER) of cells responsible for bone growth.

“The increased ER stress caused by accumulation of mutant protein inside the cells disrupts the cellular processes required to produce efficient bone growth and results in dwarfism.”

The team’s latest study, funded by the European Union, US National Institutes of Health and Wellcome Trust and published in open access journal PLoS Genetics today (Monday 19th October 2009), proved that the mutant gene causing one genetic form of dwarfism had its effect as a direct result of the ER stress.

Professor Boot-Handford says: “We have triggered ER stress in normal cartilage cells and achieved the same effects as in the naturally occurring disorder caused by the mutant extracellular matrix protein (type X collagen) thus showing that the intracellular stress response was at the heart of the disorder.

“The cells are constipated in their secretion of proteins and we know there are already drugs developed that can relieve this type of problem, and they are currently being tested to treat diabetes.

“We could be close to finding new ways of treating many connective tissue disorders. If you screened young patients to find out the exact nature of their gene mutation, you could then select an appropriate drug to help their cells deal better with the mutant protein and therefore improve the growth of the patient.”

He adds: “Manchester discovered type X collagen 30 years ago and we were the first to describe the complete human gene sequence; subsequently, we were one of the first to describe mutations in type X collagen that lead to the dwarfism (metaphyseal chondrodysplasia type Schmid). Now we understand much more about the mechanism by which the gene affects the growth of the skeleton.

“This research is very exciting - it is a paradigm for many connective tissue disorders where mutant protein is misfolded during secretion, causing this form of cellular constipation. Type 2 diabetes is also thought to be caused by a similar mechanism involving ER stress and there are trials of stress-relieving drugs currently underway.

“So we may soon be able to use drugs that have a laxative effect on the cells secretion system to address a wide range of diseases.”

More information: Research paper: www.plosgenetics.org/article/info